

Review

Investigation of the Association between Long-term Ozone Exposure and Cardiovascular Disease: A Meta-Analysis Addressing Exposure Windows, Vulnerable Populations, and Spatial Variation

Jingqiao Liu¹; Xiaochen Wang^{1,2}; Xiu Ye^{1,3}; Yi Zhang^{1,†}

ABSTRACT

In this study, cohort studies retrieved from PubMed, Web of Science, and Embase were systematically evaluated to clarify the link between long-term ozone exposure and cardiovascular disease (CVD)-related mortality and morbidity, addressing gaps in previous reviews that were not comprehensive or did not distinguish specific CVD types. For every 10 $\mu\text{g}/\text{m}^3$ increase in ozone concentration, the relative risk (RR) of CVD mortality was 1.0105 [95% confidence interval (CI): 1.0027, 1.0185], and that of CVD morbidity was 1.0578 (95% CI: 1.0289, 1.0874). In different exposure windows, the CVD mortality risk associated with warm-season ozone exposure (RR=1.0186, 95% CI: 1.0119, 1.0253) was higher than that associated with annual average ozone exposure (RR=0.9971, 95% CI: 0.9781, 1.0164). The RRs for CVD mortality were 1.1135 (95% CI: 1.0057, 1.2328) for females and 1.0707 (95% CI: 0.9855, 1.1633) for males. By region, the RRs were 1.0129 (95% CI: 1.0085, 1.0173) in Europe and the USA, and 1.0326 (95% CI: 0.9323, 1.1436) in Asia. Long-term ozone exposure is associated with a modest increase in the risk of cardiovascular mortality and morbidity. However, evidence regarding the long-term effects of ozone exposure on cardiovascular disease-related health outcomes remains sparse, and further studies covering a broader range of regions and vulnerable populations are urgently required.

Cardiovascular disease (CVD) remains a major global public health issue with consistently high morbidity and mortality. Its burden has increased due to industrialization, urbanization, and population aging, leading to an increase in the number of CVD

deaths from 12.4 million in 1990 to 19.8 million worldwide in 2023. Within the multifactorial disease paradigm, mounting epidemiological evidence underscores the critical role of ambient air pollution, including ambient ozone, in the onset of CVD. Ozone enters the human body predominantly through the respiratory route, triggering inflammatory responses and oxidative stress that adversely affect the cardiovascular system (1). Long-term exposure (typically measured in months or years) may lead to a range of chronic health issues, including cerebrovascular diseases (2–4). Some studies have shown that long-term exposure to air pollutants poses a greater cardiovascular risk than short-term exposure (5–6). In three previously conducted meta-analyses, the health effects of long-term ozone exposure were investigated using data collected before February 1, 2022; however, CVD was considered a single disease, and the specific types were not distinguished (7–9). However, emerging evidence has led to contradictory conclusions across different regions. Studies from European countries such as Denmark (10), France (11), and the UK (12) reported no or negative associations, whereas investigations conducted in South America indicated positive associations (13). This systematic review aims to provide an updated and complete overview of the health effects of long-term exposure to ozone using sensitive populations and regional distribution characteristics.

INCLUDED STUDIES AND KEY INDICATORS

Following a systematic literature screening procedure and predefined eligibility criteria, 30 eligible articles were identified. Each article contained one to two independent cohort studies, collectively yielding 31 distinct cohorts for qualitative synthesis (Figure 1).

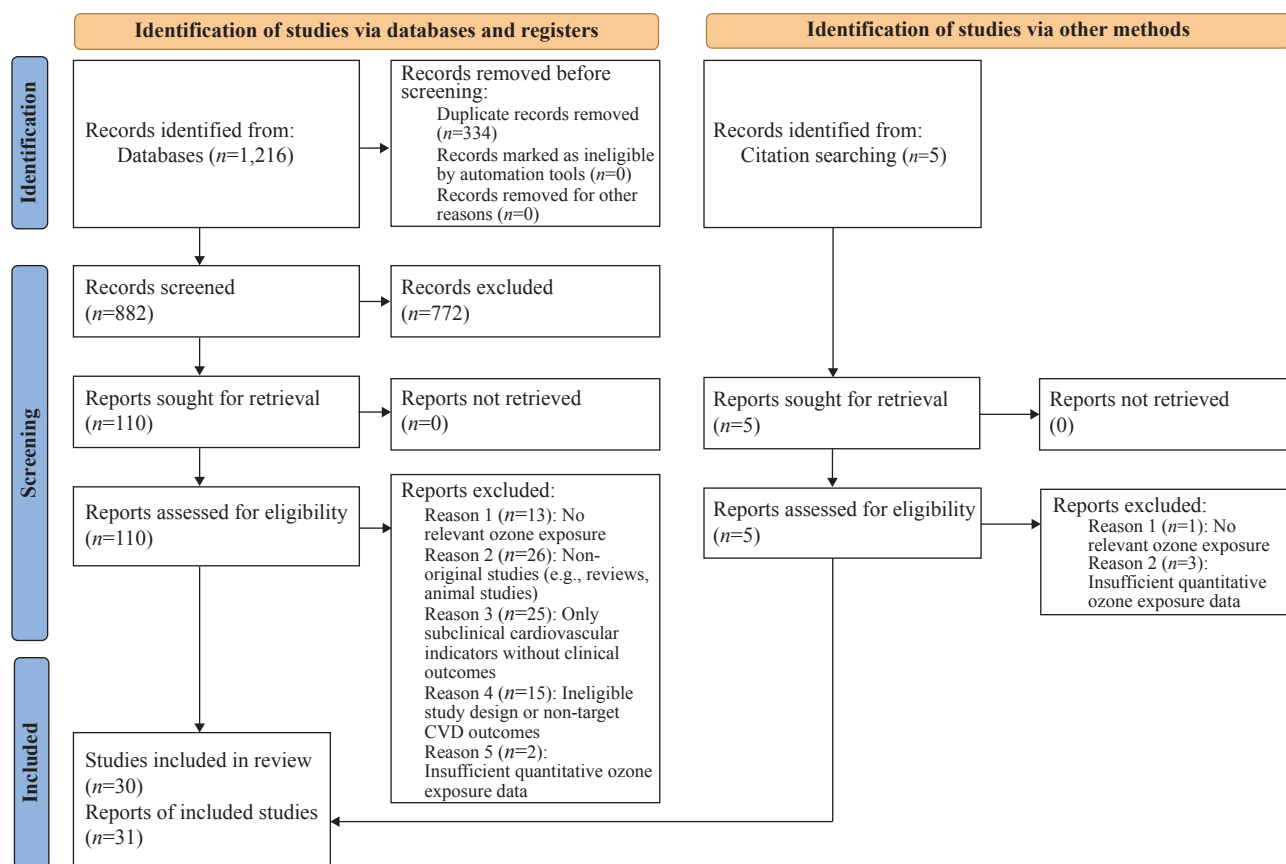


FIGURE 1. Flow diagram of the literature screening and study selection process for the systematic review of the association between long-term ozone exposure and cardiovascular disease risk. Abbreviation: CVD=cardiovascular disease.

The objectives of the evaluation were defined according to three elements: 1) study population, 2) exposure (referring to long-term ozone exposure), and 3) CVD-related morbidity and mortality (Supplementary Table S1, available at <https://weekly.chinacdc.cn/>). The specific inclusion and exclusion criteria and methods are provided in the Supplementary Materials. Health endpoints predominantly included mortality outcomes (total cardiovascular disease, ischemic heart disease (IHD), acute myocardial infarction, and cerebrovascular mortality) and morbidity indicators [total cardiovascular disease, IHD, hypertension, and heart failure (HF)]. This systematic review included 14 CVD mortality studies and six CVD morbidity studies (Supplementary Table S2, available at <https://weekly.chinacdc.cn/>). The predominant exposure indicator of the raw dataset was the daily maximum eight-hour average ozone concentration, with most analyses incorporating co-pollutant adjustments [e.g., particulate matter with a diameter of 2.5 μm or less ($\text{PM}_{2.5}$) and NO_2] through multivariate regression

models. Cox proportional hazards regression emerged as the predominant analytical framework.

LONG-TERM OZONE EXPOSURE INCREASES CVD RISK

Ozone Exposure and Diverse CVD Risk

The included studies were published between 1982 and 2024 with cohort sizes ranging from 4,866 to 22.2 million participants. For every 10 $\mu\text{g}/\text{m}^3$ increase in ozone concentration, the pooled relative risk (RR) was 1.0105 [95% confidence interval (CI): 1.0027, 1.0185] for CVD mortality (Figure 2) and 1.0578 (95% CI: 1.0289, 1.0874) for CVD morbidity.

Sensitivity analyses restricted to studies reporting hazard ratios (HRs) yielded comparable estimates, with pooled RRs of 1.0076 (95% CI: 0.9948, 1.0205) for CVD mortality and 1.0737 (95% CI: 1.0314, 1.1178) for CVD morbidity, supporting the robustness of the primary findings. Exploratory meta-regression analyses identified the $\text{PM}_{2.5}$ adjustment status as the main

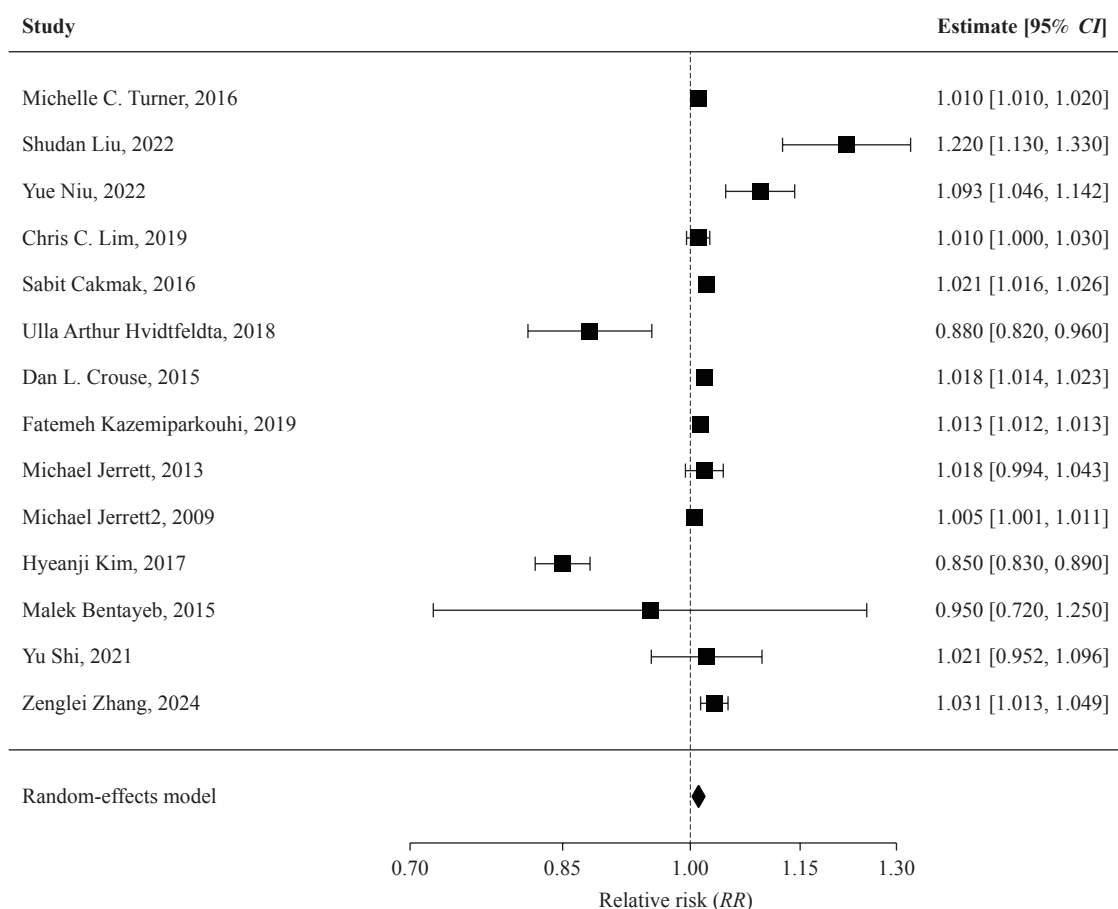


FIGURE 2. Forest plot of the association between long-term ozone exposure and cardiovascular disease mortality per 10 $\mu\text{g}/\text{m}^3$ ozone increment.

Note: Squares represent study-specific RR, horizontal lines represent 95% CI, and diamonds represent the pooled RR under the random effects model. Heterogeneity: $I^2=92.41\%$, $P<0.001$.

Abbreviation: CI=confidence interval; RR=relative risk.

source of heterogeneity for CVD mortality, explaining 34.0% of the between-study variance ($R^2=34.0\%$, $QM=6.47$, $P=0.011$). In contrast, the geographic region, exposure window, and follow-up duration were not significant moderators. No significant moderators were detected for CVD morbidity, which may be attributed to the limited number of available studies.

For specific cardiovascular outcomes, the pooled RR was 1.0443 (95% CI: 1.0272, 1.0617) for IHD mortality, 1.0399 (95% CI: 0.9239, 1.1705) for stroke mortality, and 1.0395 (95% CI: 1.0182, 1.0539) for stroke morbidity. One included study reported an HR of 1.150 (95% CI: 1.038, 1.274) for coronary heart disease (CHD), with HRs of 1.23 (95% CI: 1.03, 1.47) in women and 1.06 (95% CI: 0.93, 1.21) in men. For hypertension, the pooled RR was 1.1166 (95% CI: 1.0383, 1.2007) per 10 $\mu\text{g}/\text{m}^3$ increase in ozone concentration, which is broadly consistent with previous epidemiological studies reporting positive

associations between ozone exposure and hypertension risk (14–15).

Biological Mechanisms Linking Ozone to CVD Risk

Several biological mechanisms have been hypothesized to explain the association between ozone exposure and CVD mortality. Oxidative stress is considered to be the primary biological response to ozone exposure (16), followed by the activation of systemic inflammation (17–18). Inflammatory mediators can enter the bloodstream, trigger the release of coagulation factors (19), damage blood vessel function (20), and increase thrombosis (16), all of which may contribute to mortality from IHD, CHD, and CVD. In contrast, hypertension may be more strongly associated with autonomic nervous system imbalance, vasoconstriction, and vascular dysfunction induced by air pollution exposure (21). For stroke, the

limited number of available studies precluded a meta-analysis of stroke subtypes, suggesting that hemorrhagic and ischemic strokes may involve distinct pathophysiological mechanisms that could contribute to differences in the observed associations (22). Similarly, HF may involve additional pathways related to chronic inflammation, oxidative stress, and myocardial remodeling (23). These mechanistic differences may partly explain the heterogeneity in the associations observed across cardiovascular endpoints and support the need for endpoint-specific analyses.

CVD RISK VARIES BY EXPOSURE WINDOW, POPULATION, AND REGION

Warm-season Ozone and Enhanced CVD Mortality Risk

Analysis by exposure window revealed that the RRs

of CVD mortality were 0.9971 (95% CI: 0.9781, 1.0164) for annual ozone exposure and 1.0186 (95% CI: 1.0119, 1.0253) for warm-season exposure (Figure 3). This study revealed that the correlation was stronger when the exposure window was during the warm season for the same unit of increase in ozone concentration ($P=0.039$). When stratified by exposure period, the corresponding relative risks for IHD were 1.0489 (95% CI: 1.0177, 1.0810) for annual ozone exposure and 1.0436 (95% CI: 1.0139, 1.0742) for warm-season ozone exposure. This finding is similar to that of a study involving seven cohorts that reported RRs of 0.9906 (95% CI: 0.9667, 1.0185) for each 10 $\mu\text{g}/\text{m}^3$ increase in annual ozone exposure and 1.0047 (95% CI: 1.0000, 1.0093) for warm-season ozone exposure in relation to CVD mortality (7). A possible explanation is the longer working hours for outdoor activities during the warm season, which leads to increased ozone exposure. Another plausible hypothesis is that the impact of ozone on human health is

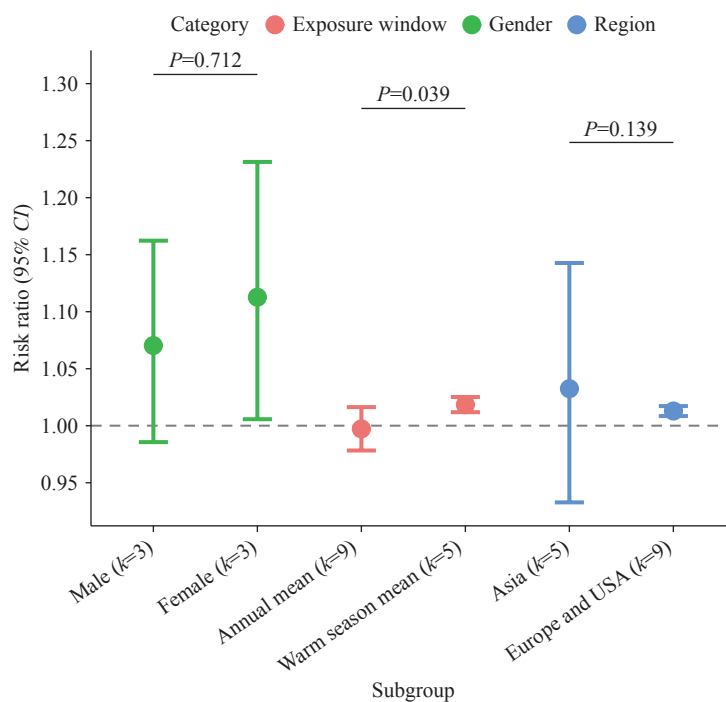


FIGURE 3. Subgroup analysis of cardiovascular disease mortality risk associated with long-term ozone exposure.

Note: Stratified analyses were conducted according to sex, exposure window, and geographic region. Sex-specific analyses showed pooled RRs of 1.1135 (95% CI: 1.0057, 1.2328) for females and 1.0707 (95% CI: 0.9855, 1.1633) for males. For exposure window, the pooled RR for CVD mortality was 1.0186 (95% CI: 1.0119, 1.0253) for warm-season mean ozone exposure and 0.9971 (95% CI: 0.9781, 1.0164) for annual mean ozone exposure. Regional analyses showed pooled RRs of 1.0129 (95% CI: 1.0085, 1.0173) for studies conducted in Europe and the USA, and 1.0326 (95% CI: 0.9323, 1.1436) for studies conducted in Asia. Each point represents the RR for CVD mortality associated with a 10 $\mu\text{g}/\text{m}^3$ increase in ozone concentration; error bars indicate 95% CI. The horizontal dashed line at RR=1 indicates no association. The P -values above each subgroup pair represent the P for interaction (test for subgroup differences). K indicates the number of studies contributing to each subgroup.

Abbreviation: CI=confidence interval; CVD=cardiovascular disease; RR=relative risk.

modulated by temperature. Kahle et al. revealed that the ozone-induced systemic effects vary with temperature. Specifically, at elevated temperatures (32.5 °C), ozone impairs the fibrinolytic pathway, whereas at moderate temperatures (22 °C), it activates this pathway (24).

Sex Disparities in Ozone-related CVD Mortality Risk

Notably, sex-stratified analyses were available in only three studies and suggested potential differences in the association between long-term ozone exposure and cardiovascular outcomes. The pooled RRs were 1.1135 (95% *CI*: 1.0057, 1.2328) for females and 1.0707 (95% *CI*: 0.9855, 1.1633) for males. Although the estimated risk appeared numerically higher among females, these findings should be considered exploratory because of the limited number of studies and lack of formal tests for subgroup differences. Other studies have reported sex-based differences in the association between air pollutants and health outcomes. One study on the association between air pollutants and hypertension revealed that women were more sensitive to long-term ozone exposure [odds ratio (*OR*)=1.61, 95% *CI*: 1.15, 2.23] (25). Another study linked women's exposure to air pollution with a higher risk of adverse cardiovascular outcomes (26). This sex-specific difference in risk may originate from the fundamental biological mechanisms governing adipocyte distribution. In men, androgen levels are inversely related to the fat content in the visceral and subcutaneous compartments, whereas the opposite is true in women (27–28). These hormonally modulated fat-partitioning patterns may accelerate atherosclerosis progression through distinct pathways (29).

Regional Differences in Ozone-related CVD Mortality Risk

Among the 31 included cohorts, geographical distribution analysis revealed 19 investigations conducted in Europe and the USA, and 12 in Asia (all of which were from China and the Republic of Korea). The pooled RRs for CVD mortality associated with long-term ozone exposure were 1.0129 (95% *CI*: 1.0085, 1.0173) for studies in Europe and USA and 1.0326 (95% *CI*: 0.9323, 1.1436) in Asia. A meta-analysis of 25 cohort studies also revealed long-term ozone exposure as a risk factor for cardiovascular death, with an RR of 1.019 (95% *CI*: 1.004, 1.035) (9). However, other studies have shown that long-term

ozone exposure may have protective effects against cardiovascular mortality. A pooled analysis of 64 studies reported that per 10 µg/m³ increment in ozone levels corresponded to a CVD mortality RR of 0.993 (95% *CI*: 0.952, 1.035) (30). These differing results may be related to the different regions included in these studies. Evidence shows areas with low total mortality generally have higher relative death risks: while China and India bear a larger absolute burden of pollution-related deaths, urban populations in Europe and North America suffer greater relative risks of cardiovascular and acute respiratory mortality at equivalent PM_{2.5} concentrations (31).

STUDY LIMITATIONS, HETEROGENEITY, AND FUTURE DIRECTIONS

We observed a slight increase in CVD mortality risk after excluding studies with a high risk of bias, possibly because these studies often had inadequate adjustments for essential confounders (e.g., co-pollutants) or less precise ozone exposure assessments. Residual heterogeneity may also reflect differences in environmental, social, and behavioral contexts. Notably, exploratory meta-regression analyses suggested that differences in PM_{2.5} adjustment strategies across studies may partially explain the between-study heterogeneity, highlighting the difficulty of isolating the independent effect of ozone in observational studies. In addition, combining different effect measures (e.g., HRs, RRs, and ORs) may introduce additional uncertainty, particularly for relatively common outcomes such as hypertension. Due to the limited number of eligible cohort studies, subgroup findings regarding sex, regional variation, and exposure windows should be considered exploratory and interpreted cautiously. Funnel plots and Begg's and Egger's tests had limited statistical power in several subgroup or outcome-specific analyses and should not be regarded as definitive evidence for or against publication bias (Supplementary Table S3, Figure S1, available at <https://weekly.chinacdc.cn/>). Furthermore, studies from low- and middle-income regions remain scarce, limiting the global representativeness of the findings. Therefore, future multicenter prospective studies with broader geographic coverage and standardized exposure assessments are warranted.

SUMMARY

This study presents a comprehensive systematic review of the relationship between long-term ozone exposure and CVD risk. The findings of the reviewed studies indicate that long-term ozone exposure is associated with a modest increase in the risk of cardiovascular mortality and morbidity. The most sensitive outcomes included IHD mortality, stroke morbidity, and stroke mortality. Higher risk values were observed when warm-season ozone exposure was used as the exposure window than with year-average ozone exposure. The results of this review offer a plausible rationale for further development of ozone reduction measures to prevent and manage CVD.

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Corresponding author: Yi Zhang, zhangyi@nieh.chinacdc.cn.

¹ China CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention & Chinese Academy of Preventive Medicine, Beijing, China; ² School of Public Health, Southern Medical University, Guangzhou City, Guangdong Province, China; ³ School of Public Health, Nanjing Medical University, Nanjing City, Jiangsu Province, China.

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SUPPLEMENTARY MATERIAL

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1) Literature demonstrating an exposure-response relationship between long-term ozone exposure and the risk of death or disease in a population, including uncertainty representations such as 95% confidence interval (*CI*), the percentage or risk of population death or morbidity increase for each specified unit of ozone concentration increase, relative risk (*RR*), hazard ratio (*HR*), and 95% *CI*. The cause of death was classified according to the International Classification of Diseases (ICD) published by the World Health Organization (WHO). 2) The main study design was a cohort study. 3) Because most studies use single-pollutant models, for studies with multiple models, the results of their main models should be included. 4) Air pollution and meteorological data should come from relevant monitoring authorities, and all data should comply with quality assurance and quality control.

Exclusion Criteria

1) Original literature that did not address the exposure-response relationship between long-term ozone exposure and the risk of population mortality. 2) Repeated reports and literature with poor quality and incomplete information were excluded; 3) For the original data that could not be expressed or converted into a specified unit of ozone concentration, the increase in the percentage of population death or risk, *RR*, and *HR* values were excluded. 4) Review articles. 5) Studies that did not meet the inclusion criteria.

METHODS

Literature Screening and Data Collection

The objectives of the evaluation were defined according to three elements: 1) study population, 2) exposure (referring to long-term ozone exposure), and 3) CVD-related morbidity and mortality. We searched for studies on the relationship between ozone exposure and CVD in PubMed, Web of Science, and Embase. The main search terms were "ozone", "cardiovascular disease", and "exposure". Eligible studies were identified via a systematic search and reference screening of relevant reviews. A literature search was conducted for studies published between January 1, 2009, and December 31, 2024. The literature search and selection processes were repeated independently by two researchers, and parts such as data extraction (including risk values, environmental pollutant levels, and study time) were checked by a third person.

SUPPLEMENTARY TABLE S1. Literature search strategy.

Database	Search strategies	Results
Web of Science	(TS=(ozone OR O ₃) AND TS=("long-term exposure" OR "chronic exposure") AND TS=("cardiovascular disease" OR "heart disease" OR "myocardial infarction" OR "stroke" OR "heart failure" OR "arrhythmia" OR "cardiovascular mortality" OR "cardiovascular death" OR "cardiovascular incidence" OR "cardiovascular morbidity")) AND PY=(2009-2024)	461 records
PubMed	((("Ozone"[Mesh] OR ozone[tiab] OR O ₃ [tiab]) AND ("Long-Term Exposure"[tiab] OR "Chronic Exposure"[tiab] OR "Environmental Exposure"[Mesh:NoExp]) AND ("Cardiovascular Diseases"[Mesh] OR "Heart Diseases"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Heart Failure"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR ("cardiovascular mortality"[tiab] OR "cardiovascular death"[tiab] OR "cardiovascular incidence"[tiab] OR "cardiovascular morbidity"[tiab]))) AND ("2009/01/01"[Date - Publication] : "2024/12/31"[Date - Publication]))	454 records
Embase	((('ozone'/exp OR ozone:ti,ab OR O ₃ :ti,ab) AND ('long term exposure'/exp OR 'chronic exposure'/exp OR 'long-term exposure':ti,ab OR 'chronic exposure':ti,ab) AND ('cardiovascular disease'/exp OR 'heart disease'/exp OR 'myocardial infarction'/exp OR 'stroke'/exp OR 'heart failure'/exp OR 'cardiac arrhythmia'/exp OR ('cardiovascular mortality':ti,ab OR 'cardiovascular death':ti,ab OR 'cardiovascular incidence':ti,ab OR 'cardiovascular morbidity':ti,ab)))AND [2009-2024]/py	301 records

Note: *=wildcard character used in database searching to retrieve words with different endings.

Abbreviations: O₃=ozone; TS=Topic (Web of Science field tag); OR=Boolean operator; MeSH=Medical Subject Headings; tiab=title/abstract; exp=Emtree explosion; py=publication year.

SUPPLEMENTARY TABLE S2. Characteristics of studies included in the review.

Author	year	period	Study design	Country	Age	Sample size	Men	Women	Ozone indicator	Average ozone exposure ($\mu\text{g}/\text{m}^3$)	Exposure window	Model	Other controlled pollutants	Outcome
Michelle C. (1)	2016	1982-2004	cohort study	USA	≥ 30 years old	669,046	292,772	376,274	daily mean	81.90	year	Cox proportional hazards models	PM _{2.5} , NO ₂	mortality
Shudan Liu (2)	2022	2009-2018	cohort study	Yinzhou, China	≥ 18 years old	744,882	366,715	378,167	annual mean	68.05	year	Cox proportional hazards models	PM _{2.5}	mortality
Yue Niu (3)	2022	2010-2018	cohort study	China	≥ 18 years old	96,955	52,631	44,324	warm season means	89.70	warm season	Cox proportional hazards models	PM _{2.5}	mortality
Chris C. Lim (4)	2019	2002-2010	cohort study	USA	/	548,780	324,084	224,696	/	83.62	year	Cox proportional hazards models	PM _{2.5} , NO ₂	mortality
Shuru Liang (5)	2023	2011-2018	cohort study	China	≥ 45 years old	18,177	9,216	8,961	MAD8 ozone	109.41	warm season	Cox proportional hazards models	PM _{2.5}	morbidity
Shuru Liang (5)	2023	2011-2018	cohort study	China	≥ 45 years old	30,226	14,609	15,617	MAD8 ozone	109.67	warm season	Cox proportional hazards models	PM _{2.5}	morbidity
Sabit Cakmak (6)	2016	1991-2006	cohort study	Canada	> 25 years old	2,415,505	/	/	MAD8 ozone	/	warm season	Cox proportional hazards models	PM _{2.5}	mortality
Ulla Arthur Hvidtfeldt (7)	2018	1993-2015	cohort study	Denmark	50-64 years old	57,053	/	/	annual mean	55.40	year	Cox proportional hazards models	/	mortality
Lifeng Zhu (8)	2024	2010-2018	cohort study	China	all ages	36,948	/	/	MAD8 ozone	107.00	warm season	Cox proportional hazards models	/	morbidity
Dan L. Grouse (9)	2015	1991-2006	cohort study	Canada	≥ 25 years old	2,521,525	1,254,800	1,266,725	annual mean	84.90	warm season	Cox proportional hazards models	PM _{2.5} , NO ₂	mortality
Fatemeh Kazempourk uhi (10)	2019	2000-2008	cohort study	USA	/	2.22 million	/	/	MAD8 ozone	117.92 (median)	warm season	log-linear regression models	PM _{2.5} , NO ₂	mortality
Sabit Cakmak (11)	2018	1991-2011	cohort study	Canada	25-90 years old	2,291,250	/	/	MAD8 ozone	84.04	year	Cox proportional hazards models	PM _{2.5}	mortality
Katherine B.Ensor (12)	2013	2004-2011	case-control study	USA	≥ 18 years old	11,677	/	/	MAD8 ozone	31.75	year	logistics regression	/	morbidity
Richard W. Atkinson (13)	2013	2003-2007	cohort study	UK	40-89 years old	836,557	405,169	431,388	annual mean	51.70	year	Cox proportional hazards models	/	morbidity
Michael Jerrett (14)	2013	1982-2000	cohort study	USA	/	73,711	/	/	monthly mean	51.84 (IQR)	year	Cox proportional hazards models	/	mortality
Michael Jerrett 2 (15)	2009	1982-2004	cohort study	USA	≥ 30 years old	448,850	/	/	daily mean	71.40-222.98	year	Cox proportional hazards models	PM _{2.5}	mortality

Continued

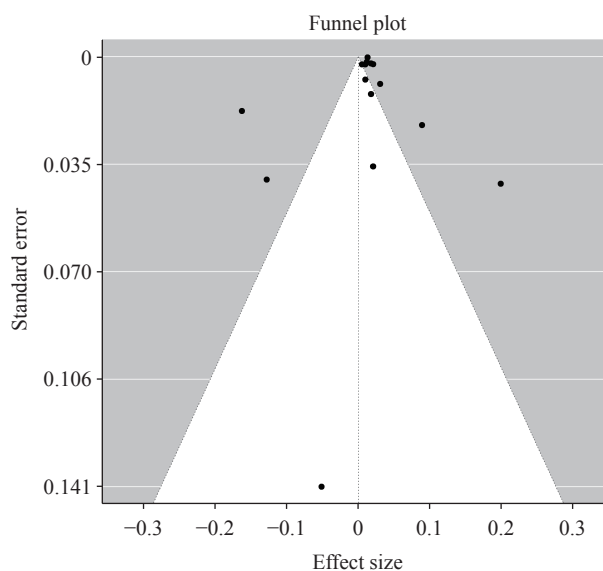
Author	year	period	Study design	Country	Age	Sample size	Men	Women	Ozone indicator	Average ozone exposure ($\mu\text{g}/\text{m}^3$)	Exposure window	Model	Other controlled pollutants	Outcome
Li Bai (16)	2019	2001–2015	cohort study	Canada	≥ 18 years old	5,062,146	/	/	annual mean	99.48	year	Cox proportional hazards models	/	morbidity
Mahdiah Danesh Yazdi (17)	2019	2000–2012	cohort study	USA	/	11,084,660	4,873,526	6,211,134	annual mean	/	/	Cox proportional hazards models	/	morbidity
Yu Shi (18)	2021	2016–2018	cohort study	China	≥ 18 years old	4,866	3,039	1,827	MAD8 ozone	93.50	year	Cox proportional hazards models	/	morbidity/mortality
Hyeonji Kim (19)	2017	2007–2013	cohort study	South Korea	≥ 18 years old	136,094	66,851	69,243	daily mean	42.73	year	Cox proportional hazards models	/	mortality
Tingfan Jin (20)	2022	2000–2016	cohort study	USA	≥ 65 years old	/	/	17,597,195	MAD8 ozone	91.98	warm season	Cox proportional hazards models	/	morbidity
Naizhuo Zhao (21)	2021	2001–2016	cohort study	Canada	≥ 65 years old	/	/	18,955,470	MAD8 ozone	91.98	year	Cox proportional hazards models	/	mortality
Malek Bentayeb (22)	2015	1989–2013	cohort study	France	/	20,327	14,790	5,537	MAD8 ozone	101.00	warm season	Cox proportional hazards models	/	mortality
Neil Wright (23)	2021	2013–2015	cohort study	China	30–79 years old	50,407	20,846	29,561	annual mean	97.60	year	Cox proportional hazards models	NO_2 , SO_2 , and $\text{PM}_{2.5}$	morbidity
Fuyan Zhang (24)	2024	2010–2012/2016–2020	cohort study	Guizhou, China	≥ 18 years old	5,563	2,529	3,034	daily mean	67.21	year	Cox proportional hazards models	$\text{PM}_{2.5}$	morbidity
Patricia F. Coogan (25)	2017	1995–2011	cohort study	USA	21–69 years old	33,771	0	33,771	daily mean	80.19	year	Cox proportional hazards models	$\text{PM}_{2.5}$, NO_2	morbidity
Toylb Olaniyan (26)	2022	2006–2016	cohort study	Canada	25–89 years old	2,687,900	1,386,000	1,301,900	annual mean	80.40	year	Cox proportional hazards models	$\text{PM}_{2.5}$, NO_2	morbidity
Li Yang (27)	2023	2014–2021	cohort study	Zhejiang, China	35–75 years old	202,042	86,499	115,543	daily mean	70.25	year	Cox proportional hazards models	$\text{PM}_{2.5}$	morbidity
Zenglei Zhang (28)	2024	2015–2020	cohort study	China	35–75 years old	3,206,871	1,287,393	1,919,478	daily mean	86.82	year	Cox proportional hazards models	$\text{PM}_{2.5}$	mortality
Chengrong Liu (29)	2024	2013–2019	cohort study	Shandong, China	≥ 40 years old	45,771	25,119	20,652	daily mean	106.44	warm season	Cox proportional hazards models	/	mortality
Spencer-Hwang R (30)	2011	1997–2003	cohort study	USA	≥ 18 years old	38,101	22,276	15,825	monthly mean	54.67	year	Cox proportional hazards models	PM_{10}	mortality

Note: "n" indicates that the corresponding information was not reported in the original studies. $\text{PM}_{2.5}$ =particulate matter with a diameter of $2.5 \mu\text{m}$ or less; MAD8 ozone=Maximum Daily Eight-hour Average Ozone. Abbreviation: IQR=interquartile range.

SUPPLEMENTARY TABLE S3. Statistical tests of publication bias using the Begg and Egger methods.

Health outcome	Begg's rank correlation test (<i>P</i>)	Egger's linear regression test (<i>P</i>)	Whether there is significant publication bias
CVD mortality	1.0000	0.8818	no
CVD morbidity	0.1361	0.3545	no
IHD mortality	1.0000	0.2178	no
stroke mortality	1.0000	0.3272	no
stroke morbidity	0.7726	0.4788	no
HF morbidity	0.7500	0.2789	no
hypertension morbidity	0.3333	0.0480	yes

Abbreviation: CVD=cardiovascular disease; IHD=ischemic heart disease; HF=heart failure.



SUPPLEMENTARY FIGURE S1. Funnel plot of CVD mortality.

Note: Funnel plots of studies investigating the association between ambient ozone exposure and CVD mortality. Each point represents the relative risk (RR) for CVD mortality associated with a 10 $\mu\text{g}/\text{m}^3$ increase in ozone concentration from an individual included study. The horizontal and vertical axes denote the effect size and the standard error of the effect estimate, respectively. The central vertical dashed line indicates pooled effect sizes. Publication bias assessment for CVD mortality showed no significant asymmetry, and Begg's rank correlation test ($P=1.0000$) and Egger's linear regression test ($P=0.8818$) indicated no significant publication bias. Detailed results of the other outcomes are presented in the Supplementary Materials.

Abbreviation: CVD=cardiovascular disease.

The literature that passed the screening criteria was included in the analysis database, and the following three parts of data were extracted: 1) research information: study name, first author, and publication year; 2) research methods: study location, data year, and study design. Results: RR or HR and 95% *CI* of each effect size of the population morbidity or mortality with each increase in a certain concentration of pollutants. To ensure the accuracy of the data entry, it was checked at least three times.

Statistical Analysis

The results must be translated into the expression "RR or HR value and 95% *CI* for every 10 $\mu\text{g}/\text{m}^3$ increase in ozone concentration". The ozone concentration is converted according to 1 ppb=2.144 $\mu\text{g}/\text{m}^3$. The specific conversion formula can be found in the Supplementary Information.

The extracted data were summarized and sorted, and the heterogeneity of the included studies was tested and expressed using the I^2 statistic. Data processing and meta-analysis were performed using the metafor package implemented in R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). The Begg and

Egger methods were used to check for bias in the analysis, and the funnel plot revealed publication bias.

Statistical Analysis Formula

The specific conversion formula is as follows:

$$RR_1 = e^{\frac{\Delta X_1}{\Delta X_2} \ln RR_2} \quad (1)$$

RR_1 refers to the relative risk when the ozone concentration is unified to $10 \mu\text{g}/\text{m}^3$, RR_2 refers to the relative risk of a cardiovascular disease in the original literature, ΔX_1 refers to $10 \mu\text{g}/\text{m}^3$, and ΔX_2 refers to the unified ozone concentration when the relative risk is calculated in the original literature.

We conducted stratified analyses according to sex, exposure window, and region. To determine whether there were statistical differences in the risk estimates of ozone between subgroups a and b (with the null hypothesis $H_0: \beta_a = \beta_b$), we used the following formula:

$$Z = \frac{\beta_a - \beta_b}{\sqrt{\text{se}(\beta_a)^2 + \text{se}(\beta_b)^2}} \quad (2)$$

β_a and β_b refer to the $\log(RR)$ for subgroups a and b, respectively, and $\text{se}(a)$ refers to its standard error, giving a P value according to Z .

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