Fundamental Research 5 (2025) 249–263

Contents lists available at ScienceDirect

Fundamental Research

journal homepage: http://www.keaipublishing.com/en/journals/fundamental-research/

Review

Ozone exposure and cardiovascular disease: A narrative review of epidemiology evidence and underlying mechanisms

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ARTICLE INFO

Article history:
Received 24 September 2023
Received in revised form 27 February 2024
Accepted 29 February 2024
Available online 23 March 2024

Keywords:
Ozone exposure
Cardiovascular disease
Epidemiologic study
Mechanism
Susceptibility

ABSTRACT

Ozone (O_3) poses a significant global public health concern as it exerts adverse effects on human cardiovascular health. Nevertheless, there remains a lack of comprehensive understanding regarding the relationships between O_3 exposure and the risk of cardiovascular diseases (CVD), as well as the underlying biological mechanisms. To address this knowledge gap, this narrative review meticulously summarizes the existing epidemiological evidence, susceptibility, and potential underlying biological mechanisms linking O_3 exposure with CVD. An increasing body of epidemiological studies has demonstrated that O_3 exposure heightens the incidence and mortality of CVD, including specific subtypes such as ischemic heart disease, hypertension, and heart failure. Certain populations display heightened vulnerability to these effects, particularly children, the elderly, obese individuals, and those with pre-existing conditions. Proposed biological mechanisms suggest that O_3 exposure engenders respiratory and systemic inflammation, oxidative stress, disruption of autonomic nervous and neuroendocrine systems, as well as impairment of coagulation function, glucose, and lipid metabolism. Ultimately, these processes contribute to vascular dysfunction and the development of CVD. However, some studies have reported the absence of associations between O_3 and CVD, or even potentially protective effects of O_3. Inconsistencies among the literature may be attributed to inaccurate assessment of personal O_3 exposure levels in epidemiologic studies, as well as confounding effects stemming from co-pollutants and temperature. Consequently, our findings underscore the imperative for further research, including the development of reliable methodologies for assessing personal O_3 exposure, exploration of O_3 exposure's impact on cardiovascular health, and elucidation of its biological mechanisms. These endeavors will consolidate the causal relationship between O_3 and cardiovascular diseases, subsequently aiding efforts to mitigate the risks associated with O_3 exposure.

1. Introduction

Ozone (O_3) is a secondary air pollutant known for its high reactivity and oxidizing properties [1–3]. In recent years, the issue of O_3 pollution has gained increasing attention worldwide [4]. Background O_3 levels significantly increased in the Northern Hemisphere by on average 0.3 μg/m^3/year over the past three decades [5]. In China, the maximum daily average 8-hour O_3 concentrations increased from 2014 to 2022 at 1.7–3.0 μg/m^3 per year [6]. Notably, the global O_3 exposure level has risen from approximately 94 μg/m^3 in 2010 to nearly reaching 100 μg/m^3 in 2019 [7]. The escalating atmospheric levels of O_3 present a significant peril to public health. According to Global Burden of Disease estimates, O_3 exposure accounted for 365 thousand premature deaths and 6.21 million disability-adjusted life-years worldwide in 2019 [7]. In China, the number of deaths attributed to short-term O_3 exposure rose from 51.4 thousand [95% confidence interval (CI): 28.9, 74.8 thousand] in 2013 to 80.2 thousand (95%CI: 44.5, 114.5 thousand) in 2020 [8].

Cardiovascular diseases (CVD), predominantly ischemic heart disease and stroke, reign as the foremost culprits behind mortality and the burden of illness worldwide [9]. An expanding array of epidemiological and toxicological studies implies that both short- and long-term exposure to environmental O_3 increases the risk of CVD. Nevertheless, the current understanding of this relationship remains constrained, and policy formulation relies predominantly on scant investigations conducted in affluent nations, which primarily emphasized the mortality rates associated with chronic obstructive pulmonary disease, disregarding the ramifications of O_3 on cardiovascular health [10].

In light of the incessant rise in global O_3 levels and the mounting burden of CVD, there arises an imperative need to further delve into the

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https://doi.org/10.1016/j.fmre.2024.02.016

cardiovascular hazards and pathogenic mechanisms associated with O_3 exposure. This narrative review systematically compiles the existing epidemiological evidence, susceptibility factors, and potential underlying biological mechanisms linking O_3 exposure to CVD.

We performed a comprehensive search on Web of Science, Pubmed, and Embase for articles published between 1 January 1990 and 31 December 2022. We employed specific keywords pertaining to the pollutant of interest ("ozone", "O_3"), various types of epidemiological studies ("epidemiology", "case-crossover", "time series", "cohort study", "cross-section", "panel study", "randomized control trial", "controlled exposure"), CVD outcomes ("cardiovascular", "heart disease", "ischemic heart disease", "cerebrovascular", "hypertension", "prehypertension", "stroke", "heart failure", "arrhythmia", "mortality", "death", "hospitalization"), and biological mechanism ("mechanism", "oxidative stress", "inflammation", "autonomic nervous system", "coagulation", "glucose metabolism", "lipid metabolism", "vascular function", "endothelial function", "large artery function", "microcirculation function", "blood pressure"). A total of 6,478 publications were identified. Following the screening of titles and abstracts, we excluded duplicate and irrelevant publications, resulting in a final inclusion of 221 articles for this study.

2. Epidemiological studies on O_3 exposure and CVD

2.1. Association of O_3 exposure with CVD and its subtypes

A number of epidemiological studies and meta-analyses (Table 1) have shown an increased overall CVD risk associated with short- and long-term exposure to O_3 at different locations, times, populations, and exposure levels. Time-series studies from the United States (US) [11–14], Europe [15–18], Canada [19,20], Latin America [21–23], and China [24–27] have linked CVD mortality rates to short-term O_3 exposure. Several recent meta-analyses reported that the excess risks (ER) increase for CVD mortality related to each 10 μg/m^3 increment in short-term O_3 concentration ranged from 0.62% to 1.279% in China [28–32], and the estimates were generally slightly higher than those from early meta-analysis [33–36]. Concerning morbidity, a meta-analysis demonstrated that a 3-hour acute O_3 exposure increased the risk of total CVD morbidity by 0.722% (95%CI: 0.071%, 1.377%) per 10 μg/m^3 increase [37]. Limited reports on the associations between long-term O_3 exposure and CVD mortality were mainly conducted in high-income regions like the US, Europe, and Canada. Some studies observed significant increase in CVD mortality ranging from 1.3% to 7.5% for every 10 μg/m^3 increase in six-month warm-season mean of the daily maximum 8-h average O_3 concentration [4,38-44], while some studies reported non-significant associations [10,45-50]. The pooled risk for CVD mortality risks was ER = 0.51% to 1.87% per 10 μg/m^3 additional O_3 exposure [51,52]. Two cohort studies derived from Cancer Prevention Study II found that with the improvement of exposure models and increase of statistical power derived from longer follow-up, robust associations between O_3 and CVD mortality would be observed [10,39]. Two recent cohort studies conducted in China observed a 9.3% to 11% increase in the risk of CVD mortality for every 10 μg/m^3 increase in O_3 concentration during the warm season [53,54].

O_3 exposure also increases the risk of a wide array of specific subtypes of CVD. Ischemic heart disease (IHD), characterized by an imbalance of the cross-talk between myocardial energy state and coronary blood flow, is the most common subtype of CVD and the top cause of mortality globally [55]. Inflammation, oxidative stress, and vascular dysfunction contribute to the multifaceted and complex pathophysiology of IHD [56]. Cohort studies [4,10,38,40,45] estimate that the ER range from 0.763% to 3.283% per 10 μg/m^3 O_3. Associations between O_3 and IHD mortality over the long term were generally of greater magnitude than that observed from short-term exposure increases [20,25,27] (RR between 0.45% and 1.725% per 10 μg/m^3 O_3). Short-term exposure also increased the risk of hospitalization [57–59]. Furthermore, patients with higher O_3 exposure levels had poorer health status within 1 year after myocardial infarction [60], suggesting that greater O_3 pollution not only increases the risks of dying but also worsens patients' symptoms, function, and quality of life.

Exposure to O_3 was positively associated with mortality [18,26,38], emergency admissions [61], and recurrence of cerebrovascular disease (CeVD) [62], a group of diseases characterized by inadequate blood flow to the brain. Stroke is the most common type of CeVD, with underlying mechanisms including inflammatory responses, thrombosis, autonomic system dysfunction, endothelial dysfunction, and artery calcification. There remains no consensus on the impact of O_3 exposure on stroke. Studies from the US [63], China [25,27,64], and Korea [65] reported positive associations between short-term O_3 exposure and stroke mortality. Other health endpoints, including prevalence [66], onset [67,68], first-ever stroke [69], recurrent stroke [70], emergency admissions [61,71], and hospital admissions [72–74] for stroke were also associated with short-term O_3 levels. However, some studies demonstrated negative associations between average O_3 levels and the risk of strokes [75,76]. Meta-analysis revealed a slightly increased overall risk for stroke associated with O_3 exposure (ER = 0.051% per 10 μg/m^3, 95%CI: 0%, 0.102%) [77]. Notably, a higher and significant risk was observed for hospital admission (0.2% per 10 μg/m^3, 95%CI: 0%, 0.4%), while no significant associations were found for stroke incidence or mortality [78,79]. Furthermore, the effects of O_3 on stroke subtypes differ, with a significant pooled effect on ischemic stroke (1.243% per 10 μg/m^3, 95%CI: 0.178%, 2.318%), but not for hemorrhagic stroke [80]. A time-stratified case-crossover study revealed a non-linear V-shaped cumulative exposure-response curve between short-term O_3 exposure and ischemic stroke onset [68], suggesting that O_3 exposure may exert neuroprotective effects against the onset and death of strokes within a specific concentration range. Limited long-term studies reported an increase in hospital admissions [81] and mortality [54] of stroke related to O_3 exposure. Additional investigations need to control for confounding factors to further validate the intricate association between O_3 and stroke, and determine the high-risk range of O_3 concentration.

Hypertension is a leading cause of disability and death worldwide [82]. Inflammation, oxidative stress, sympathetic neural activation, vascular dysfunction, deviant sodium homeostasis, and aldosterone excess lead to the development of hypertension [83]. Short-term O_3 exposure affects hypertension-related mortality [25,27] and hospital admissions [84–86]. A meta-analysis revealed that short-term exposure had positive relationships with hypertension risk, but lacked statistical significance [87]. Regarding the long-term effects, a rise in 1-year average O_3 concentration was significantly associated with the prevalence of hypertension in children (ER = 61.301% per 10 μg/m^3; 95%CI: 24.9%, 108.31%) [88]. Another study found every 10 μg/m^3 increase in 2-year O_3 exposure concentration led to an increase in the incidence of hypertension by 6.783% (95%CI: 0%, 14.025%) among African-American women [89]. Prehypertension is the intermediate stage between normal blood pressure and hypertension. Yang et al. showed that prolonged O_3 exposure was linked with prehypertension, and this association was more robust than hypertension, especially in seniors and women [90].

Heart failure (HF) is a severe condition in which the impaired heart can not pump sufficient blood to meet systemic metabolic needs. The underlying mechanisms for HF include oxidative stress, inflammation, coagulation disorder, aortic endothelial dysfunction, and right ventricle remodeling [91]. The pooled estimates of ERs for associations between short-term O_3 exposure and HF hospitalization or death ranged from 0.234% to 1.268% [92–94], and effect size varied across regions, with significant impacts observed in non-USA regions, but not within the USA [95]. Long-term O_3 exposure was also associated with the mortality and morbidity of HF. For instance, one cohort study in the US reported that a 10 μg/m^3 increase in the yearly summer average O_3 concentration was linked to a 6% increase in mortality among patients with congestive heart failure (CHF) [96]. Another cohort study found that for every 10 μg/m^3 increase in annual average O_3 exposure, the hazard ratio of

Table 1
Meta-analyses of associations between O_3 exposure and cardiovasucular risk.

Reference	Year of publication	Database	Exposure duration	Health outcome	Excess risk	No. of Studies	I^2	*p* for heterogeneity	*p* for publication bias
Short-term exposure with total CVD mortality									
[32]	2023	Pubmed, Web of Science, Cochrane Library, Embase, Wanfang, SinoMed, VIP Database, CNKI.	short-term	CVD mortality in China	**1.279% (0.921%, 1.638%)**	19	83%	< 0.001	\
[31]	2023	Google Scholar, Scopus, PubMed	short-term	CVD mortality in low- and middle-income countries	**0.4% (0.05%, 0.751%)**	9	86%	0.0237	\
				CVD mortality in China	**0.7% (0.2%, 1.202%)**	6	\	0.0452	\
[30]	2022	Web of science, PubMed, CNKI, Wanfang	short-term	CVD mortality in China	**1.128% (0.958%, 1.298%)**	26	0	< 0.001	\
[29]	2022	Web of Science, PubMed, CNKI, Wanfang, VIP	short-term	CVD mortality in China	**1.128% (0.902%, 1.355%)**	9	65%	0.001	\
[28]	2017	PubMed, Web of Science, Cochrane library, Wanfang, CNKI	short-term	CVD mortality in China	**0.62% (0.33%, 0.911%)**	6	62%	\	0.048
[79]	2014	Medline, Embase, Web of Knowledge	short-term	CVD mortality	**0.075% (0.051%, 0.099%)**	11	0	\	\
				Stroke mortality	**0.15% (0.024%, 0.276%)**	6	73.9%	\	\
[36]	2013	Pubmed, SCI (Science Citation Index), CNKI, Wanfang	short-term	CVD mortality in China	**0.827% (0.319%, 1.337%)**	6	62%	0.007	\
[35]	2012	PubMed, EMBASE, Web of Science, KoreaMed, CNKI	short-term	CVD mortality in Asia	0.225% (−0.543%, 0.999%)	4	\	0.138	0.648
[34]	2005	Pubmed	short-term	CVD mortality	**0.565% (0.346%, 0.784%)**	25	\	\	\
[33]	2004	APED (Air Pollution Epidemiology Databases)	short-term	CVD mortality in Europe	**0.751% (0.563%, 0.94%)**	13	\	\	\
Short-term exposure and CVD morbidity									
[37]	2022	PubMed, Web of Science	short-term(3 h after exposure to O_3)	CVD morbidity	**0.722% (0.071%, 1.377%)**	9	74%	< 0.01	\
Long-term exposure and CVD mortality									
[52]	2022	Medline, Embase, Web of Science	long-term (warm season)	CVD mortality	**1.866% (0.393%, 3.36%)**	15	97.6%	< 0.01	\
				CHF mortality	**7.263% (5.301%, 9.262%)**	4	85.8%	< 0.01	\
[51]	2016	Embase, Medline, PubMed	long-term term (warm season)	CVD mortality	**0.509% (0%, 1.021%)**	3	0%	\	\
Short-term and long-term exposure and CVD subtype risk									
[78]	2021	PubMed, Embase, Web of Science	short-term	stroke hospital admission	**0.2% (0%, 0.4%)**	15	80.2%	0.000	\
				stroke incidence	−0.1% (−0.1%, −0.1%)	10	34.1%	0.135	\
				stroke mortality	0.5% (−0.1%, 1.104%)	6	84.8%	0.000	\
[77]	2015	Medline, Embase, Global Health, CINAHL, Web of Science	short-term	stroke admission and mortality	**0.051% (0%, 0.102%)**	*37*	68%	\	\
[80]	2014	Medline, Embase, Web of Science	short-term	stroke hospitalization and mortality	0.245% (−0.02%, 0.51%)	20	66.2%	< 0.01	0.55
				ischemic stroke	**1.243% (0.178%, 2.318%)**	\	\	\	\
				hemorrhagic stroke	0.899% (−1.361%, 3.211%)	\	\	\	\
[87]	2018	PubMed, Embase, ISI, Web of Science, CNKI, VIP, China Biological Medicine, Wanfang	short -term	hypertension	5% (−2%, 12.5%)	4	89%	< 0.001	0.313
[94]	2023	PubMed, Web of Science, EMBASE, OVID	short-term	HF hospitalization or mortality	**0.484% (0.122%, 0.846%)**	*19*	87%	\	0.143
[93]	2023	PubMed, EMBASE, and Web of Science	short-term	HF incidence or mortality	**0.6% (0.2%, 1.002%)**	6	0%	0.883	0.015
			long-term	HF incidence or mortality	1.7% (−1.9%, 5.432%)	4	92.1%	0.000	\
[92]	2023	PubMed, Ovid Medline, Embase	short-term	HF hospitalization, incidence, or mortality	0.509% (−0.102%, 1.124%)	40	97.99%	\	0.079
			short-term(lag 0–6)	HF hospitalization, incidence, or	**1.268% (0.407%, 2.136%)**	\	\	\	\
			Long-term	HF hospitalization, incidence, or	0.56% (−7.406%, 9.211%)	5	99.9%	0.00	\
[95]	2013	Ovid Medline, Embase, Global Health, CINAHL, Web of Science	short-term	HF hospitalisations or mortality	0.234% (−0.051%, 0.521%) Significant increase **in non USA regions**(data not report)	18	87%	\	0·304
[100]	2021	PubMed, Embase, Cochrane library, Web of Science	short-term	AF prevalence	0.509% (−1.542%, 2.603%)	4	24%	0.27	\
[99]	2016	PubMed, Ovid, Embase, Web of Science	short-term	AF development	**0.56% (0.102%, 1.02%)**	4	65.1%	0.035	< 0.05
[98]	2016	PubMed, Embase, CINAHL,Web of Science	short-term	arrhythmia hospitalization or mortality	0.61% (−0.153%, 1.38%)	10	82.60%	0.115	0.305

(*continued on next page*)

Table 1 (*continued*)

Reference	Year of publication	Database	Exposure duration	Health outcome	Excess risk	No. of Studies	I^2	*p* for heterogeneity	*p* for publication bias
Susceptibility									
[111]	2014	PubMed	short-term	CVD mortality for younger persons	**0.507% (0.191%, 0.824%)**	12	70.6%	\	0.48
				CVD mortality for older persons	**0.698% (0.411%, 0.986%)**	\	64.4%	\	0.18
Modification effects of temperature									
[158]	2017	Embase, PubMed, ProQuest Dissertations and Theses, Elsevier Science Direct databases	short-term	CVD mortality in low temperature strata	**0.59% (0.27%, 0.911%)**	6	0.00%	0.96	0.01
				CVD mortality in normal temperature strata	**0.27% (0.03%, 0.511%)**	6	21.80%	0.02	0.90
				CVD mortality in high temperature strata	**1.63% (1.14%, 2.122%)**	6	64.20%	0.00	0.23
Biomarkers									
[199]	2022	PubMed, Web of Science, Scopus, Embase	short-term	CRP	**1.05% (0.09%, 2.019%)**	11	69%	< 0.001	\
			long-term	CRP	0.06% (−2.13%, 2.299%)	3	66%	0.0051	\
			short-term	IL-6	0.72% (−0.84%, 2.305%)	5	59%	0.045	\
			short-term	TNF-α	0.52% (−0.9%, 1.96%)	3	50%	0.113	\
[213]	2022	PubMed, Embase, Web of Science	short-term	SDNN	**−0.568% (−0.691%, −0.445%)**	9	0.0%	0.493	\
				rMSSD	**−1.677% (−2.803%, −0.537%)**	9	77.7%	0.000	\
				HF	**−1.547% (−2.405%, −0.682%)**	9	53.2%	0.019	\
				LF	**−1.098% (−1.973%, −0.215%)**	8	56.6%	0.014	\
[223]	2022	PubMed, Web of Science, EMBASE, Scopus	short-term	PAI-1	**1.62% (0.01%, 3.256%)**	6	91.0%	< 0.001	
				P-selectin	**9.59% (2.78%, 16.851%)**	3	99.3%	< 0.001	\
[87]	2018	PubMed, Embase, ISI Web of Science, CNKI, VIP, China Biological Medicine, Wanfang	long-term	SBP	0.65 mmHg (−0.19, 1.48)	4	97.5%	< 0.001	0.678
			long-term	DBP	0.17 mmHg (−0.02, 0.36)	4	80.4%	0.002	0.149
			short-term	SBP	0.06 mmHg (−0.25,0.36)	10	96.6%	< 0.001	0.917
			short-term	DBP	0.13 mmHg (−0.01, 0.28)	10	88.1%	< 0.00	0.934

Note: Meta analysis-specific estimates were all converted to standardized excess risk (ER) per 10 μg/m^3 increment in average O_3 concentration as follows:
First, we converted the original exposure unit to average increase in μg/m^3 unit. According to the parameters of previous studies, a relationship of 15:8 for the 8-hour maximum:daily average were used to convert 8-hour maximum to the daily average. We assumed that 1.96 μg/m^3 equals 1 ppb to convert studies into the same metric. In environmental epidemiology research, relative risk (RR) and odds ratio (OR) provide an equivalent estimate of risk. RR or OR were converted to ER using the formula below: ER% = (RR − 1) × 100. The ER and 95%CI values extracted from the meta analyses on a log scale were back-transformed to beta coefficients (β) and standard error (SE) standardized by using the following formula:

$$\beta = \frac{\ln(\mathrm{ER}\%+1)}{increment_{ori}}.$$

$$SE = \frac{\ln(\mathrm{ER}\%+1)-\ln(\mathrm{ER}\%_l+1)}{1.96 \times increment_{ori}}.$$

where $\mathrm{ER}\%_l$ and $increment_{ori}$ are the lower bound of 95%CI and original O_3 increment, respectively. Finally, obtained β and SE values were converted for standarded ER and corresponding 95%CI per 10 μg/m^3 increment in O_3 concentration.
For the meta-analysis of blood pressure change, the pooled β for blood change associated with 10 μg/m^3 O_3 increase were reported.
"\" in the data column indicates unreported information; Bolded numbers in the Excess Risk column indicate a significant association; The italicized numbers in the 'No. of Studies' column indicate the number of estimates.
Abbreviation: VIP: China Science and Technology Journal Database; CNKI: China National Knowledge Infrastructure; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CVD: cardiovascular disease; AF: Atrial fibrillation; CHF: congestive heart failure; HF: heart failure; CRP: C-reactive protein; IL-6: interleukin-6; IL-8: interleukin-8; TNF-α: tumor necrosis factor-α; SDNN: standard deviation of NN intervals; r-MSSD: root mean square of successive differences between intervals; HF: high frequency; LF: low frequency; PAI-1: Plasminogen activator inhibitor; SBP: systolic blood pressure; DBP: diastolic blood pressure.

hospitalization for HF was 1.12 (95%CI: 1.115, 1.126) [81]. In Ontario, Canada, an increase of 10 μg/m^3 in the 3-year moving average O_3 concentration corresponded to a hazard ratio of 1.045 (95%CI: 1.03, 1.061) for CHF [97]. The pooled relative risk (RR) of death from CHF mortality was 1.074 (95%CI: 1.054, 1.093) per 10 μg/m^3 rise in average levels of O_3 during the warm season [52].

Arrhythmia, denoting abnormal heart rhythm, is triggered by a complex interplay of factors including autonomic dysfunction, ionic remodeling, altered calcium homeostasis, inflammation, and oxidative stress. The overall estimates for arrhythmia hospitalization or mortality exhibited a positive correlation with short-term peaks in O_3 levels, although statistical significance was not reached (ER = 0.61% per 10 μg/m^3, 95%CI: −0.153%, 1.38%) [98]. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population. Regarding to short-term exposure effect, for every 10 μg/m^3 increment in the O_3 concentration, the combined RR of AF development and AF prevalence was 0.56% (0.102%, 1.02%) [99] and 0.509% (−1.542%, 2.603%) [100], respectively. For other subtypes of arrhythmia, statistically significant associations of ventricular arrhythmias with mean O_3 were observed in the 24 h before the episode of arrhythmia (ER = 8.3% per 10 μg/m^3, 95%CI: 1.9%, 15.1%) in a cohort of patients with implantable cardioverter defibrillator [101], and more acute O_3 exposure (concurrent hour, lag hour 0) triggered episodes of paroxysmal AF (ER = 108% per 44 μg/m^3, 95%CI: 22%, 254%) [102]. Elevated levels of ambient O_3 also increase the risk of supraventricular arrhythmia in the elderly (ER = 21.348% per 10 μg/m^3, 95%CI: −1.707%, 49.811%) [103].

Based on the existing epidemiological studies examining the associations between O_3 exposures and various subtypes of CVD, using different health outcome measures, many meta-analyses showed moderate to high between-study heterogeneity, publication bias was also observed. Discrepancies among studies could be attributed to differences in study populations, exposure assessment methodologies, and the presence of confounding factors.

2.2. Susceptible populations

Exposure to O_3 may induce cardiovascular health effects to different levels for populations with different susceptibilities. Research on susceptible populations helps to elucidate the pathophysiological mechanisms of air pollution and to establish air quality standards [63].

2.2.1. Age

Children are more vulnerable to air pollution exposure than adults because they are in the stage of development. An increase of O_3 exposure at 1-day moving average was associated with more changes in cardiovascular function among children [104,105], compared to the elderly [106] and adults [107]. The effects of O_3 exposure during childhood may predispose these children to earlier development of cardiovascular pathologies and disease in later life [108].

In elderly people, physiological and metabolic changes weaken the body's defense ability to respond to environmental stress, thus increasing sensitivity to pollution [109]. Stratified analysis showed that the risk of cardiovascular death [22,24], stroke [64,69], prehypertension [90], and venous thromboembolic disease were more strongly associated with O_3 exposure in elderly people than younger adults [110]. An earlier meta-analysis of O_3 and CVD mortality also recommended that the elderly are more sensitive to short-term O_3 exposure compared to younger persons [111].

2.2.2. Sex and gender-based differences

The conclusion regarding sex differences in the association between O_3 exposure and cardiovascular risk remains uncertain and may vary across different health endpoints and cardiovascular diseases. Generally, higher associations between O_3 exposure and stroke occurrence and hospitalizations were observed in males than in females [67]. For example, in Pennsylvania, US, O_3 exposure on the current day (odds ratio = 1.001 per 10 μg/m^3, 95%CI: 1, 1.002) was significantly related to stroke hospitalizations in males, while no significant relation was observed in females [72]. Studies in China and France [67] also reported higher occurrences of stroke in males [69,71]. Conversely, the death risk in females was higher. One study observed a stronger association between exposure to O_3 and increased mortality and years of life lost from stroke in females compared to males [64]. The elevated risk of total mortality [112–116] and CVD mortality [117,118] associated with O_3 were also greater in females than males. Regarding abnormal blood pressure, O_3 exposure had a stronger impact on a higher risk of hypertension in males [86,87], but exerted stronger impacts on prehypertension and blood pressure in females [90].

The reasons for the sex differences in associations between O_3 and CVD risk remain unclear, possibly stemming from both sex-linked biological differences and gender-linked behavior differences. Several possible mechanisms have been postulated in relation to higher effects of O_3 in males. Males have larger lung capacity than females which allows them to inhale more O_3 per breath than females. A greater prevalence of smoking among men can also increase susceptibility to O_3 exposure effects. Another explanation might be that men tend to spend more time outdoors, leading to less exposure misclassification [119]. In contrast, females may have different hormonal levels and greater airway reactivity [120]. Reduced absorption of O_3 in the upper airways of females may promote its deeper penetration [121]. Gendered differences in hospitalization and treatment seeking overall may also influence the susceptibility [116]. Variability among studies may be attributed to differences in exposure levels and the age of subjects. Subgroup analysis of sex showed that males were more vulnerable to low-O_3 level, and females were vulnerable to high-O_3 level [122]. Involvement in hormonal levels and airway reactivity changes with age in women may therefore change their susceptibility. Therefore, the absence of sex consistency may be indicative of the lack of strong O_3-cardiovascular associations, not the lack of an effect modification by sex. The potential sex differences in the associations between O_3 and cardiac effects remain to be determined.

2.2.3. Body weight

Compared to adults with normal weight (body-mass index, BMI < 25), the overweight (25 ≤ BMI < 30) and obese population (BMI ≥ 30) showed stronger associations between O_3 and CVD outcomes such as death [123], hypertension, and stroke [66,124]. Overweight and obese children displayed more pronounced associations between exposure and hypertension compared to children with normal weight [125]. This may be attributed to obese individuals having a higher inhalation rate, resulting in increased exposure to O_3 [126]. Obesity may also enhance inflammation and oxidative stress, making obese individuals more susceptible to O_3 exposure [127].

2.2.4. Medical history

Individuals previously hospitalized for myocardial infarction showed a higher risk of CVD mortality associated with O_3 exposure [128]. A large cohort study in 105 cities in the US found that for every 10 μg/m^3 increase in summer average O_3 level, the RR of death from CHF and myocardial infarction was 1.06 (95%CI: 1.03, 1.08) and 1.09 (95%CI: 1.06, 1.12), respectively [96], and the RRs were higher compared to those reported in the American Cancer Society cohort [10]. For every 10 μg/m^3 increase in O_3, hypertensive patients had a 0.26% higher risk of emergency stroke compared to non-hypertensive patients [71]. The associations between O_3 and CVD incidence in subjects with pre-existing hypertension, type 2 diabetes, hyper-triglyceridemia, and high beta-lipoprotein were higher than those in control groups [129]. Subjects with more cardiovascular risk factors were found to be more sensitive to O_3 exposure [62].

2.3. Challenges of O_3 health risk assessment in epidemiological studies

Despite an increasing body of evidence indicating cardiovascular effects associated with O_3 exposure, some studies did not observe such significant associations and even reported seemingly "beneficial" effects. Several challenges in epidemiological studies of O_3 exposure may hinder accurate assessments of its health effects.

2.3.1. Exposure assessment of O_3

Numerous studies used ambient O_3 concentration data collected from fixed monitoring stations as the exposure levels of individuals, particularly in time series and cross-sectional studies. O_3 is a highly reactive pollutant with substantial spatial and temporal variability, and the inadequate and uneven distribution of monitoring sites makes it difficult to capture an accurate distribution of O_3 concentrations. Failing to account for the spatial variation by using fixed-site measurements to estimate personal exposures may lead to relative errors of up to 127% [130].

Several cohort studies used exposure models as effective supplements to monitoring networks to increase the spatiotemporal variability [45,53,108,131]. High-resolution modeling plays a pivotal role in human exposure studies, which requires a more detailed depiction of air pollutants in spatial gradients. The effect of spatial resolution on simulated O_3 concentration has been investigated across various regions utilizing diverse models. Higher resolutions generally enhance modeling efficiency and accuracy, as demonstrated in studies such as those conducted in Morocco [132], China [133], the eastern US [134], Georgia [135], and Mexico [136], where finer resolutions improved forecasting and performance compared to coarser resolutions. However, it should be noted that higher resolution does not inevitably lead to an improvement in model performance. Some studies suggested the existence of an optimal point where the equilibrium between model resolution and input errors is inversed because uncertainty is introduced into air quality modeling at almost every step of the modeling process [137,138]. Therefore, the selection of the optimal resolution should be assessed on a case-by-case basis, considering factors such as data availability, computation time, and the study's specific goals. Finer resolution can better resolve the texture of small-scale inhomogeneities in O_3 response, while medium resolution may be sufficient to capture many of the broad features of O_3 response in some cases [135].

However, the results of models have yet to consider the variability of O_3 concentrations across different microenvironments and the impact of individual activity patterns. Personal O_3 exposure levels are proportional to ventilation conditions and outdoor activity time, and inversely proportional to outdoor temperature and humidity. Typically, personal O_3 exposure levels amount to approximately one-third to one-half of the environmental O_3 levels [139]. Only a limited number of small sample-sized panel studies monitored the real-time O_3 exposure levels of participants. A panel study in Taipei monitored the O_3 exposure of 17 postal workers using the Aeroqual Series 500 (Auckland, New Zealand) personal O_3 monitor and found that O_3 exposure was associated with elevated right ventricular arterial index, a biomarker of artery stiffness [140]. Xia et al. used a Personal Ozone Monitor (POM, 2B Technologies, US) to measure the real-time O_3 concentration of each participant over a continuous 3-day period and observed positive associations between personal O_3 exposure and both blood pressure and biomarkers indicating vascular endothelial dysfunction [141]. The assessment of both Aeroqual [142] and POM [143] showed accurate measurement of O_3 levels in comparison to reference analyzers.

2.3.2. The effect of co-pollutants

The intricate relationship between O_3 and other air pollutants makes it difficult to accurately estimate the independent effect of O_3 exposure in epidemiological studies. To address this issue, researchers often employ a two-pollutant model to control for the confounding effects of co-pollutants [45,144]. Nevertheless, it is still very challenging to differentiate the effects of O_3 from the effects of other correlated pollutants.

The levels of O_3 and fine particulate matter ($PM_{2.5}$) are often highly anti-correlated, due to their shared precursors and interactions through atmospheric chemistry processes [145]. Consequently, $PM_{2.5}$ may be an important confounder in the study of O_3 [10,146]. Some studies found that sulfate components in particulate matter confounded the association between O_3 and mortality [147], but others did not observe such a confounding effect of $PM_{2.5}$ on the relationship between O_3 and mortality [148] or cardiovascular function [149], indicating that the effect of O_3 may be independent of $PM_{2.5}$ effects. To address the issue of collinearity, some studies adopted Bayesian kernel machine regression (BKMR) to model the effects of exposures to the mixture of ambient O_3, $PM_{2.5}$, and other pollutants on total mortality [150], anti-nuclear antibodies [151], and child behavioral problems [152], but individual effects of O_3 exposures were not seen in these studies. BKMR models have not been used to analyze the effects of O_3 exposure on cardiovascular health.

Black carbon (BC) is another important confounder of relationships between O_3 and health outcomes. Huang et al. found stronger associations between O_3 exposure and changes in heart rate and heart rate variability among children exposed to higher BC concentrations [153]. Zhang et al. observed that, after adjusting for BC in the model, the correlation between the reactive hyperemia index and O_3 changed from a positive to a negative one [154]. Black carbon can be oxidized by oxidants such as O_3, and toxicological studies showed that O_3-oxidized BC had higher oxidative potential and cellular toxicity compared to BC alone [155,156].

2.3.3. The effect of temperature and season

Meteorological factors, such as temperature, may modify the effects of O_3 exposure on the health of the cardiovascular system [157]. Models of air pollution-related health risks often included temperature as a control variable [19]. Some studies quantitatively assessed the risk of O_3 under different temperature conditions, and found modification effects of temperature on O_3-cardiovascular associations varied with regions. Most of them observed that high temperature enhances the risk of O_3-related cardiovascular events. A meta-analysis reported that the effect of O_3 on CVD mortality was strongest on high-temperature days with a pooled estimate of 1.63% (95%CI: 1.14%, 2.13%) per 10 $\mu g/m^3$ increase [158]. For example, in the northern regions of the US [12] and 8 cities in Europe [15], O_3-related cardiovascular mortality was found higher in high-temperature conditions compared to low temperatures. An analysis of 128 counties in China showed that a 10 $\mu g/m^3$ increase in O_3 concentration was associated with a 0.41% (95%CI: 0.31%, 0.51%) increase in CVD mortality under high-temperature conditions (> 23.2 °C), while no significant increase was observed under low-temperature conditions (< 6.6 °C). High temperature enhances the formation of O_3 and exposure to high temperatures also increases cardiovascular stress [24].

However, several studies conducted in Shanghai [159] and Suzhou [160] in China, and the southern region of the US found that the risk of cardiovascular death was significantly associated with O_3 at lower temperatures. Some studies also indicated that the association between O_3 and death risk was unlikely to be confounded by temperature [14,161]. They may stem from the varied climatic and demographic conditions across regions, influencing indoor and outdoor activities, and consequently, exposure levels. The strength of the O_3-temperature correlation is another crucial factor in data analysis. Additionally, residents' physical adaptation to long-term exposure to high O_3 and temperature levels may reduce sensitivity to these factors [12]. Various temperature control approaches used in different studies also play a role in determining O_3-related risks [162].

The concentration of O_3 exhibits noticeable seasonal variation. Some studies examined seasonal differences in associations between O_3 and cardiovascular mortality between "cold seasons" and "warm seasons" [163,164]. Most of those studies observed stronger and more signifi-

cant associations between O_3 and cardiovascular risk in warm seasons, such as in Canada [165], Detroit [11], Chile [22], and Beijing [73]. However, in Shanghai, China, a 10 μg/m^3 increase in O_3 was associated with a 1.53% (95%CI: 0.54%, 2.52%) increase in cardiovascular mortality in the cold season, while no significant effect was observed during the warm season [112]. In Hong Kong, China, a significant association was observed between cool-season O_3 and CVD hospitalization (excess risk = 0.9% per 10 μg/m^3, 95%CI: 0.2%, 1.6%) [166]. The modifying effect of season on the relationship between O_3 and daily mortality may be impacted by residents' exposure patterns, air conditioning usage, ventilation rate between indoor and outdoor air, and other factors [167,168].

3. Biological mechanisms underlying the cardiovascular effects of O_3 exposure

It is crucial to elucidate the mechanisms through which O_3 exposure leads to the development and progression of diseases, for the purpose of crafting interventions to mitigate and remedy the associated health burdens. Several potential pathophysiological mechanisms have been proposed to explain the increasing risk of CVD in relation to O_3 exposure (Fig. 1).

3.1. Oxidative stress and inflammatory response of respiratory system

Inhalation is the primary route of O_3 exposure, with the human respiratory system being the main target that O_3 can attack. Once inhaled, O_3 could rapidly react with the proteins and lipids in the epithelial lining fluid of the airway, and generate reactive oxygen species (ROS), lipid peroxidation products, and other oxidative products. O_3 also damages the antioxidants and antioxidant enzymes in the lining fluid of the airway and alveoli, such as vitamin C, vitamin E, catalase, superoxide dismutase, and glutathione peroxidase, and impaires their antioxidant capacity [169–171]. The oxidative stress generated by O_3 exposure could lead to cell damage and changes in respiratory cell signaling [172].

Oxidative products generated by O_3 can also activate the nuclear factor-κB signaling pathway, stimulate immune cells, and release pro-inflammatory cytokines and chemokines such as tumor necrosis factor (TNF), interferon-gamma, interleukin (IL) −8, IL-1β, and IL-6 [173–175]. The accumulation of neutrophils in the bronchial lumen can lead to inflammation and tissue damage in the respiratory system [176].

Short-term exposure to sub-lethal doses of O_3 can result in changes in lung function, such as airflow limitation and airway hyperreactivity [177]. Over a period of several days following a single short-term O_3 exposure, damaged ciliated airway epithelial cells are gradually replaced by underlying cells. Additionally, damaged type I alveolar epithelial cells are replaced by type II cells that exhibit greater resilience to the damaging effects of O_3 exposure [178,179]. Long-term O_3 exposure may lead to emphysema and pulmonary fibrosis [180].

3.2. Systemic oxidative stress and inflammatory response

Unlike the particles, which are potentially small enough to translocate from the lungs into the circulation and directly trigger acute cardiovascular episodes, O_3 could not penetrate the respiratory epithelial cells to enter the bloodstream since it can be completely consumed in the lining fluid of the epithelial cells [181]. However, the reactive oxygen species, oxidation products, and inflammatory factors generated in the lungs by O_3 can cross the air-blood barrier, causing and spreading inflammatory responses and oxidative stress in the bloodstream.

O_3 exposure can increase the level of inflammation in the body. Multiple panel studies and controlled exposure studies found positive associations between short-term O_3 exposure and systemic inflammatory biomarkers, including C-reactive protein (CRP) [182–184], immune cells [185–187], and inflammatory cytokines, such as IL-6 [186,188,189], IL-8 [190], TNF-α [191], monocyte chemoattractant protein-1 [185], indicating an acute systematic inflammation status after short-term exposure. A quasi-experimental study reported that reduced O_3 pollution was associated with alleviated systemic inflammation in healthy adults [192]. Long-term exposure to O_3 also led to increases in CRP [193] and neutrophils [194]. But existing studies present inconclusive evidence, with null association and even inverse association reported [195–198]. A meta-analysis found that the overall associations of short-term exposure to O_3 with CRP were significantly positive, while associations with IL-6 and TNF-α were positive but insignificant [199]. In toxicological experiments, a 5-day O_3 exposure increased oxidative modifications in the mouse aorta [200], and a 13-day O_3 markedly elevated plasma TNF-α protein levels in a Diabetic Mouse Model [201].

Furthermore, O_3 exposure induced oxidative stress. Studies in adult rats showed that O_3 exposure was associated with a decrease in antioxidant reserve and an increased production of inflammatory mediators [200,202,203]. Oxidative stress is capable of exerting many adverse biological effects, including causing oxidative damage to DNA and lipids. Two panel studies observed increases in blood 8-hydroxy-2′-deoxyguanosine, a biomarker of DNA oxidative damage, following O_3 exposure [182,183]. Exposure to O_3 was also associated with an increase in the 8-iso-prostaglandin F2α (8-iso-PGF), a plasma lipid peroxidation damage marker [204]. After acute exposure to 400 μg/m^3 O_3 for 4 h, the level of 8-iso-PGF increased from 28.5 to 51.1 pg/mL. Estimated 2 weeks, 1 month, and lifetime exposure to O_3 were significantly associated with an increase in 8-iso-PGF [131]. Damage caused by inflammation and oxidative stress contributes to the progression of atherogenesis, IHD, hypertension, HF, and other CVD.

3.3. Imbalance in the autonomic nervous and neuroendocrine systems

Exposure to O_3 can lead to functional abnormality of the autonomic nervous system (ANS). Heart rate variability (HRV) is a commonly used indicator to assess ANS function [205]. A higher level of HRV is generally considered a positive indicator, as it reflects a better heart's ability to respond to rapid environmental changes. Conversely, a lower level of HRV is indicative of increased sympathetic nervous tension, which is associated with increased risks of arrhythmia, myocardial infarction, hypertension, HF, and other CVD [206–208].

Numerous studies have reported decreases in frequency-domain measures such as root mean square of successive differences (rMSSD), standard deviation of normal-to-normal intervals (SDNN), the proportion of NN50 divided by total number of NNs, and time-domain measures including high-frequency (HF) and low-frequency (LF) following short-term O_3 exposure [105,182,190,209-212]. A recent meta-analysis found that per 10 μg/m^3 increase in O_3 was significantly associated with decreases in SDNN, rMSSD, HF, and LF by −0.568% (−0.691%, −0.445%), −1.677% (−2.803%, −0.537%), −1.547% (−2.405%, −0.682%), −1.098% (−1.973%, −0.215%), respectively. Specifically, associations with SDNN showed low between-study heterogeneity [213]. The effects were particularly strong in patients with pre-existing CVD [209,214] and individuals with long-term exposure to high concentrations of lead [211]. Exposure to low levels of O_3 also caused changes in HRVs in children [153]. These results suggest that O_3 may increase sympathetic nervous tension and decrease parasympathetic nervous tension. Toxicological studies observed that O_3 activated C-fibers via transient receptor potential A1 (TRPA1) channels [215]. C-fibers are a major type of sensory nerve fibers in the airways. O_3 may regulate ANS by stimulating nerve endings in the lungs, thereby affecting heart and vascular function.

Acute exposure to O_3-induced changes in HRV was accompanied by increases in stress hormones in the neuroendocrine system (DNES), including corticotropin-releasing factor, corticotropin, adrenaline, and noradrenaline [212]. Acute O_3 exposure also increased levels of circulating stress hormones in rats [216,217]. This suggests that O_3 exposure may

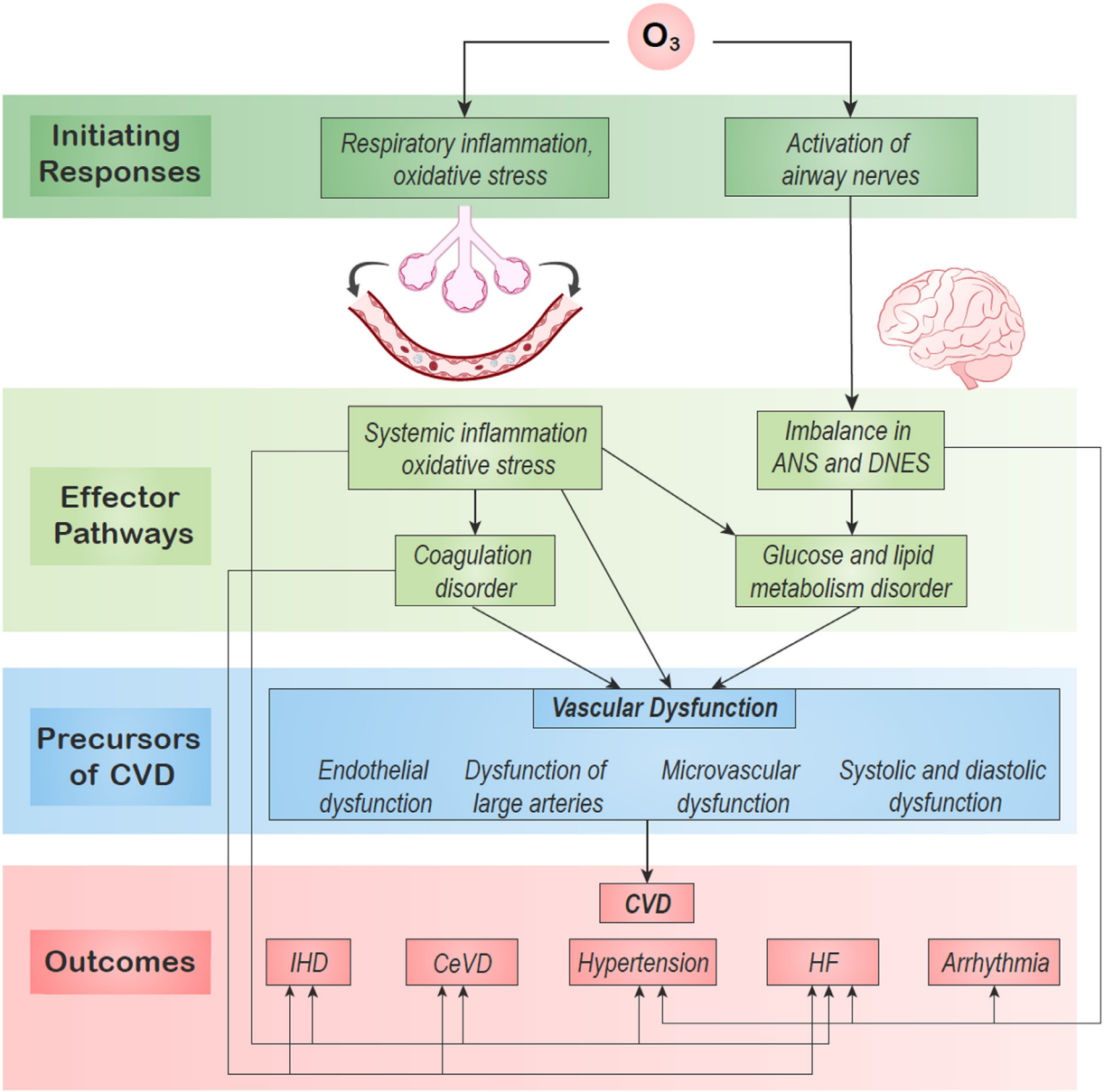

Fig. 1. Mechanisms underlying the adverse cardiovascular effects of O_3 exposure. *Note:* ANS: autonomic nervous system; DNES: neuroendocrine system; CVD: cardiovascular disease; IHD: ischemic heart disease; CeVD: cerebrovascular disease; HF: heart failure.

trigger ANS imbalance and activate the sympathetic-adrenal medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes [212].

3.4. Coagulation disorder

Elevated levels of coagulation and thrombosis factors increase the risk of thrombosis, stroke, IHD, and HF [218,219]. Short-term exposure to O_3 was related to increased levels of some coagulation factors, such as fibrinogen, plasminogen activator fibrinogen inhibitor-1 (PAI-1), tissue factor, and von Willebrand factor [182,193,220], along with decreased levels of anticoagulant proteins such as thrombomodulin [221]. Low-level O_3 exposure was also positively correlated with changes in P-selectin, a biomarker of platelet activation, and this correlation remained robust independent of other pollutants [109,192,222]. Results from a previous meta-analysis indicated that short-term exposure to ambient O_3 was significantly linked to increases in PAI-1 (1.62%, 95%CI: 0.01%, 3.25%) and P-selectin (9.59%, 95%CI:2.78%, 16.86%) [223]. However, some studies found that O_3 exposure shifted the balance towards pro-fibrinolysis. For instance, in healthy subjects exposed to O_3 for 2 h at 0 and 600 μg/m^3, tissue-type plasminogen activator (t-PA), a pro-fibrinolytic factor, significantly increased after 24 h, while PAI-1 and plasminogen decreased [190,224]. In the aorta of rats, tPA, PAI-1, and vWf increased after exposure to O_3, and possibly triggered by oxidatively modified lipids and proteins [225]. Regarding more long-term exposures, a cohort study revealed that yearly O_3 exposure increased factor VII clotting activity (2.869% per 10 μg/m^3, 95%CI: 1.469%, 4.287%), indicating an elevated risk of arterial thrombosis in IHD [193].

The association between O_3 and coagulation function may be modified by temperature. A controlled-exposure studies in humans found that 300 ppb O_3 exposure at moderate temperature (22 °C) significantly reduced PAI-1 and plasminogen by 51.8% (95%CI: 12.7%, 90.8%) and 12.1% (95%CI: 1.8%, 22.3%), respectively. While at high temperature (32.5 °C), they significantly increased by 44.9% (95%CI: 5.9%, 83.9%) and 27.9% (95%CI: 17.1%, 38.2%), respectively [226], indicating that O_3 exposure at moderate temperature activates fibrinolysis, while at high temperature, it may impair this pathway.

3.5. Glucose and lipid metabolism disorder

Increased O_3 exposure may disrupt blood lipid and glucose levels. For every 24.3 μg/m^3 increase in 3-day averaged O_3 in Taiwan, apolipoprotein B, the primary apolipoprotein of low-density lipoprotein [227], increased by 0.78 (95%CI: −0.06, 1.62) mg/dL [228]. Acute O_3 exposure studies using ApoE-/- mice models have shown elevated total cholesterol (TC), triglycerides, and low-density lipoprotein-cholesterol (LDL-C) levels, along with decreased high-density lipoprotein -cholesterol (HDL-C) levels [229]. With the extension of exposure windows, one-month exposure to O_3 was significantly associated with increased liver fat content, triglycerides, very-low-density lipoprotein -cholesterol, and decreased HDL-C levels among young people in Southern California [230]. In a study of elderly people in Beijing, O_3 exposure was positively correlated with TC, LDL-C, Castelli risk index I and II (CRI-I and CRI-II), with the greatest increase observed in the 28-day moving average. For every 10 μg/m^3 increase in O_3 concentration of 28-day moving average, TC, LDL-C, CRI-I, and CRI-II increased by 3.9% (95%CI: 1.0%, 6.9%), 8.2% (95%CI: 4.2%, 12.4%), 4.8% (95%CI: 1.1%, 8.5%), and 7.0% (95%CI: 2.7%, 11.5%), respectively, indicating a cumulative effect from prolonged exposure to O_3 [231]. In a controlled exposure human study [232], serum metabolomic assessment further revealed altered lipid metabolic processes, including increased levels of several circulating free fatty acids and glycerols as observed in rat models [233], likely through a neurohormonally mediated stress response.

Short-term [234] and long-term [194] O_3 exposure increase glucose levels in the elderly [234]. O_3 exposure also influences the level of hemoglobin A1c [194,228], which is often used to monitor the degree of glycemic control [235]. Impaired glucose homeostasis may be due to the decreased insulin activity. Increased ambient O_3 levels have been shown to significantly induce insulin resistance in the Korean Elderly Environmental Panel study [234]. Previous toxicological studies also demonstrated that O_3 inhalation can induce insulin resistance in several animal models through muscle c-Jun N-terminal Kinases activation [217,236]. Lipid and glucose metabolic disorders potentially accelerate the atherosclerotic process [237].

3.6. Vascular dysfunction

The evaluation of the effects of O_3 exposure has documented a deleterious effect on vascular function. Vascular dysfunction refers to impaired function of blood vessels, including endothelial dysfunction, large artery dysfunction (due to arterial stiffness), microcirculation dysfunction, and systolic and diastolic dysfunction. Vascular dysfunction is an early initiator of many CVD subtypes [238], and it was found to be associated with O_3 exposure.

3.6.1. Endothelial dysfunction

Endothelial dysfunction is referring to the impairment of normal steady state of the vascular endothelium and is the initial stage of CVD, such as hypertension and atherosclerosis [239]. O_3 exposure has been associated with an increase in intercellular adhesion molecule 1 (ICAM-1) [184,191,192,240], which plays an important role in leukocyte activation and transmigration across the endothelium, and elevated ICAM-1 level is related to inflammation and cardiovascular risk [241].

In another study, it was found that each 56.2 μg/m^3 increase in O_3 was significantly associated with a 6.7% (95%CI: 0.9%, 12.8%) increase in total homocysteine (tHcy) [242], and elevated tHcy leads to endothelial cell dysfunction, and it is related to oxidative stress and dyslipidemia. It is an independent risk factor for CVD, including atherosclerosis and ischemic CeVD. Oxidative stress may promote an increase in plasma tHcy levels by reducing the synthesis of homocysteine and methionine donors used to compensate for cell oxidative damage [243].

In a prospective longitudinal study of patients with myocardial infarction, an increase of 61.9 μg/m^3 in O_3 on the same day was found to be associated with a 2.34% (95%CI: 0.15%, 4.54%) increase in lipoprotein-associated phospholipase A2 (Lp-PLA2) [244]. Human plasma Lp-PLA2 is mainly synthesized and secreted by several inflammatory cells that play a crucial role in atherosclerotic plaques, such as mature macrophages, T lymphocytes, monocytes, and mast cells, and it is an independent predictor of IHD and stroke.

Endothelin-1 (ET-1) has potent and long-lasting vasoconstrictor effects, and nitric oxide (NO) can inhibit the effects of ET-1 to assist endothelial function. Animal studies further demonstrated the imbalance between NO and ET-1 following exposure to O_3, with significant decrements in vascular endothelial NO synthase protein and NO levels [245], and enhanced expression of ET-1 [225], which can result in increased vascular tone. Matrix metalloproteinases (MMPs) play a major role in the degradation of proteins in the extracellular matrix, influencing the endothelial cell function. O_3 exposure up-regulated MMP-2 and MMP-3 in the aorta of rats, and the effects progressively increased over the course of exposure [225].

3.6.2. Large artery dysfunction

Arteriosclerosis, a condition characterized by the thickening, hardening, and loss of elasticity in the arterial wall, can gradually reduce blood supply to organs and tissues. Many studies used non-invasive methods to measure the severity of arteriosclerosis.

One study found that a 50 μg/m^3 increase in O_3 concentration was significantly associated with a 5.5% (95%CI: 1.3%, 9.8%) increase in the augmentation index (AIx) [246]. AIx is calculated as the difference between the first and second systolic peaks in a pulse wave divided by pulse pressure. A higher AIx value indicates higher reflection wave velocity and earlier return in the pulse wave, mainly due to increased arterial stiffness or vascular resistance [246].

Atherosclerosis, a typical form of chronic arteriosclerosis, is a lifelong process that begins in fetal and early postnatal life [247]. Long-term exposure to O_3 in childhood may be an important risk factor for carotid intima-media thickness (CIMT) increase in young adults. An increase of 2 standard deviations in exposure to O_3 during childhood (ages 0–5) and elementary school (ages 6–12) was found to be linked with an elevation of 7.8 μm (95%CI: −0.3, 15.9) and 10.1 μm (95%CI: 1.8, 18.5) in CIMT, respectively [248], and CIMT is a reliable marker of atherosclerosis in young people. The Multi-Ethnic Study of Atherosclerosis, spanning almost a decade of follow-up, established a connection between outdoor O_3 concentrations with increased rate of carotid wall thickness progression and risk of new plaque formation [249]. Animal exposure and toxicological studies provide similar evidence. Following a short-term repeated O_3 exposure, myocardial tissue of ApoE-/- mice exhibited disordered smooth muscle cells, accumulated fat cells, and typical plaque formation [200,229]. In a monkey model, annual exposure to high levels of O_3 led to 179% thickening of the intima and medial layer of small arteries around the bronchioles [250].

3.6.3. Microcirculation dysfunction

Microvasculature refers to small arteries, arterioles, venules, and capillaries with a diameter of less than 0.5 mm . Damaged microvasculature can result in secondary obstruction and further affect tissue perfusion. In a panel study of 93 non-smoking elderly people in the Los Angeles metropolitan area, a negative correlation was observed between O_3 exposure and the reactive hyperemia index (RHI) after adjusting for BC [154]. A reduction in RHI is an important indicator of microvascular dysfunction.

3.6.4. Systolic and diastolic dysfunction

Blood pressure changes are complex physiological responses regulated by various vascular homeostatic mechanisms. Most studies observed that short-term [21,109,141,183,228,246,251-254] and long-term [84,88,90,125,194,255] exposure to O_3 increased systolic and diastolic blood pressure. A previous meta-analysis observed the positive relationships between O_3 and blood pressure but lacked statistical significance [87]. Elevation of blood pressure may lead to an increase in

myocardial oxygen demand and left ventricular afterload. Vasoconstriction also may lead to a narrowing of arteries, causing ischemia, or triggering the rupture of unstable atherosclerotic plaques [256]. Changes in blood pressure due to O_3 exposure were accompanied by an increase in levels of angiotensin-converting enzyme (ACE) and ET-1 in blood circulation [141]. ACE can regulate blood pressure by enhancing the production of angiotensin II, which constricts blood vessels [257]. ET-1 is a potent vasoconstrictive peptide that plays an important role in maintaining endothelial homeostasis and is upregulated in CVD associated with endothelial dysfunction [258]. O_3 inhalation induces the release of circulating bioactive factors capable of impairing vasorelaxation to acetylcholine via a cluster of differentiation receptor 36-dependent signaling mechanism in mice [259]. Some studies have observed a negative correlation between O_3 exposure and systolic and/or diastolic blood pressure [253,260-262]. The inconsistent results may be due to the compensatory role of cardiac output, which is another important factor determining blood pressure, in counterbalancing the BP changes following short-term air pollution exposure [260]. The decrease in systolic blood pressure may indicate a decrease in cardiac contractility [262].

4. Conclusion

An increasing body of epidemiological evidence suggests the association between O_3 exposure and the risk of CVD. According to the current mechanistic hypothesis, when inhaled, O_3 molecules undergo rapid and complete reactions at the respiratory tract surface. This process generates inflammatory factors and oxidative products that permeate into the bloodstream, thereby triggering systemic inflammation and oxidative stress. Furthermore, O_3 exposure stimulates the nerves in the lung, leading to an imbalance in the autonomic and neuroendocrine systems. These alterations further disrupt coagulation function, as well as glucose and lipid metabolism, ultimately resulting in vascular dysfunction and the progression of CVD (Fig. 1).

Nonetheless, the existing evidence remains inadequate in establishing a definitive causal relationship between O_3 and CVD. Numerous uncertainties persist regarding factors including methods for assessing exposure, variations in exposure levels, characteristics of the subjects, and possible synergistic effects of co-pollutant effects. Our understanding of the biological mechanisms underlying the relationship between cardiovascular effects and O_3 exposure is also presently limited. Gaps in knowledge persist concerning the temporal sequence of various mechanisms and their intricate interactions. The current state of understanding falls short in fully elucidating the cardiovascular injury induced by O_3 exposure, thereby impeding our capacity to delve deeper into the epidemiological results.

Hence, there exists a pressing imperative for systematic research aimed at unraveling the health consequences and biological mechanisms of O_3 exposure. Present O_3 regulatory standards primarily focus on respiratory effects [263], thereby not fully taking into account the impact on cardiovascular well-being. Future policy-making ought to consider the implications for cardiovascular health, as the association between O_3 and CVD may manifest at levels lower than those inducing respiratory effects [153]. Although the individual increase in relative risk of CVD attributed to air pollution is marginal when compared to well-established cardiovascular risk factors like smoking, hyperlipidemia, and hypertension, the sheer magnitude of individual affected by pollution can result in a substantial escalation in overall mortality rates. Imposing more stringent environmental O_3 standards has the potential to markedly diminish premature mortality and morbidity linked with O_3 [264,265]. Through the implementation of rigorous epidemiological inquiry, government regulations can be facilitated [266].

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (42293324).

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