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Climate-Related Exposome and Cardiovascular Outcomes: A Narrative Review of Epidemiological Evidence, Biological Mechanisms, and Policy Implications

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ABSTRACT

Cardiovascular diseases are the leading cause of death globally and in Iran. Climate change has intensified human exposure to extreme temperatures, thermal variability, and bioclimatic indices. The climate exposome framework offers a comprehensive approach to assessing environmental exposures across the lifespan. This narrative review synthesizes evidence on the climate exposome's role in the development of cardiovascular diseases and its biological mechanisms. Epidemiological evidence indicates that exposure to extreme temperatures, temperature variability, climate-related air pollution, and extreme events is significantly associated with increased cardiovascular disease mortality, hospitalizations, myocardial infarction, stroke, and heart failure. These effects follow non-linear patterns with temporal lags and are more pronounced among the elderly, individuals with pre-existing heart disease, and lower socioeconomic groups. Proposed biological mechanisms include thermoregulatory disruption, sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis activation, systemic inflammation, oxidative stress, endothelial dysfunction, coagulation abnormalities, and emerging mechanisms such as epigenetic modifications and gut microbiome dysbiosis. Interactions between climatic factors and air pollution generate synergistic effects. Adopting the climate exposome approach in cardiovascular research provides a comprehensive understanding of cumulative environmental exposures, playing a critical role in designing preventive interventions, shaping health policies, and enhancing health system adaptation to climate-related hazards.

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality and disability worldwide and in Iran, accounting for a substantial proportion of disease burden, reduced quality of life, and healthcare system costs (Gaziano, 2022). According to reports from the World Health Organization, approximately 17.9 million people die from CVDs each year globally, and this trend is increasing, particularly in developing countries (Dehghani et al., 2022). In Iran, these diseases also rank as the foremost cause of death, making the control of their associated risk factors a primary priority for the health system (Vahidi-Kolur et al., 2025). Although the role of classic risk factors such as age, sex, genetics, unhealthy diet, physical inactivity, tobacco use, and stress is well established, recent decades have witnessed growing attention toward the role of environmental factors, particularly climate-related components, in the onset and exacerbation of cardiovascular outcomes (Baaghideh & Mayvaneh, 2017; Gasparrini et al., 2015). Climate change, as

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one of the greatest public health challenges of the 21st century, has altered patterns of temperature, humidity, precipitation, and extreme weather events, creating conditions for complex, cumulative, and multi-factorial human exposures (Bhatnagar, 2017). Numerous epidemiological studies have demonstrated that temperature fluctuations and other climatic indices are associated with increased incidence and mortality from CVDs, with the pattern of this association often described as U-shaped or J-shaped; that is, both very high and very low temperatures are associated with an increased risk of cardiovascular outcomes (Buck Louis et al., 2017; Chaulin & Duplyakov, 2021; Dastoorpoor et al., 2019). Exposure to heat can lead to acute cardiovascular consequences through dehydration, increased cardiac workload, impaired thermoregulation, arrhythmias, and hemodynamic changes (Malambo et al., 2016). In contrast, exposure to cold is associated with vasoconstriction, elevated blood pressure, increased blood viscosity, and a heightened risk of thrombosis and cardiac and cerebral strokes (Zangeneh et al., 2024). In response to the reality that humans are simultaneously and chronically exposed to a multitude of environmental factors in the real world, the concept of the exposome was introduced as a comprehensive framework to describe the totality of environmental exposures from preconception through death (Fan et al., 2023). The climate exposome specifically addresses the set of climate-related exposures, including temperature, humidity, heatwaves and cold spells, extreme weather events, and secondary climate-driven pollutants. This approach, by emphasizing the dynamic, cumulative, and interactive nature of exposures, enables a more realistic analysis of the role of climate in the development and outcomes of CVDs and moves beyond the limitations of single-exposure studies (Haddad et al., 2019). From a biological perspective, diverse mechanisms have been proposed to explain the association between climatic factors and cardiovascular outcomes. Hemodynamic changes, sympathetic nervous system (SNS) activation, coagulation alterations, increased stress hormones, systemic inflammation, and oxidative stress are among the primary pathways implicated in response to climate exposures (Sharafkhani et al., 2020). Emerging evidence also points to the role of epigenetic modifications, alterations in the microbiome, and disruption of metabolic regulation resulting from long-term climate exposures (Haddad et al., 2019). These mechanisms indicate that climatic effects are not limited to acute outcomes but can also manifest as chronic and cumulative processes. The impact of climatic factors on cardiovascular health varies across populations, and individual and social factors can modulate susceptibility. Older adults, patients with chronic CVDs, children, individuals of lower socioeconomic status, residents of areas lacking adequate infrastructure for heat and cold adaptation, and those occupationally or environmentally exposed to adverse climatic conditions are among the more vulnerable groups (Ahmadnezhad et al., 2013; Analitis et al., 2008). Identifying these populations is of particular importance for designing targeted preventive interventions and reducing health inequalities. Despite the accumulation of evidence, a considerable proportion of previous studies have focused primarily on a single climatic factor and have rarely employed the comprehensive exposome framework to analyze exposures and their interactions simultaneously. Furthermore, substantial variation in the climatic indices used, study designs, populations studied, and reported health outcomes has made it difficult to obtain an integrated picture of the evidence base (Baaghideh & Mayvaneh, 2017; Buck Louis et al., 2017). Existing reviews have also often focused separately on temperature, heatwaves, or air pollution, with less attention paid to cardiovascular outcomes within the climate exposome framework (Baaghideh & Mayvaneh, 2017; Buck Louis et al., 2017). Accordingly, this narrative review aims to synthesize and analyze the available epidemiological evidence on the association between the climate exposome and cardiovascular outcomes, and to elucidate the proposed biological mechanisms underlying this relationship. This narrative review was conducted following the SERGE (Scoping, Evaluation, Reporting, and Generation of Evidence) framework for non-systematic reviews. A comprehensive search was performed in international databases (PubMed, Scopus, Google Scholar, and ScienceDirect) and national databases (SID, Magiran, and Irandoc) using key terms including "Exposome", "Climate change", "Temperature", "cardiovascular diseases", "Mortality", and "Environmental health". Articles published between 2000 and 2025 in English or Persian were considered. Eligible studies included time-series, cohort, systematic reviews, meta-analyses, and scientific statements examining the association between climatic factors and cardiovascular outcomes.

2. Discussion

2.1 The concept of climate exposome: Definition, components, and advantages over single-exposure approaches

Understanding the relationship between environmental factors and health outcomes requires acknowledging that, in the real world, humans are never exposed to a single isolated agent. Instead, they simultaneously face a complex array of physical, chemical, biological, and social exposures throughout their lifespan. In response to this complexity, the concept of the exposome was first introduced by Christopher Wild in 2005 as the environmental counterpart to the genome, referring to the totality of human environmental exposures from conception to death (Malambo et al., 2016). This conceptual framework provides a comprehensive, holistic approach to examining the effects of the environment on health, enabling researchers to analyze the cumulative, simultaneous, and interactive effects of exposures rather than adopting a reductionist, single-exposure approach. The exposome is typically divided into three main domains, each covering different layers of exposure from the external environment to the internal milieu (Haddad et al., 2019): (a) General external exposome:

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This domain encompasses large-scale, population-level environmental exposures over which individuals have limited control. The most important components include climatic conditions (temperature, humidity, precipitation, and wind), air pollution (particulate matter, ozone, and nitrogen oxides), water pollution, socioeconomic status (income, education, and occupation), and urban or rural environment (population density, access to green spaces, and infrastructure). Climatic factors fall within this general external exposome domain because they occur on a broad, population-wide scale, and while exposure intensity may vary depending on geographic location, season, and local characteristics, individuals are widely exposed to them. (b) Specific external exposome: This domain includes exposures of a more specific nature that are largely influenced by individual behaviors, lifestyle, and the proximal environment. Its components include: chemical agents (environmental toxins, heavy metals such as lead and cadmium, pesticides, plasticizers), physical factors (noise, ionizing and non-ionizing radiation, electromagnetic fields), biological factors (allergens, microorganisms, mycotoxins), and lifestyle factors (diet, tobacco and alcohol use, physical activity, sleep patterns). (c) Internal exposome: This domain refers to the body's biological response to external exposures and encompasses the set of biochemical, physiological, and molecular changes that occur within the organism. Its components include: metabolic products (metabolites resulting from the processing of exogenous and endogenous substances), inflammation and oxidative stress (markers such as C-reactive protein (CRP), Interleukin-6 (IL-6), malondialdehyde, total antioxidant capacity), hormonal changes (cortisol, catecholamines, thyroid hormones), and the body's microbiome (composition and diversity of microorganisms residing in the gut, skin, and other areas).

Figure 1 illustrates the conceptual framework of the climate exposome and cardiovascular outcomes. This framework demonstrates how the climate exposome, comprising extreme temperatures (heat and cold), temperature variability, climate-related air pollution ($PM_{2.5}$, PM_{10}, ozone), and extreme climate events (floods, storms, wildfires, droughts), along with accompanying climatic factors (humidity, air pressure, seasonal variations) that exert acute or chronic and often simultaneous effects on an individual, increases the risk of cardiovascular outcomes through a set of interconnected biological pathways. These biological pathways include disruption of thermoregulation, systemic inflammation and oxidative stress, activation of the SNS and the hypothalamic-pituitary-adrenal (HPA) axis, hemodynamic changes (increased heart rate and cardiac workload), endothelial dysfunction, coagulation abnormalities and thrombogenesis, and emerging mechanisms (epigenetics, metabolic dysregulation, microbiome alterations). Activation of these pathways first produces measurable intermediate outcomes, including elevated blood pressure, increased inflammatory markers (CRP, IL-6), endothelial dysfunction, heart rhythm disturbances, and increased blood viscosity, which subsequently lead to ultimate cardiovascular outcomes such as coronary artery disease, myocardial infarction, stroke, heart failure, arrhythmias, and cardiovascular mortality. The magnitude of these effects is modulated by individual and social modifiers, including demographic characteristics (age, sex), baseline health status (pre-existing cardiovascular disease, diabetes, hypertension, obesity), socioeconomic factors (income, education, housing), lifestyle behaviors (physical activity, smoking, diet), and access to healthcare services (early warning systems, air conditioning, medical care). The overlapping pathways indicate synergistic and cumulative effects. Modifiers are positioned above the pathways, while bidirectional arrows at the bottom emphasize the life-course perspective and cumulative effects of repeated or chronic exposures. Finally, this framework emphasizes that climate exposures and their biological effects accumulate over time and, through negative feedback loops such as reduced physiological adaptive capacity, increase an individual's vulnerability to subsequent exposures. This framework provides a comprehensive basis for interpreting epidemiological evidence and designing future interventions.

The difference between the exposome approach and traditional single-exposure studies represents one of the most important conceptual points that must be emphasized. In conventional single-exposure studies, researchers typically examine the association between a specific risk factor (e.g., air temperature or $PM_{2.5}$ concentration) and a health outcome (e.g., cardiac mortality) while controlling for other factors as confounding variables. Although this approach is methodologically simpler and more feasible, it fails to reflect the complex reality of real-world exposures. In practice, an elderly individual living in Tehran on a hot summer day is not only exposed to high temperatures but is simultaneously exposed to high ozone concentrations (which increase on hot days), particulate matter, urban noise, psychological stress from traffic, and possibly dehydration resulting from physical activity. By emphasizing the dynamic, cumulative, and interactive nature of exposures, the exposome approach enables a more realistic analysis of the role of climate in the development and outcomes of CVDs and moves beyond the reductionism of single-exposure studies (Haddad et al., 2019; Zangeneh et al., 2024).

In other words, while single-exposure studies ask, "Is temperature associated with cardiac mortality?", the exposome approach asks, "How does the totality of climate-related exposures over an individual's lifetime, through multiple interacting biological pathways, lead to increased cardiovascular risk, and what factors modify these effects?"

The scoping review by Haddad et al. (2019), examined in this narrative review, found that of 82 published studies containing the term "exposome" up to 2019, only 48% covered all three domains of the exposome (general external, specific external, and internal), and the use of this concept was often non-systematic and incomplete. This finding indicates that although the exposome framework is theoretically very powerful, its practical and comprehensive application in experimental studies still faces challenges.

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Nevertheless, these early studies have shown that applying the exposome approach can explain a greater variance in health outcomes compared to single-exposure models and can reveal interactive and threshold effects that are not identifiable in traditional analyses. In the context of the climate exposome and cardiovascular outcomes, studies that have simultaneously modeled temperature, humidity, air pollution, socioeconomic status, and inflammatory biomarkers have demonstrated that the synergistic effects of these factors on cardiovascular mortality are significantly greater than the sum of their independent effects (Baaghideh & Mayvaneh, 2017; Chaulin & Duplyakov, 2021; Dehghani et al., 2022). Therefore, this narrative review, by emphasizing the climate exposome framework, attempts to take a step beyond single-exposure studies and provide a more comprehensive and practical understanding of the relationship between climate and cardiovascular health. To provide a clear picture of the state of research on the association between the climate exposome and cardiovascular outcomes, key studies with diverse designs (time-series, cohort, systematic review, and meta-analysis) are summarized in Table 1. This table presents information including the country where the study was conducted, study design, climate exposome component investigated, study population, primary outcome, key findings, and risk ratio or odds ratio with 95% confidence intervals.

Table 1. Summary of key epidemiological studies on the association between climate exposome and cardiovascular outcomes

Row	Country/region	Study design	Climate exposome component	Study population	Primary outcome	Key finding	Risk ratio (RR/OR) (95% CI)	References
1	13 countries (multi-country)	Multi-center time-series	Temperature (heat and cold)	74,225,200 deaths	Cardiovascular mortality	U-shaped association; cold contributes more to overall mortality burden	Extreme heat: RR = 1.12 (1.09-1.15); Extreme cold: RR = 1.43 (1.35-1.52)	(Gasparrini et al., 2015)
2	15 European cities (PHEWE)	Time-series	Low apparent temperature	Urban population	Cardiovascular mortality	1°C decrease in temperature associated with 1.72% increase in cardiovascular mortality	1°C decrease: 1.72% increase (1.12-2.32%) in cardiovascular mortality	(Analitis et al., 2008)
3	United States	Cohort (6 years)	$PM_{2.5}$ (climate-related)	500,000 adults	Cardiovascular mortality	Increased cardiovascular mortality risk with chronic $PM_{2.5}$ exposure	10 $\mu g/m^3$ increase: HR = 1.12 (1.08-1.16)	(Pope III et al., 2004)
4	272 Chinese cities	Time-series	Temperature + air pollution	Urban population (182 million)	Stroke	Synergistic effects of heat and air pollution on stroke	Temperature (99th percentile): RR = 1.53 (1.37-1.71); $PM_{2.5}$ + temperature: synergistic effect	(Chen et al., 2018)
5	Europe (multi-country)	Multi-center time-series	Heatwaves (anthropogenic climate change)	General population	Cardiovascular mortality	One-third of heat-related deaths attributable to anthropogenic climate change	RR = 1.18 (1.15-1.21) for heatwaves	(Vicedo-Cabrera et al., 2021)
6	São Paulo, Brazil	Time-series	Temperature variability	Elderly (≥65 years)	Heart failure (hospitalization)	High temperature variability associated with increased cardiac hospitalizations	High variability (99th percentile): OR = 1.26 (1.16-1.36)	(Zhao et al., 2018)
7	Urmia, Iran	Time-series (DLNM)	Heatwaves and cold spells	General population	Non-accidental mortality	High temperature and heatwaves increase mortality risk	Main effect of heat: HR = 1.14 (1.03-1.26)	(Sharafkhani et al., 2020)
8	Tehran, Iran	Ecological time-series	Heatwaves	17 heatwaves (2001-2011)	Excess mortality	17 heatwaves associated with 1,069 excess deaths; the elderly most affected	Excess mortality in elderly: OR = 1.18 (1.08-1.29)	(Ahmadnezhad et al., 2013)
9	Ahvaz, Iran	Time-series	Air pollution (PM_{10}, NO_2, SO_2)	Urban population	Cardiovascular hospitalization	10 $\mu g/m^3$ increase in PM_{10} associated with increased cardiac hospitalizations	PM_{10}: RR = 1.18 (1.12-1.24)	(Dastoorpoor et al., 2019)
10	Global	Systematic review and meta-analysis	Cold exposure	65 studies	Cardiovascular disease	Cold is a critical risk factor for CVDs	Effects are more severe in colder regions; further studies are needed	(Fan et al., 2023)

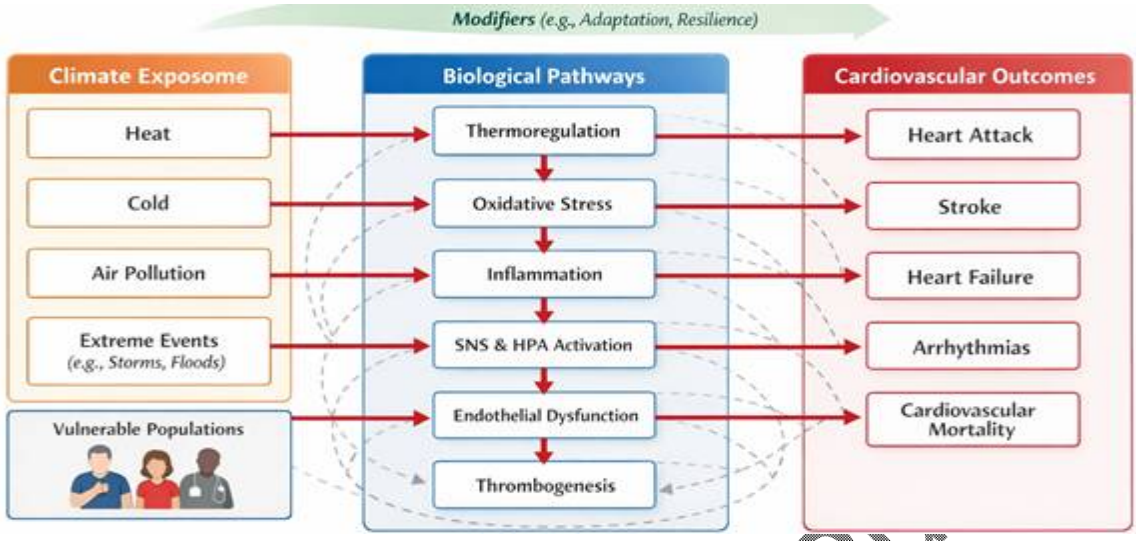


Figure 1. Conceptual framework linking the climate exposome to cardiovascular outcomes (Hanneman et al., 2026)

The substantial variability in climatic indices used across different studies represents one of the main challenges in comparing and interpreting epidemiological findings. Table 2 summarizes the most important climate exposome indices, along with their constituent components, units of measurement, advantages, limitations, and applications in cardiovascular health studies. These indices range from simple measures such as daily mean temperature and apparent temperature to more advanced indices such as the Universal Thermal Climate Index (UTCI) and the Air Quality Index (AQI). Furthermore, the operational definitions of heatwaves, cold spells, and temperature variability, which have been applied inconsistently across different studies, are described in this table. Awareness of the characteristics of each index is essential for selecting the most appropriate exposure metric in future research.

2.2 Effects of heat and heatwaves on cardiovascular outcomes

The epidemiological evidence reviewed convincingly demonstrates that increases in ambient temperature and the occurrence of heatwaves are associated with elevated cardiovascular mortality, incidence of myocardial infarction, heart failure, and arrhythmias. The multi-country study by Gasparrini et al. (2015), covering more than 13 countries worldwide, reported a U-shaped pattern for the association between temperature and cardiovascular mortality, in which both very low and very high temperatures are associated with increased risk. Notably, the effect of heatwaves typically manifests with a short lag time (a few days), with intensity being greatest during the initial days of the heatwave. In Iran, the study by Sharafkhani et al. (2020) in Urmia showed that heatwaves increase the risk of non-accidental mortality, although this study did not find a direct association with specific cardiovascular mortality. Furthermore, the study by Ahmadnezhad et al. (2013) in Tehran demonstrated that over one decade, 17 heatwaves were associated with 1,069 excess deaths, with the elderly being the most affected. These findings represent a serious warning for Iran, which is facing a rising trend of warming, and underscore the necessity of designing heat warning systems.

2.3 Effects of cold and temperature variability on the cardiovascular system

In contrast to heat, exposure to low temperatures and marked temperature variability also poses a significant risk to cardiovascular health. The study by Analitis et al. (2008) across 15 European cities within the PHEWE project showed that a 1 °C decrease in temperature was associated with a 1.72% increase in cardiovascular mortality, with this increase being substantially greater among the elderly than other groups. The systematic review and meta-analysis by Fan et al. (2023) also demonstrated that cold exposure is a critical risk factor for CVDs, and that its effects vary across different disease types (myocardial infarction versus heart failure) and climatic regions. Importantly, the effect of cold typically manifests with a longer lag time (up to several weeks) compared to heat, and the overall mortality burden attributable to cold exceeds that of extreme heat in many regions. Temperature variability (sudden temperature changes over a short period) is also independently associated with increased cardiac hospitalizations, as it reduces the capacity of the body's thermoregulatory system to adapt to rapid changes. These findings highlight the importance of attending to both ends of the temperature spectrum in prevention programs.

2.4 The role of air pollution as a key component of the climate exposome

Air pollution, particularly particulate matter ($PM_{2.5}$ and PM_{10}) and tropospheric ozone, represents one of the most important components of the climate exposome, as it is both influenced by climatic conditions and independently affects cardiovascular health (Nazari et al., 2016).

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The cohort study by Pope et al. (2004) demonstrated that chronic exposure to $PM_{2.5}$ significantly increases the risk of cardiovascular mortality, and this association is observed even at levels below air quality standards (Pope III et al., 2004). In Iran, the study by Dehghani et al. (2022) showed that exposure to air pollution is significantly associated with cardiovascular mortality in the elderly. The study by Dastoorpoor et al. (2019) in Ahvaz also reported increased cardiac hospitalizations on days with high pollutant concentrations. The interaction between climate and air pollution occurs through two main pathways: first, climatic conditions (temperature, solar radiation, humidity) influence the formation of secondary pollutants such as ozone; second, the co-occurrence of hot days with high air pollution concentrations creates synergistic effects on cardiovascular health (Dastoorpoor et al., 2019). The study by Chen et al. (2018) in China demonstrated that the combined effect of heat and air pollution on stroke incidence is significantly greater than the sum of their independent effects.

Table 2. Main climate exposome indices and their applications in cardiovascular health studies

Row	Index name	Constituent components	Unit of measurement	Advantages	Limitations	Application in CVDs	References
1	Mean Temperature	Average of daily minimum and maximum temperatures	Degrees Celsius (°C)	Simple, accessible, comparable across regions	Does not account for humidity or wind effects	Classic U-shaped mortality studies	(Bhatnagar, 2017; Gasparrini et al., 2015)
2	Apparent Temperature (AT)	Temperature + relative humidity + wind speed	Degrees Celsius (°C)	Better reflects human thermal stress than simple temperature	Requires more complete meteorological data	European PHEWE studies	(Analitis et al., 2008; Dastoorpoor et al., 2019)
3	Heat Index (HI)	Temperature + relative humidity	Degrees Fahrenheit/Celsius	NOAA standard; suitable for heat risk forecasting	Does not account for wind speed or solar radiation	Heat warning systems in the United States	(Chen et al., 2018; Sharafkhani et al., 2020)
4	Universal Thermal Climate Index (UTCI)	Temperature + humidity + wind + thermal radiation	Degrees Celsius (°C)	Advanced physiological model; thermal equivalent under reference conditions	Complex; requires multiple data inputs	Gold standard in bioclimatology	(Daiber et al., 2019; Franklin et al., 2015; Lee et al., 2014)
5	Heatwave (HW)	Various definitions (temperature above 90th/95th/98th percentile, duration ≥2-6 days)	Days (duration)	Operational for health warnings	Variability in definitions → lack of cross-study comparability	Excess mortality during heatwaves	(Ahmadnezhad et al., 2013; Fan et al., 2023; Sharafkhani et al., 2020)
6	Cold Wave (CW)	Temperature below 5th/10th percentile for ≥2-3 days	Days (duration)	Identifies high-risk cold periods	Inconsistent definitions across regions	Cold-related cardiac mortality and hospitalization	(Analitis et al., 2008; Fan et al., 2023; Sharafkhani et al., 2020)
7	Temperature Variability (TV)	Standard deviation of temperature over a specified time window (2-7 days)	Degrees Celsius	Independent effect from mean temperature	Ambiguity regarding optimal time window	Heart failure hospitalization	(Bhatnagar, 2017; Zhao et al., 2018)
8	Air Quality Index (AQI)	Composite of multiple pollutants ($PM_{2.5}$, O_3, NO_2, SO_2, CO)	Numeric (0-500)	Integrated, understandable to the public	Different weighting schemes across countries	Synergistic effects with temperature	(Chen et al., 2018; Dastoorpoor et al., 2019; Dehghani et al., 2022)
9	Heat Load	Temperature + solar radiation + physical activity	Watts per square meter (W/m^2)	Suitable for occupational and sports studies	Difficult to measure at population scale	Thermal stress in outdoor occupations	(Daiber et al., 2019; Gasparrini et al., 2015)
10	Local Climate Zone (LCZ)	Land cover, building density, albedo	Classification (10 classes)	Accounts for urban microclimate	Requires high-resolution spatial data	Urban heat island effects on CVDs	(Buck Louis et al., 2017; Hondula et al., 2015)

2.5 Biological mechanisms: From exposure to outcome

Exposure to the climate exposome affects the cardiovascular system through a set of multiple, overlapping, and intersecting biological mechanisms. In fact, the epidemiological findings reviewed are fully consistent with a range of biological mechanisms that elucidate the causal pathways from climate exposure to cardiovascular

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outcomes. These mechanisms can be categorized into three main groups based on their temporal course (acute versus chronic) and level of complexity (classic versus emerging), which are examined in detail below. Understanding these mechanisms is essential for explaining the reviewed epidemiological findings and for designing targeted preventive interventions.

2.5.1 Acute (short-term) mechanisms: Thermoregulatory disruption, sympathetic activation, and hemodynamic changes

Acute mechanisms are pathways that become activated within minutes to several days following exposure to climatic factors and are primarily responsible for immediate outcomes such as myocardial infarction, fatal arrhythmias, and sudden cardiac death during or immediately after heatwaves and cold spells (Chaulin & Duplyakov, 2021; Fan et al., 2023; Vahidi-Kolur et al., 2025).

Disruption of thermoregulation and homeostasis: The first and most fundamental mechanism is the body's physiological response to maintain core temperature within the normal range (approximately 37 °C). Upon exposure to heat, the thermoregulatory system responds through cutaneous vasodilation to increase heat dissipation and increased sweating for evaporative cooling (Lowe et al., 2011). Although essential, these responses have significant adverse effects on the cardiovascular system. Widespread vasodilation reduces peripheral vascular resistance and effective blood pressure, forcing the heart to increase cardiac output (increased heart rate and stroke volume) to maintain adequate blood pressure. This increased cardiac workload can lead to myocardial ischemia, angina pectoris, and myocardial infarction in individuals with underlying coronary artery disease. Furthermore, excessive sweating leads to dehydration and reduced plasma volume (hypovolemia), which in turn contributes to decreased blood pressure, reduced coronary blood flow, and increased risk of thrombosis due to hemoconcentration (increased blood viscosity) (Chaulin & Duplyakov, 2021). In contrast, exposure to cold activates the opposite response: cutaneous vasoconstriction to reduce heat loss. Although efficient, this response markedly increases peripheral vascular resistance and blood pressure (cardiac afterload). The heart requires greater oxygen consumption to pump blood against this elevated resistance, and in individuals with coronary artery stenosis, this condition can lead to myocardial ischemia (Zangeneh et al., 2024).

Activation of the SNS and HPA axis: Thermal stress resulting from extreme temperatures, whether heat or cold, is a potent activator of the autonomic nervous system. The thermoregulatory center in the hypothalamus, in addition to activating behavioral and physiological mechanisms of temperature regulation, also stimulates the SNS. Sympathetic activation leads to increased secretion of catecholamines (epinephrine and norepinephrine) from the adrenal medulla and sympathetic nerve terminals. These hormones, through β1-adrenergic receptors in the heart, increase heart rate (tachycardia), increase myocardial contractility (positive inotropy), and accelerate electrical conduction velocity, all of which increase the risk of ventricular arrhythmias (such as ventricular tachycardia and ventricular fibrillation). Concurrently, activation of the HPA axis increases cortisol secretion, which has direct and indirect effects on blood pressure, glucose metabolism, and platelet aggregation (Fan et al., 2023). Cortisol increases blood pressure by enhancing vascular sensitivity to angiotensin II and reducing nitric oxide production. Additionally, catecholamines stimulate platelet aggregation and thrombogenesis by activating α2-adrenergic receptors on platelets. Collectively, these effects create a state of "sympathetic storm" in which high heart rate, elevated blood pressure, increased cardiac excitability, and a pro-thrombotic tendency occur simultaneously, dramatically increasing the risk of acute cardiovascular events. Clinical evidence has demonstrated that on days with extremely high or extremely low temperatures, plasma catecholamine levels in cardiac patients increase significantly, and this increase is associated with the occurrence of arrhythmias and silent ischemia.

Hemodynamic changes and cardiac workload: Exposure to both heat and cold leads to significant hemodynamic changes, each increasing cardiac workload through distinct mechanisms. In heat, reduced peripheral vascular resistance and decreased plasma volume (due to dehydration) force the heart to increase heart rate in order to maintain adequate cardiac output. This condition, associated with increased myocardial oxygen consumption, can disrupt the balance between oxygen supply and demand in individuals with coronary artery disease, leading to ischemia. In cold, increased peripheral vascular resistance (due to vasoconstriction) and elevated blood pressure increase cardiac afterload. The heart must increase its contractile work to pump blood against this elevated resistance, which again increases oxygen consumption. In both scenarios, the heart is forced to work harder with the same (or even reduced, in the case of dehydration) resources-a situation that, in hearts with limited coronary reserve (patients with coronary artery stenosis, heart failure, left ventricular hypertrophy), can rapidly lead to acute heart failure, pulmonary edema, or myocardial infarction (Dastoorpoor et al., 2019; Zangeneh et al., 2024). Furthermore, sudden blood pressure fluctuations in response to temperature variability can trigger plaque rupture and myocardial infarction in individuals with unstable atherosclerotic plaques.

2.5.2 Chronic and predisposing mechanisms: Systemic inflammation, oxidative stress, and endothelial dysfunction

Alongside acute mechanisms, which act primarily through the autonomic nervous system and hemodynamic changes, chronic and predisposing mechanisms also play an essential role in exacerbating cardiovascular risk resulting from climate exposures. These mechanisms typically manifest with a longer latency (several days to several weeks) or following chronic exposures (seasonal or annual) and,

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through inflammatory, oxidative, and endothelial pathways, set the stage for the occurrence of acute events (Fan et al., 2023; Sharafkhani et al., 2020).

Systemic inflammation: One of the most important chronic mechanisms is the activation of systemic inflammatory responses triggered by air pollution (particularly $PM_{2.5}$) and, to some extent, by heat and cold stress. Following inhalation, particulate matter ($PM_{2.5}$) can cross the alveolar-capillary barrier and enter the bloodstream. These particles are recognized by macrophages and dendritic cells, initiating the inflammatory cascade through activation of Toll-like receptors and the NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) pathway. The consequence of this activation is increased production and secretion of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). These cytokines enter the circulation and exert widespread systemic effects on the cardiovascular system. Elevated IL-6 stimulates the liver to produce C-reactive protein (CRP), a sensitive marker of systemic inflammation and an independent predictor of cardiovascular events. Numerous studies have demonstrated that increased CRP levels are associated with elevated risks of myocardial infarction, stroke, and cardiovascular mortality. Systemic inflammation can also facilitate monocyte and lymphocyte adhesion and infiltration into the vessel wall by increasing the expression of adhesion molecules on the endothelium (such as Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1)), thereby contributing to the progression of atherosclerotic plaques. Systemic inflammation has also been reported in response to heat and cold exposure; thermal stress can induce a mild but significant inflammatory response through endothelial cell damage and complement activation (Sharafkhani et al., 2020).

Oxidative stress: Another mechanism, closely related to inflammation, is oxidative stress. Exposure to air pollution and climatic factors increases the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in endothelial cells, vascular smooth muscle cells, and cardiomyocytes. The main sources of ROS production include Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, xanthine oxidase, the mitochondrial electron transport chain, and inflammatory enzymes (such as cyclooxygenase-2 and lipoxygenase) (Fan et al., 2023). Elevated ROS leads to cardiovascular damage through several pathways: First, ROS reduce the bioavailability of nitric oxide (NO) by rapidly inactivating it through the production of peroxynitrite ($ONOO^-$). NO is a key molecule for endothelium-dependent vasodilation, inhibition of platelet aggregation, and inhibition of leukocyte adhesion. Reduced NO leads to vasoconstriction, increased blood pressure, and a pro-thrombotic state. Second, ROS accelerate the formation of foam cells in atherosclerotic plaques by oxidizing low-density lipoprotein (LDL) to ox-LDL. Ox-LDL is recognized by scavenger receptors on macrophages and leads to progressive atherosclerosis. Third, ROS can damage mitochondrial and nuclear DNA, leading to apoptosis (programmed cell death) of cardiomyocytes. Chronic oxidative stress gradually depletes the functional reserve of the heart, making it more vulnerable to acute stressors (such as a heatwave or strenuous physical activity).

Endothelial dysfunction: The vascular endothelium is a single-cell layer lining the inner surface of all blood vessels and plays a key role in regulating vascular tone, hemostasis, inflammation, and angiogenesis. Endothelial dysfunction is a pre-pathological condition characterized by reduced NO production, increased production of endothelin-1 (a potent vasoconstrictor), increased leukocyte adhesion, vascular permeability, and expression of adhesion molecules (Sharafkhani et al., 2020). Exposure to air pollution, oxidative stress, and systemic inflammation all contribute to endothelial dysfunction. $PM_{2.5}$ particles can directly damage the endothelium or impair endothelial function through activation of inflammatory and oxidative pathways. Endothelial dysfunction is a progressive condition exacerbated by aging, hypertension, diabetes, and obesity. In individuals with underlying endothelial dysfunction, exposure to climatic factors can rapidly disrupt the delicate balance between vasoconstriction and vasodilation, leading to vasospasm, reduced coronary blood flow, and ischemia. Evidence has shown that on days with high air pollution concentrations or extreme temperatures, flow-mediated dilation (FMD)-a gold-standard measure of endothelial function-is significantly reduced (Jasiewicz-Honkisz et al., 2023). This endothelial dysfunction can persist for several days to several weeks following acute exposure, and with repeated exposures (such as during hot seasons), it can become a chronic disorder that sustainably increases the risk of atherosclerosis and cardiovascular events.

2.5.3 Emerging mechanisms and cumulative effects: epigenetics, microbiome, and physiological feedback loops

In recent years, research has moved beyond classical mechanisms to investigate emerging mechanisms that may explain the long-term, cumulative, and even transgenerational effects of climate exposures on cardiovascular health. These mechanisms are more complex and less well understood, but growing evidence supports their central role (Sharafkhani et al., 2020).

Epigenetic changes: Epigenetics refers to changes in gene expression that do not arise from alterations in the DNA sequence itself but are generated by mechanisms such as DNA methylation, histone modifications, and non-coding RNAs. Exposure to air pollution and climatic factors (particularly chronic exposure) can alter epigenetic patterns in various cells, including endothelial cells, immune cells, and cardiomyocytes. Evidence has demonstrated that $PM_{2.5}$ exposure is associated with increased methylation of key genes such as FOXP3 (which plays a role in regulating inflammatory responses) and genes encoding antioxidant enzymes (such as GSTP1) (Sharafkhani et al., 2020). Hypermethylation of these genes leads to reduced expression, thereby weakening the immune system and the antioxidant defense system. Epigenetic changes can persist

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for months or even years following exposure and exert long-term effects on cardiovascular health. In other words, a single intense heatwave during one summer can leave epigenetic imprints that render an individual far more vulnerable to subsequent exposures (next summer's heat or air pollution) (van der Harst et al., 2017). This mechanism may explain why residents of areas with chronic air pollution or frequent temperature variability have higher cardiovascular risk even after controlling for known confounding factors. Furthermore, limited evidence suggests that these epigenetic changes may be transmitted to the next generation (transgenerational effects), which, if confirmed, would have profound implications for health policy (van der Harst et al., 2017).

Gut microbiome alterations: The gut microbiome (the composition and diversity of microorganisms residing in the gastrointestinal tract) plays an important role in host metabolism, immune system regulation, and even cardiovascular health. Emerging evidence indicates that exposure to climatic factors and air pollution can alter gut microbiome composition (dysbiosis). For example, heat exposure can disrupt the microbiome through changes in splanchnic blood flow (reduced intestinal blood flow), increased intestinal permeability, and alterations in dietary habits. Gut dysbiosis leads to increased production of toxic metabolites such as trimethylamine (TMA) from foods containing choline and carnitine. TMA is oxidized in the liver to trimethylamine-N-oxide (TMAO). TMAO is an important metabolite associated with increased risk of atherosclerosis, myocardial infarction, and cardiovascular mortality (Sharafkhani et al., 2020). TMAO contributes to vascular damage through several mechanisms: increasing cholesterol uptake by macrophages, increasing platelet adhesion, impairing reverse cholesterol transport, and activating inflammatory pathways. Thus, climate exposure-induced alterations in the gut microbiome may represent an indirect but important pathway for long-term effects on cardiovascular health. Although this field is still in its early stages, preliminary findings are promising and warrant further human studies.

Metabolic dysregulation and physiological feedback loops: Climate exposures can affect glucose and lipid metabolism through multiple mechanisms (HPA axis activation, inflammation, oxidative stress). Evidence has shown that chronic exposure to air pollution and extreme temperatures is associated with an increased risk of type 2 diabetes, insulin resistance, and metabolic syndrome (Dlamini et al., 2025). Diabetes and metabolic syndrome are themselves strong risk factors for CVDs; therefore, climate effects on metabolism represent an indirect but highly important pathway for increasing the burden of cardiovascular disease. Cumulative effects and physiological feedback loops represent one of the most important concepts in the exposome approach. Repeated or long-term exposures to climatic factors gradually deplete the body's physiological adaptive capacity. For example, an elderly individual with underlying heart disease who experiences several heatwaves over a single summer may partially recover after the first heatwave, but with each successive event, their physiological reserve diminishes, and the likelihood that the next heatwave will trigger an acute event (stroke, heart failure) increase. This phenomenon, known as "physiological reserve depletion," is particularly pronounced in vulnerable groups. Furthermore, the interaction and synergism among different mechanisms (e.g., oxidative stress → endothelial dysfunction → increased blood pressure → increased cardiac workload → arrhythmia → stroke) demonstrate that these pathways do not operate in isolation but rather form a complex causal network in which activation of one pathway amplifies others, exponentially increasing the ultimate effect. Understanding these cumulative effects and feedback loops is essential for designing effective and timely interventions. For example, a heat warning system that activates only once at the onset of a heatwave may be insufficient for individuals with severely depleted physiological reserve (such as elderly residents of unventilated nursing homes) and may require more frequent and intensive interventions.

Coagulation changes and thrombogenesis: Cold exposure creates a pro-thrombotic state by increasing blood viscosity, increasing fibrinogen and factor VII concentrations, and reducing fibrinolytic activity. Heat exposure can also increase blood viscosity through dehydration and hemoconcentration (Kriebel-Gasparro, 2024). This section organizes biological mechanisms from simple to complex and from acute to chronic, providing a comprehensive picture of the causal pathways linking the climate exposome to cardiovascular outcomes. Furthermore, these mechanisms demonstrate that the effects of climate exposures are not limited to acute outcomes but can also exert long-term and even transgenerational effects on cardiovascular health through epigenetic reprogramming. The interaction and overlap among these pathways (e.g., systemic inflammation → endothelial dysfunction → thrombogenesis) generate synergistic effects that explain the exacerbated cardiovascular risk observed under combined exposures (Gluckman et al., 2009). Table 3 categorizes the identified biological mechanisms into three general levels (acute, chronic, and emerging mechanisms). For each mechanism, the corresponding sub-pathway or component, key biomarker for measurement, time course of effect (from acute to chronic), ultimate effects on the cardiovascular system, and supporting scientific references are provided. The biomarkers introduced in this table can be used in future studies as intermediate outcomes or as biomarkers of damage.

2.6 Vulnerable groups and effect modifiers

The impact of the climate exposome on cardiovascular health is not uniform across all populations, and a wide range of individual and social factors act as effect modifiers. Older adults are considered the most vulnerable group due to reduced thermoregulatory capacity (decreased sweating, reduced skin blood flow), higher prevalence of underlying diseases (hypertension, diabetes, heart failure), and use of medications that impair thermoregulation (such as diuretics

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and beta-blockers) (Martínez-Milla et al., 2021). Patients with pre-existing CVDs (heart failure, coronary artery disease, history of stroke) are at higher risk due to the limited capacity of the heart to respond to hemodynamic stressors (Shahmohamadi et al., 2011). Children are also at risk due to their higher body surface area-to-mass ratio and immature thermoregulatory system (Smith, 2019). Individuals of lower socioeconomic status have greater vulnerability due to more limited access to cooling systems (air conditioning), poor housing quality, outdoor occupations, and poorer access to healthcare (Smith, 2019). Numerous studies have demonstrated that socioeconomic inequalities explain a substantial proportion of the excess burden of cardiovascular disease attributable to climate exposures (Bann et al., 2024; Muenzel et al., 2023). Residents of hot and polluted urban areas (such as metropolitan areas in Iran) are exposed to more intense and prolonged exposures due to the urban heat island effect and pollutant accumulation (Aghazadeh et al., 2025; Shahmohamadi et al., 2011). Sex also plays a modifying role; some studies have shown that women may be more sensitive to heat, while men are more affected by cold. Accurate identification of these groups is essential for designing targeted preventive interventions and reducing health inequalities (Vicedo-Cabrera et al., 2021).

Table 3. Biological mechanisms of climate exposome effects on the cardiovascular system: levels and molecular pathways

Row	Mechanism category	Sub-pathway/component	Key biomarker	Time course	Ultimate cardiovascular effects	References
1	Thermoregulatory and Homeostatic Disruption	Dehydration and hemoconcentration	Hematocrit (Hct), plasma osmolality	Acute (minutes to hours)	Increased blood viscosity, reduced cardiac output, thrombosis risk	(Bhatnagar, 2017; Dastoorpoor et al., 2019; Malambo et al., 2016)
2	Thermoregulatory and Homeostatic Disruption	Vasoconstriction (cold) / vasodilation (heat)	Total peripheral resistance (TPR), blood pressure	Acute (minutes to hours)	Increased cardiac afterload (cold) or reduced preload (heat)	(Bhatnagar, 2017; Dastoorpoor et al., 2019; Sharafkhani et al., 2020)
3	SNS Activation	Catecholamine release (epinephrine, norepinephrine)	Plasma catecholamines, metanephrines	Acute (minutes to hours)	Tachycardia, arrhythmias, increased blood pressure	(Vahidi-Kolur et al., 2025; Zangeneh et al., 2024)
4	HPA Axis Activation	Increased cortisol	Plasma cortisol, salivary cortisol	Acute to chronic (hours to days)	Hypertension, insulin resistance, central obesity	(Sharafkhani et al., 2020; Zangeneh et al., 2024)
5	Systemic Inflammation	NF-κB activation, increased cytokines	CRP, IL-6, TNF-α, IL-1β	Chronic (days to weeks)	Atherosclerosis progression, plaque instability	(Brook et al., 2010; Pope III et al., 2004; Zangeneh et al., 2024)
6	Oxidative Stress	Increased ROS, reduced antioxidant capacity	MDA, 8-OHdG, GSH, SOD, Catalase	Acute to chronic	Endothelial dysfunction, DNA damage	(Brook et al., 2010; Fan et al., 2023; Zangeneh et al., 2024)
7	Endothelial Dysfunction	Reduced NO, increased endothelin-1	FMD (flow-mediated dilation), vWF	Chronic (days to weeks)	Vasoconstriction, hypertension, thrombogenesis	(Brook et al., 2010; Fan et al., 2023; Pope III et al., 2004)
8	Coagulation Changes and Thrombogenesis	Increased coagulation factors, reduced fibrinolysis	Fibrinogen, factor VII, PAI-1, D-dimer	Acute to chronic (hours to days)	Increased risk of myocardial infarction and stroke	(Bhatnagar, 2017; Malambo et al., 2016; Zangeneh et al., 2024)
9	Epigenetic Changes	DNA methylation (FOXP3, GSTP1)	Gene-specific methylation	Chronic (weeks to years)	Altered expression of inflammatory and antioxidant genes	(Daiber et al., 2019; Fan et al., 2023)
10	Microbiome Dysbiosis	Altered gut microbiota composition	TMAO (trimethylamine-N-oxide)	Chronic (weeks to months)	Increased atherosclerosis, systemic inflammation	(Daiber et al., 2019; Fan et al., 2023)

Abbreviations: NF-κB, nuclear factor kappa B; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; ROS, reactive oxygen species; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; GSH, reduced glutathione; SOD, superoxide dismutase. Catalase is not an abbreviation and does not require definition; FMD, flow-mediated dilation; vWF, von Willebrand factor; PAI-1, plasminogen activator inhibitor-1; Factor VII, coagulation factor VII; D-dimer, a fibrin degradation product; FOXP3, Forkhead Box P3; GSTP1, Glutathione S-Transferase Pi 1; TMAO, trimethylamine N-oxide.

2.7 Methodological challenges and knowledge gaps in climate exposome studies

Despite significant advances in this field, research on the climate exposome and cardiovascular outcomes faces numerous methodological challenges. First, accurate and simultaneous measurement of exposures is difficult; data from meteorological stations typically represent broad areas and do not reflect individual-level exposure. Novel technologies such as portable sensors and high spatial resolution satellite data could partially address this issue, but they have not yet been widely implemented in large-scale

epidemiological studies (Ganji et al., 2019). Second, disentangling the independent and interactive effects of different climatic factors (temperature, humidity, wind, radiation) and air pollution is extremely challenging due to high collinearity (significant correlation among variables). Advanced statistical models, such as distributed lag non-linear models (DLNM) and machine learning approaches, can partially mitigate this challenge. Third, many studies have focused on short-term exposures (days to weeks), while data on cumulative and long-term effects (seasons to years) remain limited (Noori et al., 2026). Fourth, substantial heterogeneity in the definition of exposure indices (heatwave definitions, different temperature indices), study designs (time-series versus cohort), study populations, and reported health outcomes has made direct comparison of results and meta-analysis difficult (Patel et al., 2017). Fifth, the lack of exposome-based studies in Iran and many low-resource countries, particularly regarding the integration of environmental, biological (biomarkers), and genetic data, represents a major knowledge gap (Sarigiannis et al., 2025). Sixth, challenges related to lagged and threshold effects of climate exposures require high-quality daily data and complex statistical models that are not available in many regions (Patel et al., 2017). These challenges indicate that the path forward for climate exposome research requires interdisciplinary collaboration, method standardization, and investment in data infrastructure.

2.8 Scientific and policy implications for health systems

The findings of this narrative review have important implications for public health policy and health systems. First, integrating climate considerations into cardiovascular disease prevention and management programs is an unavoidable necessity. This integration can occur at multiple levels: at the individual level (educating cardiac patients to reduce exposure on hot and cold days), at the community level (designing climate-resilient urban spaces, developing green spaces), and at the health system level (strengthening capacity to respond to peak service demand during heat and cold periods) (Labarthe & Dunbar, 2012; Zareipour & Asgari, 2023). Second, designing and implementing early warning systems for heat and cold is essential for timely notification of vulnerable groups and activation of protective measures (opening cooling centers, distributing drinking water, public education). The experience of successful countries has shown that such systems can reduce heat-related mortality by 30-50% (Bassey et al., 2025). Third, improving housing quality and urban infrastructure, particularly in deprived areas and informal settlements, through thermal insulation, adequate ventilation, and access to clean energy for cooling and heating, can significantly reduce the vulnerability of low-income groups. Fourth, strengthening health surveillance systems to identify and respond to climate-related disease and mortality peaks, including the development of clinical protocols for managing cardiac patients under extreme climatic conditions. Fifth, attention to the role of environmental health in educating students and professionals to understand the link between climate and cardiovascular health, as well as participation in intersectoral policy-making (collaboration with meteorological organizations, energy ministries, municipalities), is essential (Franco et al., 2011; Ouria et al., 2025). Sixth, planning for climate change adaptation at the national and regional levels, taking into account projections of rising temperatures, increasing heatwave frequency, and changing precipitation patterns, must be incorporated into the country's national health strategic documents (Lorenz et al., 2017). Failure to address this issue will confront Iran's health system with a double burden of climate-related CVDs in the coming decades.

2.9 Future research recommendations

Based on the knowledge gaps and methodological challenges identified in this review, the following recommendations are proposed for future research. First, conducting longitudinal and multi-center studies at national and regional scales to investigate the cumulative and interactive effects of climate exposures on cardiovascular outcomes, using daily data on temperature, air pollution, and health outcomes (mortality, hospitalizations, emergency visits). These studies should employ advanced statistical models such as DLNM and machine learning approaches. Second, developing exposome approaches by integrating environmental data (remote sensing, ground-based stations), biological data (inflammatory, oxidative, and coagulation biomarkers), and genetic data (polymorphisms of genes related to thermoregulation and stress response) to identify causal pathways and high-risk groups. Third, evaluating emerging mechanisms such as epigenetic changes (DNA methylation), metabolic dysregulation (lipid profile, insulin resistance), and gut microbiome alterations in human studies using cohort and case-control designs. Fourth, focusing on policy and community-based interventions by designing field trials to assess the effectiveness of warning systems, housing interventions, and public education in reducing the effects of climate exposures on cardiovascular health. Fifth, analyzing socioeconomic differences and access to care in order to design targeted and equitable prevention programs that reduce health inequalities. Sixth, developing national databases with high spatial and temporal resolution for climate exposures and health outcomes in Iran, through collaboration between the Meteorological Organization, the Environmental Protection Organization, the Ministry of Health, and medical universities. Table 4 categorizes these recommendations. For each recommendation, specific actions, target groups, expected outcomes, level of evidence of effectiveness, and responsible implementing bodies are specified. This table can serve as a roadmap for prioritizing actions at different levels.

2.10 Limitations of the study

This narrative review has faced several limitations. First, most of the studies reviewed were limited to urban areas and

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countries with robust data, while evidence from low-resource regions (including many areas of Iran) is scarce. Second, substantial heterogeneity in exposure indices (different definitions of heatwaves, various temperature indices) and outcomes (cardiovascular mortality, hospitalization, incidence) has made direct comparison of results difficult. Third, many studies have focused on short-term exposures, while data on cumulative and long-term effects remain limited. Fourth, some biological mechanisms (such as epigenetic changes and microbiome alterations) have been proposed primarily based on laboratory and animal evidence and require confirmation in human studies.

Table 4. Policy and research recommendations for reducing the effects of climate exposome on cardiovascular health by level of intervention

Level of intervention	Type of intervention	Specific actions	Target population	Expected outcomes	Evidence of effectiveness	Responsible body	References
Individual	Education and behavior change	Training on reducing exposure on hot days (use of ventilation, adequate fluids); adjusting physical activity	Cardiac patients, elderly, athletes	20-30% reduction in heat-related mortality	Strong (trial studies)	Primary healthcare system, public media	(Basu & Samet, 2002; Lowe et al., 2011; Sharafkhani et al., 2020)
Individual	Self-care and monitoring	Blood pressure monitoring during temperature fluctuations; medication adjustment (reducing diuretics in heat)	Patients with hypertension and heart failure	Reduced cardiac hospitalizations	Moderate	Family physicians, patients	(Bhatnagar, 2017; Dastoorpoor et al., 2019; Malambo et al., 2016)
Community/Neighborhood	Climate-resilient urban design	Increasing green spaces, reflective surfaces (high albedo), shading	Residents of hot urban areas	2-4°C reduction in surface temperature	Strong	Municipalities, Ministry of Roads and Urban Development	(Buck Louis et al., 2017; Hondula et al., 2015)
Community/Neighborhood	Cooling centers	Establishing public air-conditioned centers in low-income neighborhoods	Homeless individuals, low-income elderly	Reduced excess mortality during heatwaves	Strong (Chicago, Toronto experiences)	Municipalities, welfare organizations	(Basu & Samet, 2002; Guo et al., 2018; Lowe et al., 2011)
Systemic/Health system	Heat and cold early warning systems (HEWS/CWES)	Meteorological forecasting + activation of health protocols + public communication	General population, high-risk groups	30-50% reduction in temperature-related mortality	Strong (Europe, United States)	Meteorological Organization, Ministry of Health	(Lowe et al., 2011; Sharafkhani et al., 2020; Vicedo-Cabrera et al., 2021)
Systemic/Health system	Strengthening hospital capacity	Increasing emergency beds during heatwaves; training staff on management of heat-related cardiac conditions	Hospitals, emergency centers	Reduced in-hospital mortality	Moderate	Medical Universities	(Ahmadnezhad et al., 2013; Analitis et al., 2008; Gasparrini et al., 2015)
National policy	Air quality standards	Reducing $PM_{2.5}$ permissible threshold to 5-10 $\mu g/m^3$ (aligned with WHO 2021)	General population, cardiac patients	15-20% reduction in pollution-related cardiac mortality	Strong	Environmental Protection Organization, Government	(Brook et al., 2010; Dehghani et al., 2022; Pope III et al., 2004)
National policy	National Adaptation Plan (NAP)	Incorporating cardiovascular health component into NAP; budgeting for adaptation measures	Entire population	Reduced long-term vulnerability	Emerging	Plan and Budget Organization, Ministry of Health	(Daiber et al., 2019; Hondula et al., 2015; Vahidi-Kolur et al., 2025)
National research	Development of national exposome database	Integration of meteorological, air pollution, GIS, and health outcomes data	Researchers, policymakers	Enables longitudinal studies and accurate modeling	Essential for domestic evidence	Ministry of Health, Universities	(Daiber et al., 2019; Haddad et al., 2019; Vahidi-Kolur et al., 2025)
International research	Multi-center exposome studies	Regional collaboration (West Asia) for method standardization	International scientific community	Production of comparable evidence	Severe shortage in the region	WHO-EMRO, Universities	(Daiber et al., 2019; Fan et al., 2023; Haddad et al., 2019)

3. Conclusion

This narrative review synthesizes the available epidemiological evidence and biological mechanisms associated with the climate exposome and cardiovascular outcomes. The findings suggest that the climate exposome comprising extreme temperatures (heat and cold), thermal variability, climate-related air pollution, and extreme climate events is associated with an increased risk of cardiovascular diseases and mortality. These associations appear to be more pronounced among vulnerable groups, including the elderly, patients with pre-existing heart

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disease, and low-income populations. Several biological pathways, including disruption of thermoregulation, activation of the sympathetic nervous system and the HPA axis, systemic inflammation, oxidative stress, endothelial dysfunction, and coagulation changes, are proposed as potential mediators. Emerging mechanisms such as epigenetic modifications and gut microbiome dysbiosis warrant further investigation in future human studies. Given the heterogeneity of exposure metrics and outcome definitions across studies, the findings should be interpreted with caution. The climate exposome framework, by emphasizing the dynamic, cumulative, and simultaneous nature of exposures, offers a more comprehensive understanding of the relationship between climate and cardiovascular health; however, further well-designed longitudinal and multi-center studies are needed to strengthen the evidence base. In summary, the climate exposome appears to represent a growing challenge to cardiovascular health in Iran and worldwide. Addressing this challenge requires a holistic perspective, interdisciplinary approaches, and coordinated action across research, policy, and implementation. Attention to this framework is recommended in environmental health education, future research, and public health policy-making.

Authors' Contributions

Mina Esmaeili: Investigation; Data curation; Writing original draft. **Esrafil Asgari:** Supervision; Software; Conceptualization; Funding acquisition; Writing-review & editing. **Maryam Salimi:** Methodology; Formal Analysis.

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Conflicts of Interest

The authors have declared no competing interests.

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Ethical Considerations

The article is extracted from the project with the ethics code of IR.ZUMS.REC.1405.012.

Using Artificial Intelligence

During the preparation of this manuscript, artificial intelligence (AI) tools were used as supportive aids in content organization and language editing. All scientific content, data analysis, interpretation of findings, and conclusions were performed and verified by the authors. The authors take full responsibility for the integrity and accuracy of the content.

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