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Review

Review of Ground-Level Ozone Impact in Respiratory Health Deterioration for the Past Two Decades

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Abstract: Background: Ground-level ozone has been gaining notoriety with increasing evidence of its nefarious effects on health, especially respiratory diseases. Where do we stand on the solidity of this data and is there room for improvement? Objectives: Evaluate this evidence for incongruities or heterogeneity in this field of research. How is the exposure assessment conducted, where does Portugal stand in this field, and what can be improved? Health deterioration concerning asthma, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS) are analysed. Methods: A review of 1735 studies was conducted through PubMed and Google Scholar engines for the past two decades. We identified 59 eligible studies and included an array of variables, including O_3 measurements, number of air-quality monitoring stations used, relative risks, odds ratios, hazard ratios, number of hospital admissions, visits, or mortality, and size of population dataset used. Results: Approximately 83% of data in this review presents significant correlations of ozone with asthma, COPD, and ARDS. Studies that report negative or not significant associations mention a lack of data or topographic differences as the main issue with these divergent results. Studies consistently report summer as a period of particular concern. Portuguese data in this field is lacking. Conclusions: This research field is growing in interest and there is evidence that ozone plays a non-negligible role in health deterioration. The few Portuguese studies in this field seem aligned with the literature reviewed but more research is needed. Suggested improvements are more and better data through denser air-quality networks to accurately depict personal exposure to ozone. Homogenization of the exposure assessment concerning averaging times of ozone to daily maximum 8 h averages whenever possible. Risk increments based on 10 ppb instead of interquartile ranges. Lastly, contrary to some studies in this review, the topographic effect on concentrations and health deterioration should not be underestimated and seasonality should always be checked.

Keywords: air quality; pollutants exposure; mortality; morbidity; asthma; COPD; ARDS; topographic variance

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1. Introduction

In 1952, a severe air pollution event took place in London named "the great smog of 1952". This adverse episode brought the attention of the general public and policymakers to take action. Provisions such as the Clean Air Act of 1956 [1] and Clean Air Act of 1993 were intended to prevent these situations from happening again. Our knowledge of air pollution's insidious impacts on health and the environment [2], require standards to be continuously adjusted and applied by global and local organizations. Most notoriously, these measures include enforcing the most stringent regulations on road transport through the Certification and Compliance for Vehicles and Engines and the Euro Emission Standards through directives 2008/50/EC and 2004/107/EC. These are enforced by the Environmental Protection Agency (EPA) in the United States and the European Commission in the European Union (EU), respectively. Despite these regulations and limitations, air pollution is still a worldwide concern deeply correlated with human activity. Outdoor air pollution is

usually comprised of nitrogen dioxide (NO_x), volatile organic compounds (VOCs), carbon monoxide, ground-level ozone (O_3) and particulate matter, associated with a range of acute and chronic health effects. The importance given to some of these pollutants varies over time as the academic body of work increases and humanity develops new technologies. In recent decades, health impacts from particulate matter have been extensively researched; however, secondary pollutants such as ground-level ozone are usually not the focus of health-pollution correlation studies [3–5]. Moreover, studies of this nature are often complex due to confounding factors that may or may not influence health risk assessment. These include meteorological variables, the dynamic interactions of some pollutants [6], lack of data, type of exposure assessment used, topography of the location, and statistical methodology used.

In Lippman (1989)'s critical review, the health effects of short-term exposure to O_3 through carefully elaborated laboratory experiments or workplace case studies were well understood, but its impacts on health over the years were not as explicit [7]. Nevertheless, the information gathered was useful to help set the first recommendations and legal limits to O_3 exposure. Thus, in 1989, it was agreed that the National Ambient Air-Quality Standards (NAAQS) for O_3 should be 120 ppb by volume for 1 h of exposure. As the O_3 body of research grew, policies were implemented and adjusted for both short-term and long-term impacts. In July 1997, the EPA replaced the 1-h standard with an 8-hour standard of 0.08 parts per million (converted to 84 ppb—parts per billion) which was then replaced in 2015 for 70 ppb, the current standard [8]. The current standards or legal limits for the World Health Organization (WHO), EPA, EU, and Portugal are observed in Table 1.

Table 1. Pollutant standards.

Air Pollutant (8-h Mean)	World Health Organization	Environmental Protection Agency	European Union	Portugal
O_3 (ppb)	50	70	60	60

The damage of ground-level O_3 to health, presumably caused by its irritant nature, provokes oxidative stress and inflammatory reactions in the lungs [9]. Epidemiological studies have shown that short-term O_3 exposure reduces respiratory function, increases hospital admissions and even death. Although these short-term studies on exposure to O_3 are usually robust time-series showing correlations with both morbidity and mortality factors, long-term exposure to O_3 has presented mixed results, often due to the limited nature of the monitoring data or what disease is being studied [6]. Despite this, current large-cohort study data suggests enough evidence to link long-term O_3 exposure to respiratory and cardiovascular mortality [10], hence why standards have seen the decrease of concentration limits. Regardless of this progress, there is no consensus on the correlation of long-term O_3 exposure and morbidity factors. Continuous research is needed to corroborate and isolate O_3 as the cause of certain health impacts. In the medical context, morbidity is used to discuss chronic and age-related diseases, i.e., worsening of a disease over a lifetime. In recent decades, some morbidity studies have suggested correlations between long-term exposure to O_3 and increased respiratory symptoms in asthmatics [11] and asthma admissions, especially among children [12].

In Jerret et al. (2009), it was shown that the association of O_3 with the risk of death from respiratory causes was insensitive to adjustment for confounders ($PM_{2.5}$) and the type of statistical model used, proving that a significant increase in O_3 concentration increases the risk of death from respiratory causes [13]. In this review we focus our attention on asthma, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS). These three wide encompassing diseases are analysed in an attempt to try and better understand the role of O_3 in health deterioration and check the claims previously made. Their nomenclature is represented in the 9th and 10th revision of the International Classification of Diseases (ICD). Before 2015, ICD-9 codes 460–519 are used. After 2015,

ICD-10 codes J00-J99, become the norm. Asthma is a common chronic respiratory disease that provokes hyperresponsiveness and inflammation of the airways, leading to cascades of pro-inflammatory mediator releases and airflow limitations. It is estimated that asthma affects 262 million individuals worldwide accounting for 461,000 deaths [14]. Its increasing prevalence in industrialized countries and the fact that it disproportionately affects children and older adults by reducing their quality of life throughout the years or towards their end of life is alarming and non-negligible [15]. Another respiratory disease, COPD, was the fifth-highest cause of death in 2002 and was predicted to be the third-highest cause of death in 2021 [16]. Beating this prediction by two years, in 2019 COPD was already the third-highest cause of death in the world [17]. Lastly, ARDS is a syndrome of noncardiogenic pulmonary edema and acute respiratory failure characterized by inflammation and alveolar–capillary barrier dysfunction. In a study encompassing 50 country intensive care units, ARDS occurred in 7% of intensive care unit (ICU) admissions [4,18].

Why is studying O_3 complex? The difficulty in correlating O_3 with health is due to how particularly hard to predict and control O_3 is. Ground-level O_3 is formed through sunlight-initiated reactions of precursor emissions of NO_x and VOCs. These primary emissions are often associated with anthropogenic sources such as industrial activity or motorized traffic. It is common knowledge that to control O_3 we must control its precursor emissions [19], thus, if NO_x and VOCs are reduced, so should O_3. Unfortunately, this is not always the case. The interactions of VOCs and NO_x ($NO + NO_2$) are now suspected to play a key role on a counterintuitive phenomenon called the "Weekend Effect" (WE), in which O_3 concentrations are higher during the weekend, a time when it would be expected that lower NO_2 production would form less O_3 [20,21]. This counterintuitive trend is not restricted to short-term variations. Other studies conducted in the Pearl River Delta have recorded similar trends with near-surface O_3 concentrations increasing 0.86 ppbV per year accompanied by a NO_2 reduction of 0.61 ppbV per year [22]. This is further corroborated by the authors' previous work conducted in Lisbon, Portugal and other studies of the 2020 pandemic outbreak, highlighting that short-term reductions of NO_2 emissions can also lead to O_3 increase. However, it is argued that these are highly localized [21,23]. This "localization problem" has been known for a while, and in 2015 it was already recognized by the WHO that changes in the O_3 modeling approach were necessary [24]. In 2015, new-model O_3 variations with adjustment methodology were adopted by allowing for both increases and decreases in O_3 concentrations. This more accurately reflects the scientific understanding that increases in O_3 concentrations may occur in response to reductions of NO_x emissions, especially in areas surrounding urban centers. These fit previous statements about the complexity of modeling O_3, giving rise to continued discussion about locality and health impacts that differ from area to area [21,23].

Sources and O_3 Dynamics

To further understand the complexity of O_3, we must understand its sources and dynamics. Air pollution is caused by natural and anthropogenic factors but is mainly associated with combustion by-products [25] produced by internal combustion engine vehicles (ICEV), i.e., motorized traffic. As the human population expands and concentrates in urban centers, huge energy demand drives huge energy consumption. The fuel we burn in motorized urban mobility emits harmful substances into the atmosphere, such as NO_x, VOCs and particles with less than 10um. These air pollutants are believed to be the main precursors of O_3, a secondary pollutant formed through complex photochemical reactions. It is argued that NO_2 and NO are photochemical precursors of O_3. Thus, NO_x (NO_2 + NO) is agreed to have a catalytic effect while VOCs are oxidized during the O_3 formation process[26,27]:

$$RO_2 + NO \rightarrow RO + NO_2 \quad (1)$$

$$RO + O_2 \rightarrow R'CHO(R'COR'') + HO_2 \quad (2)$$

$$HO_2 + NO \rightarrow OH + NO_2 \quad (3)$$

$$NO_2 + hv \rightarrow NO + O(^3P) \quad (4)$$

$$O(^3P) + O_2 + M \rightarrow O_3 + M \quad (5)$$

$$O_3 + NO \rightarrow NO_2 + O_2 \quad (6)$$

In this proposed formation mechanism, the R represents a group of carbon and hydrogen atoms (radical groups) existent in VOCs, and M stands for a non-reacting molecule. The NO is formed in the photolytic (hv) reaction (4) and returns to NO_2, preferentially reacting with HO_2 and RO_2 by reactions (1) and (3), without consuming O_3 by reaction (6). From the reproduced NO_2, O_3 is produced again along with oxidation of NO to NO_2 and, in turn, O_3 is accumulated and results in high concentrations as the cycle repeats [28–30]. Therefore, it is believed that the main sources of O_3 stem from the complex relationship between nitrogen oxides (NO_x) and volatile organic compounds (VOCs). It is hypothesized that increases in VOCs concentrations always lead to more O_3 formation. However, increasing NO_x can lead to more or less O_3, depending on the ratio between NO_x and VOCs. In other words, at low VOCs/NO_x ratios, the main reaction is between OH and NO_2, in which the radical is removed and the formation of O_3 is delayed. At higher VOC/NO_x ratios, the OH radical reactions are favored increasing O_3 formation [31]. These interactions of VOCs, NO_x, NO and NO_2, are now suspected to play a key role on a counterintuitive phenomenon called the "weekend effect", in which O_3 concentrations are higher during the weekend, a time where it would be expected that lower NO_2 production would form less O_3 [32].

2. Summary and Objectives

Ground-level ozone has been associated with both acute and chronic health impacts ranging from asthma episodes, COPD, increased hospital admissions, and overall cardiovascular and cardiopulmonary morbidity and mortality [13]. Respiratory system diseases are the fifth-highest cause of internment and the biggest cause of death in Portuguese hospitals [33].

This review aims to show the historical significance of O_3 and how it correlates with health over the years. It offers a different angle as the purpose is to understand worldwide encompassing trends of O_3 and health impacts in the respiratory system and compare them with Portugal. We investigate the monitoring assessment and results obtained, what can be retained from these, and how they compare with Portuguese data. The following research questions (RQ) will be tackled in this review:

RQ1: Is there research that correlates health deterioration with O_3? How has it been evolving throughout the years?

RQ2: If so, does this research show evidence of O_3 causing health deterioration?

RQ3: Is the evidence proven globally, or is it localized?

RQ4: Are there any Portuguese studies? How do they relate to studies elsewhere?

RQ5: According to the available evidence, which age groups are the most affected?

RQ6: How does seasonality impact O_3 and consequent health deterioration?

RQ7: Is the monitoring of the exposure to O_3 adequate? Where do we stand on studies regarding short-term and long-term morbidity and mortality for asthma and COPD?

RQ8: What are the research gaps and possible improvements?

3. Materials and Methods

This review applies a similar methodology to Xing Li et al., 2019 [34] based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). A diagram type-flow based on this system can be seen in Figure 1.

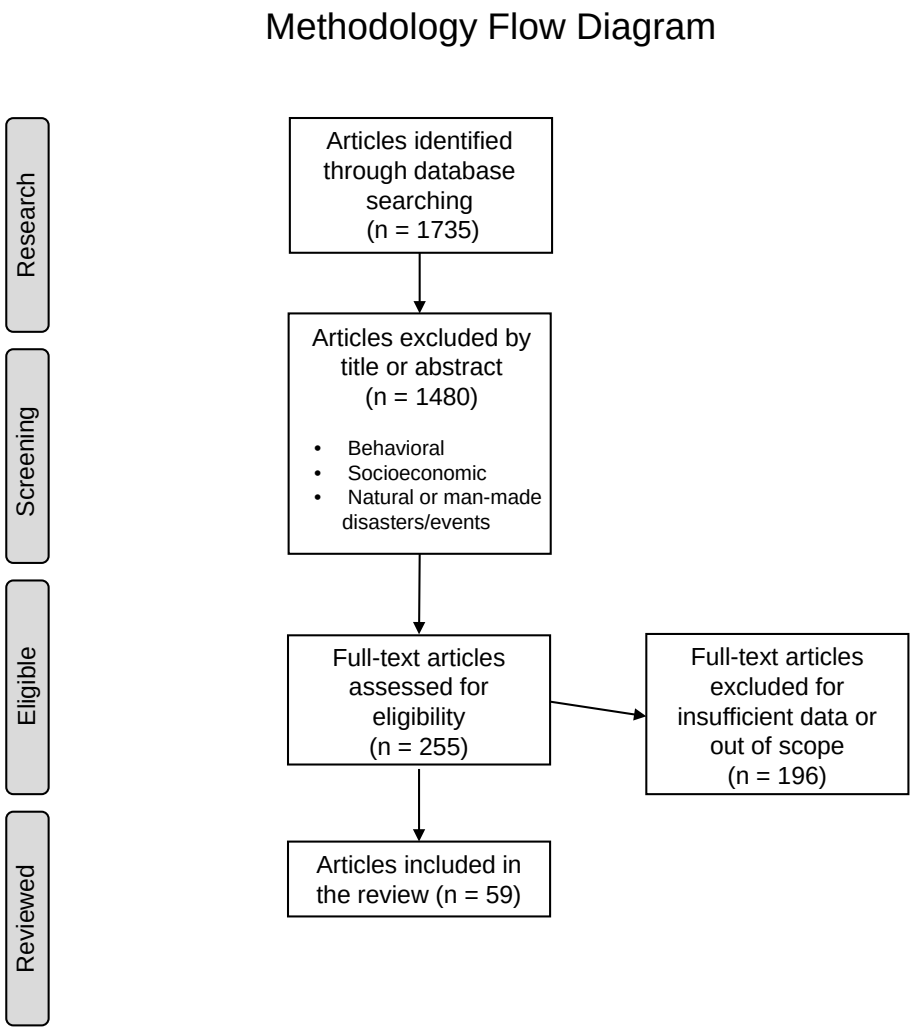

Figure 1. Methodology flow diagram based on PRISMA.

3.1. Selection and Screening Process

PubMed and Google Scholar search engines were used to explore English-written studies that correlate health with O_3 for the past two decades. The research included keyword combinations of "ground-level ozone" or "O_3" with "COPD", "ARDS", "ASTHMA", and "emergency department" (ED), "hospital admissions" (HA), "emergency visits" (EV), "emergency room" (ER), and "mortality". A total of 1735 studies were initially found. Studies were screened by title and abstract, and exclusions included: (1) publication dates or dataset periods ending prior to 2000; (2) animal or toxicological studies and meta-analysis; (3) studies based on extreme events or natural disasters such as fires, typhoons, etc.; (4) behavioral or socioeconomic studies; (5) duplicated, repeated datasets or publications by the same author; and (6) excessive data missing of the variables in the study, such as O_3 concentration, season, correlation results, population or dataset size, and type of cohort.

After the selection process, 255 studies were fully read and 59 were accepted. The remaining 196 were discarded mainly due to (6).

The data collected from these studies include: author, year of publication, period of analysis, country and how many locations, type of exposure assessment and number of air-quality monitoring stations (AQMS) used, O_3 concentrations, O_3 measurement standards (1 h, 8 h, and 24 h), increment used, relative risk (RR) or hazard ratio (HR) or odds ratio (OR), IQR, 95% confidence intervals (95% CI), seasonality, focus on O_3, cohort type, age groups, size of population or number of HA/EV, and what disease was investigated according to the International Statistical Classification of Diseases and Related Health Problems (ICD).

When it was not possible to ascertain data in a category, the value was represented by "not available" (NA), except regarding seasonality where it was assumed they studied the whole period in analysis, meaning all seasons.

3.2. Additional Considerations

During the selection process, no distinction was made on the study being time-series or case-crossover. There was no selection process based on the lag, pollutants present in the study (besides O_3), or statistical methodology used to present the results. All studies that fitted the description in the selection and screening process were accepted. This means that a wide array of studies with different lags, ranging from lag 0 to lag 90, different methodologies, such as RR, HR and OR, and both single- and multi-pollutant models were accepted. Results were never picked based on socioeconomic status, sex, or smoker and non-smoker status. The highest result chosen was always based on highest and most consistent significant result. It is understood that RR, HR and OR represent different things statistically but they were holistically included in this study as a metric that correlates O_3 with health deterioration impacts, independent of the statistical particularity of the association [35].

All $\mu g/m^3$ values in Table 2 were converted to ppb using the conversion rate of 1.9957 (1013 milibar and 20 ºC).

The summary results for this review analysis were considered either significant or not significant. A significant result ($p < 0.05$) can have a positive (RR/OR/HR > 1) or negative (RR/OR/HR < 1) association. A not significant result is used when $p > 0.05$ or the authors simply mention that no association was found in the results or conclusions.

Concerning lag, when a "lag 0–2" is mentioned, it means that a HA/EV/mortality episode today was weighted against the previous 3 days of O_3 concentration averages. A "lag 2" means that a HA/EV/mortality episode today was weighted against O_3 concentration 2 days ago. Lastly, when a "lag 0 to 2" is mentioned, it means that all lags from 0 to 2 were tested but it is not entirely specified which result is tied to which lag.

Additional considerations refer to the nomenclature of diseases in this review. For asthma, studies used ICD-9 493.0 to 493.9 and ICD-10 J45 and 46, with one study taking into account 786.07 (wheezing) [36]. For COPD we have ICD-9 493 and ICD-10 J40-J44, and for ARDS ICD-9 codes 518.51, 518.52, 518.53, and 518.82 and ICD-10 codes J20, J21 and J80.

Additionally, the use of "warm season" refers to the months from April until September while "cold season" refers to October until March. Lastly, several nomenclatures exist to categorize age groups. In this review, Nophar Geifman et al. (2013) [37] was used as a basis and therefore ages are classified as: children ages 0–12; adolescents ages 13–18; adults ages 19–64; and elderly ages 65+.

3.3. Limitations

The results in this review were selected based on the highest single-pollutant correlation of RR, HR or OR and its corresponding lag time, IQR, and age of population found in each study. As a consequence, we have a wide range of lag times that greatly affect the homogeneity of the results. However, it would be interesting to see if there is a pattern.

The selection of the highest correlation can have shortcomings with respect to the solidity of the data presented. A study can have consistent reporting of a significant result in a given category and then have a higher oddity result that, albeit statistically significant, might differ from the previous consistent results. In this review, selecting such results is avoided, especially when the authors of the paper clearly refer to these results as outliers or as an odd result. Overall, the data presented are extremely consistent within the realm of the studies quoted.

To understand the holistic rationale of accepting RR, OR and HR, we explain what they mean and how they might differ. The RR applied to air pollution and mortality or morbidity is used to compare variables of hospital admissions, emergency visits or mortality, interpreted as exacerbation of the disease, due to O_3 variation. For example,

an RR of 1 would mean that the population sample, when exposed to 20 ppb and afterwards to 30 ppb (a 10-ppb increase), would have no meaningful difference in disease exacerbation risk despite that increase in O_3. A risk greater than 1, for example 1.5, would represent a patient that is 50% or 1.5 times more likely to experience an exacerbation episode per 10 ppb increase. The main limitation of RR is that the sample must be representative of the population as risk ratio is an estimate based on the population as whole and thus is only effective with randomized sampling. For the OR case, it does not suffer from the same limitations and can be more widely used. Odds ratios are a symmetric measure that can examine interventions given outcomes. In summary, odds ratios measure the association between two variables and their probability of having a certain outcome compared to another. For example, in our case, it compares someone exposed to a certain concentration of O_3 and developed symptoms or had exacerbation of asthma symptoms, versus someone that was not exposed to that concentration. Odds ratios are often depicted as a less intuitive way to present data and tend to overestimate risk. Both RR and OR concern interventions and outcomes reporting across an entire study period. A similar but distinct measure, HR, shows rates of change and temporal progression of some events within a group. In this case, an event would be the exacerbation or developing of symptoms given asthma, COPD or ARDS within a group, resulting in hospitalizations, emergency visits, or death [35]. For these reasons, we consider that they all represent the probability of health deterioration given O_3 exposure but recognize that they are not measures for direct comparison.

Another possible limitation is the use of data from single-pollutant models that can portray skewed results due to not accounting for confounding factors such as other pollutant variables. To counteract this, we added all the available multi-pollutant data from studies that had both single and multi-pollutant modeling to a version of Table 2 in the supplementary files. In this table, the highest multi-pollutant result that shared the same lag time, season, or population age as the single-pollutant result was picked. This made sense as to make a direct comparison between the two. If this was not possible, then the next statistically significant result was picked. It is worth noting that by doing so, we can affirm that the insensitivity to confounders found in Jerret et al. (2009) [13] was also found in this review as most multi-pollutant models report similar significant results to single-pollutant models.

Lastly, the main limitation might be the inclusion of studies that, despite checking all the boxes in the methodology process, present limited size datasets for the population size in study or low amount of HA or EV data. Due to the low data resolution, the results presented by these studies might be skewed.

4. Results and Discussion

There has been considerable research on air pollution and its impacts on health deterioration, more specifically O_3 impacts on asthma, COPD, and ARDS. Through the PubMed and Google Scholar database search, 1735 studies were identified. Titles and abstracts were screened, and out-of-scope studies were discarded, reducing the eligible studies to 255. Full-text reading of the eligible studies resulted in 59 studies accepted, as seen in Table 2. Five of these studies present independent data for both asthma and COPD. Thus, it means that in certain graphics, data points can and will add up to more than 59 as they will be viewed as independent datasets.

In the introduction section, it was mentioned how O_3 knowledge and the academic body of work has progressed over the years and how other pollutants, especially particulate matter, take center stage in health-related impacts. It would be interesting to see if and how the focus on O_3 research has changed over time. Overall, in Figure 2, a general trend of continuous growth in publications exists for health problems in this review, especially in recent years. The biggest focus has been on asthma, followed by COPD, and then ARDS.

Table 2. All studies analysed in this review.

Study	Period	Country	Locations (#)	Monitoring Type	AQMS (#)	Mean (Median) of O_3 (ppb)	SD	IQR	O_3 Averaging Time	Risk Related Increment of O_3 (ppb)	Lag	Correlation Results	Checks Seasonality? [a] (Strongest Association)	Focus on O_3	Covered Ages (Most Significant Association)	Cohort Type	Dataset Size	Disease	RR, OR or HR	Multi-Pollutant Model	Reference [#]
Fung KY, 2006	1995–2000	Canada	1	AQMS	NA	50.6	19.9	22.0	24 h max	22.0	lag 0–2	NS	NA (All)	No	All (65>)	HA	5574	ASTHMA	RR	No	[38]
Lee SL, 2006	1997–2002	China	1	AQMS	11	14.6	8.2	11.7	max 8 h avg [b]	11.7	lag 2	1.059 (1.041–1.079)	Yes (All)	No	<18 (<18)	HA	26,663	ASTHMA	RR	Yes	[39]
Ko FWS, 2007	2000–2005	China	1	AQMS	14	22.1	12.1	NA	max 8 h avg [b]	5.0	lag 0–5	1.034 (1.029–1.039)	Yes (All)	No	All (14–65)	HA	69,716	ASTHMA	RR	Yes	[40]
Paulu C, 2008	2000–2003	USA	1	AQMS	2	36–42	NA	14–19	max 8 h avg	10.0	lag 0–3	1.07 (1.04–1.11)	No (warm season)	Yes	All (15–34)	EV	8020	ASTHMA	RR	Yes	[41]
Halonen JI, 2009	1998–2004	Finland	1	AQMS	1	NA (36.4)	NA	NA	max 8 h avg	12.8	lag 3	1.106 (1.017–1.201)	No (warm season)	Yes	All (65>)	HA	5069	COPD	RR	Yes	[42]
											lag 1	1.268 (1.134–1.416)	No (warm season)		<15 (<15)		1972	ASTHMA			
Mar TF, 2009	1998–2002	USA	1	AQMS	5	39.2	NA	8.2	max 1 h & 8 h avg	10.0	lag 3	1.11 (1.02–1.21)	No (warm season)	Yes	All (<18)	EV	3217	ASTHMA	RR	No	[43]
Silverman RA, 2009	1999–2006	USA	1	AQMS	13	NA (41.0)	NA	NA	max 8 h avg	22.0	lag 0–1	1.2 (1.11–1.29)	No (warm season)	No	All (6–18)	HA	75,383	ASTHMA	RR	Yes	[44]
Stieb DM, 2009	1992–2003	Canada	7	AQMS	NA	18.4	NA	NA	max 8 h avg & 24 h avg	18.4	lag 2	1.032 (1.003–1.062)	Yes (warm season)	No	NA (NA)	EV	83,563	ASTHMA	RR	No	[45]
											lag 0 to 2	NS	Yes (warm season)				40,491	COPD			
Alves CA, 2010	1994–2004	Portugal	1	AQMS	3	30.8	13.5	17.6	1 h avg	5.0	lag 2	0.9704 (NA)	NA (All)	No	All (<15)	HA	NA	ASTHMA/COPD [c]	RR	No	[46]
Lee JT, 2010	2004–2005	S. Korea	2	AQMS	40	32.1	NA	15.3	max 8 h avg	15.3	lag 0–1	1.21 (1.1–1.34)	Yes (All)	Yes	<15 (<15)	HA	NA	ASTHMA	RR	No	[47]
Meng YY, 2010	2001	USA	1	AQMS	21	NA (30.3)	NA	6.9	1 h max & Annual avg	10.0	NA	1.63 (0.95–2.81)	NA (All)	No	All (1–17)	HA/EV	1512	ASTHMA	OR	Yes	[48]
Almeida SP, 2011	2000–2004	Portugal	1	AQMS	3	37.2	13.2	39.9	max 8 h avg	5.0	lag 0–1	1.015 (0.986–1.025)	Yes (warm season)	No	All (65>)	mortality	NA	ASTHMA/COPD [c]	RR	No	[49]
Zanobetti A, 2011	1985–2006	USA	105	AQMS	105	NA	NA	5.0	max 8 h avg	5.0	yearly	1.07 (1.04–1.09)	Yes (warm season)	Yes	65> (65>)	HA	3,210,511 [d]	COPD	HR	No	[50]
Santus P, 2012	2007–2008	Italy	1	AQMS	8	37.90306122	23.4	NA	1 h max	5.0	lag 0–2	1.104 (1.068–1.142)	Yes (warm season)	No	All (All)	EV	3569	ASTHMA	OR	Yes	[51]
											NA	NS	Yes (All)				1825	COPD			
Sacks JD, 2014	2006–2008	USA	1	AQMS/Models	42	43.6	NA	NA	max 8 h avg	20.0	lag 0–2	1.02 (0.997–1.044)	Yes (warm season)	Yes	All (5–17)	EV	121,621	ASTHMA	OR	Yes	[52]
SM Almeida , 2014	2005–2009	Portugal	1	AQMS	4	NA	NA	NA	24 h average	5.0	lag 0 to 6	NA	NA (All)	No	All (All)	HA	267 [d]	ASTHMA	RR	NA	[53]
Wendt JK, 2014	2005–2007	USA	1	AQMS	22	37.9	16.0	21.7	max 8 h avg	10.0	lag 0–5	1.05 (1.02–1.08)	Yes (warm season)	No	<17 (<17)	Obs.	18,289	ASTHMA	OR	Yes	[54]
Alhanti BA, 2015	1993–2007	USA	3	AQMS	NA	37.3–47.7	19.1–19.4	27–28.7	max 8 h avg	28.0	lag 0–2	1.07 (1.04–1.1)	NA (NA)	No	All (5–18)	EV	611,970	ASTHMA	RR	No	[36]
Byers N, 2015	2007–2011	USA	1	AQMS	11	53.9	12.5	16.7	1 h max & 8 h max	16.7	lag 0–2	1.048 (1.002–1.096)	Yes (warm season)	No	5> (18–44)	EV	165,056	ASTHMA	RR	Yes	[55]
Gleason JA, 2015	2004–2007	USA	1	AQMS/Models	NA	NA	NA	12.8	max 8 h avg	12.8	lag 0–2	1.1 (1.06–1.14)	No (warm season)	No	3–17 (3–17)	EV	3675	ASTHMA	OR	Yes	[56]
Kim J, 2015	2008–2011	S. Korea	9	AQMS	NA	18.1	NA	20.0	1 h avg	20.0	lag 1	1.25 (1.03–1.51)	Yes (cold season)	No	All (All)	EV	8188	ASTHMA	OR	Yes	[57]
Sheffield PE, 2015	2005–2011	USA	1	AQMS	7	50–60	NA	13.0	24 h avg	13.0	lag 1	1.134 (1.054–1.22)	No (warm season)	Yes	5–17 (14–17)	HA/EV	8009/35,907	ASTHMA	OR	No	[58]
Yamazaki S, 2015	2010–2013	Japan	1	AQMS	1	26.1	11.0	NA	24 h avg	10.0	lag 0–2	1.163 (1.046–1.293)	Yes (warm season)	No	<14 (<14)	EV [e]	1447	ASTHMA	OR	Yes	[59]
Castner J, 2016	2007–2012	USA	1	AQMS	1	39.0	13.0	17.0	max 8 h avg	17.0	NA	1.047 (1.021–1.073)	Yes (warm season)	No	NA (NA)	EV	76,651	ASTHMA	RR	No	[3]
Khaniabadi YO, 2016	2014–2015	Iran	1	AQMS	1	15.3–19.9	NA	NA	1 h avg	5.0	NA	1.041 (1.025–1.061)	NA (All)	Yes	NA (NA)	mortality/HA	NA	COPD	RR	No	[60]
Lam HCY, 2016	2004–2011	China	1	AQMS	13	18.5 (16.8)	NA	15.5	24 h avg	5.0	lag 0–3	1.33 (1.13–1.57)	Yes (warm season)	No	All (59>)	HA	56,112	ASTHMA	RR	Yes	[61]
Mohamed A, 2016	2007–2012	USA	1	AQMS	16	28.7 (29.5)	11.4	NA	24 h avg	10.0	lag 0	1.046 (1.029–1.06)	NA (All)	No	All (All)	HA	90,381	ASTHMA	RR	No	[62]
Noh J, 2016	2005–2009	S. Korea	1	AQMS	27	31.7	17.0	22.6	max 8 h avg	22.6	lag 3	1.269 (1.111–1.288)	Yes (warm season)	No	All (6–18)	EV	33,751	ASTHMA	RR	No	[63]
Ware LB, 2016	2006–2012	USA	6	AQMS	163	NA (51.5)	NA	NA	max 8 h avg	5.0	NA	1.58 (1.27–1.96)	No (warm season)	No	All (All)	Obs.	1558	ARDS	OR	Yes	[64]
Xiao Q, 2016	2002–2008	USA	1	AQMS/Models	NA	42.1	12.6	18.5	max 8 h avg	18.5	lag 0–3	1.025 (1.007–1.042)	NA (All)	No	<18 (<18)	EV	148,256	COPD	OR	Yes	[5]
Ding L, 2017	2013	China	1	AQMS	9	42.6	36.4	NA	max 8 h avg	5.0	lag 0 to 7	NS	Yes (cold season)	No	<18 (<18)	EV	2507	ASTHMA	OR	Yes	[65]
Goodman JE, 2017	1999–2009	USA	1	AQMS	NA	30.7	16.9	21.3	max 8 h avg	10.0	lag 0–1	1.027 (1.004–1.051)	Yes (warm season)	No	All (6–18)	HA	295,497	ASTHMA	RR	No	[66]
Nhung NTT, 2017	2007–2014	Vietnam	1	AQMS	2	47.4	38.3	43.5	max 8 h avg & 24 h max	43.5	lag 0–6	NS	Yes (cold season)	No	<17 (<17)	HA	17,118	ASTHMA	RR	Yes	[67]
Rush B, 2017	2011	USA	47	AQMS	NA	NA	NA	NA	max 8 h avg	10.0	NA	1.07 (1.06–1.08)	NA (All)	No	18> (18>)	HA	8,023,590	ARDS	OR	No	[18]
Yin P, 2017	2013–2015	China	272	AQMS	1265	39.3	7.1	NA	max 8 h avg	5.0	lag 0 to 10	NS	Yes (warm season)	Yes	5> (5>)	mortality	NA	COPD	RR	No	[68]
Zu K, 2017	2001–2013	USA	6	AQMS	91	32.2	12.0	16.7	max 8 h avg	10.0	lag 0–3	1.047 (1.025–1.069)	Yes (warm season)	Yes	All (5–14)	HA	155,243	ASTHMA	RR	No	[69]
Gharibi H, 2018	2015	USA	8	AQMS	18	50.7	12.6	NA	max 8 h avg	18.1	lag 3	1.052 (1.021–1.072)	No (warm season)	Yes	2> (6–18)	EV	1101	ASTHMA	OR	Yes	[70]
Qiu H, 2018	2015–2016	China	1	AQMS	6	49.4	28.5	42.7	max 8 h avg	5.0	lag 0 to 6	NS	NA (All)	No	All (All)	HA	54,966	COPD	RR	Yes	[71]
Reilly JP, 2018	2005–2015	USA	18	AQMS	14	NA (47.1)	NA	2.7	max 8 h avg	2.7	3 year	1.44 (1.12–1.86)	No (warm season)	No	13> (13>)	HA	996 [d]	ARDS	OR	No	[4]
Strosnider HM, 2018	2001–2012	USA	894	AQMS/Models	NA	8–34	NA	16.5	max 8 h avg	20.0	lag 0 to 6	1.069 (1.059–1.079)	NA (All)	No	All (19–65)	EV	5,761,712	ASTHMA	RR	Yes	[72]
												1.043 (1.028–1.058)					2,385,148	COPD			
Zielinski M, 2018	2006–2014	Poland	6	AQMS	6	18–21.5	NA	NA	NA	16.2	lag 0	0.77 (NA)	NA (All)	No	All (All)	HA	12,889	COPD	RR	No	[73]
Kazemiparkouhi F, 2019	2000–2008	USA	260	AQMS/Models	1151	NA (55.0)	NA	5.0	max 1 h & 8 h & 24 h avg	10.0	NA	1.065 (1.06–1.069)	No (warm season)	Yes	65> (65>)	mortality	328,957	COPD	RR	Yes	[74]
Kuo CY, 2019	2001–2012	Taiwan	8	AQMS	78	28.8	12.5	16.2	24 h avg	16.2	NA	0.962 (0.947–0.977)	NA (All)	No	<18 (0–5)	HA	59,204	ASTHMA	RR	Yes	[75]
Lee SW, 2019	2008–2012	S. Korea	1	AQMS	34	NA (17.0)	NA	14.3	24 h avg	14.3	lag 0	1.141 (1.075–1.213)	NA (All)	No	All (6–18)	HA	28,824	ASTHMA	RR	No	[76]
Liang L, 2019	2013–2017	China	1	AQMS	35	48.9	31.7	43.4	max 8 h avg	43.4	lag 0	1.027 (1.01–1.044)	Yes (warm season)	No	18> (65>)	HA	161,613	COPD	RR	Yes	[77]
Lim CC, 2019	2002–2010	USA	6	AQMS/Sat./Models	NA	39.0	4.6	NA	max 8 h avg	10.0	NA	1.09 (1.03–1.15)	No (warm season)	Yes	50–71 (50–71)	mortality	548,780	COPD	HR	Yes	[78]
Liu Y, 2019	2013–2018	China	1	AQMS	55	46.9	NA	NA	max 8 h avg	27.0	lag 3	1.09 (1.01–1.18)	Yes (warm season)	No	All (All)	mortality	4454	ASTHMA	OR	Yes	[79]
Rhee J, 2019	2000–2012	USA		AQMS/Sat./Models	NA	NA (39.1)	NA	4.9	24 h avg	1.0	NA	1.002 (1.002–1.003)	No (warm season)	No	65> (65>)	HA	1,164,784	ARDS	OR	Yes	[80]
Yazdi MD, 2019	2000–2012	USA	7	Sat./Models	NA	NA	NA	NA	max 8 h avg	1.0	NA	1.024 (1.023–1.025)	NA (All)	No	All (60>)	HA	1,728,689	COPD	HR	No	[81]
Baek J, 2020	2010–2014	USA	1	AQMS/Models	NA	37.4	6.8	10.6	max 8 h avg	10.6	lag 0	1.043 (1.012–1.075)	Yes (warm season)	No	5–18 (5–18)	HA	111	ASTHMA	OR	Yes	[82]
Chang Q, 2020	2013–2017	China	1	AQMS	13	31.6	NA	26.0	24 h avg	26.0	lag 0	1.05 (1.02–1.082)	Yes (warm season)	No	<17 (0–5)	EV	166,595	ASTHMA	RR	Yes	[83]
Franco P, 2020	2005–2015	Portugal	1	AQMS	6	52.5	20.4	NA	1 h avg	5.0	lag 0–6	1.048 (NA)	NA (All)	No	All (<15)	HA	4017	COPD [c]	RR	No	[84]
Niewiadomska E, 2020	2016–2017	Poland	14	AQMS	2	37.3	25.7	NA	max 8 h avg	5.0	lag 0 to 20	NS	No (warm season)	Yes	NA (NA)	HA	3815	ASTHMA	RR	No	[85]
Paulin L, 2020	2010–2018	USA	7	AQMS/Models	NA	25.1	NA	6.3	2 wk [f] mean	5.0	NA	NS	Yes (All)	Yes	40–80 (40–80)	HA/EV	1874	ASTHMA	OR	Yes	[86]
Shin SW, 2020	2005–2015	S. Korea	3	AQMS	62	NA	NA	NA	24 h avg	10.0	NA	1.012 (1.003–1.02)	Yes (warm season)	No	18–84 (18–84)	HA/EV	143 [d]	ASTHMA	OR	Yes	[87]
Chen J, 2021	2015–2018	China	1	AQMS	23	50.4	26.4	39.8	max 8 h avg	39.8	lag 0–2	1.074 (1.036–1.113)	NA (All)	No	60> (60>)	mortality	61,058	COPD	RR	Yes	[88]
Huang W, 2021	2011–2014	USA	1	AQMS/Models	NA	33.0	13.6	NA	max 8 h avg	NA	lag 4	1.08 (1.02–1.14)	Yes (cold season)	No	<18 (<18)	EV	54,632	ASTHMA	OR	Yes	[89]
Li M, 2021	2013–2018	China	1	AQMS	11	41.3	24.0	33.2	max 8 h avg	5	lag 0–3	1.012 (1.005–1.0193)	NA (All)	Yes	All (All)	mortality	296,080	COPD	RR	Yes	[90]
Shin S, 2021	2001–2015	Canada	1	AQMS/Models	NA	46.4	4.5	6.3	max 8 h avg & 3yr avg	6.3	1 year	NS	No (warm season)	No	35–85 (35–85)	HA/EV	218,005	ASTHMA	HR	Yes	[91]
												1.04 (1.03–1.04)					340,733	COPD			

[a] If it checks for seasonality then it is specified which season had the most significant association. If it did not check for seasonality then the only studied season is presented. If none of these two cases apply then "All" is used as no particular season yielded a significant result. [b] 8h averages taken from 9 to 17 h. [c] Lower respiratory diseases in which COPD/Asthma is included but is not exclusive. [d] Data represents number of patients enrolled in the study. [e] Primary care unit visits, does not spceify if it is emergency visits. [f] Week (wk) and year (yr). Other: # = number of; NA = Not available; NS = Not significant; HA = Hospital admissions; EV = Emergency visits or emergency department visits; Obs. = Observational; avg = average; max = maximum; Sat. = Satellite; AQMS = Air quality monitoring station; RR/OR/HR = Risk ratio, odds ratio, and hazard ratio; COPD = Chronic.

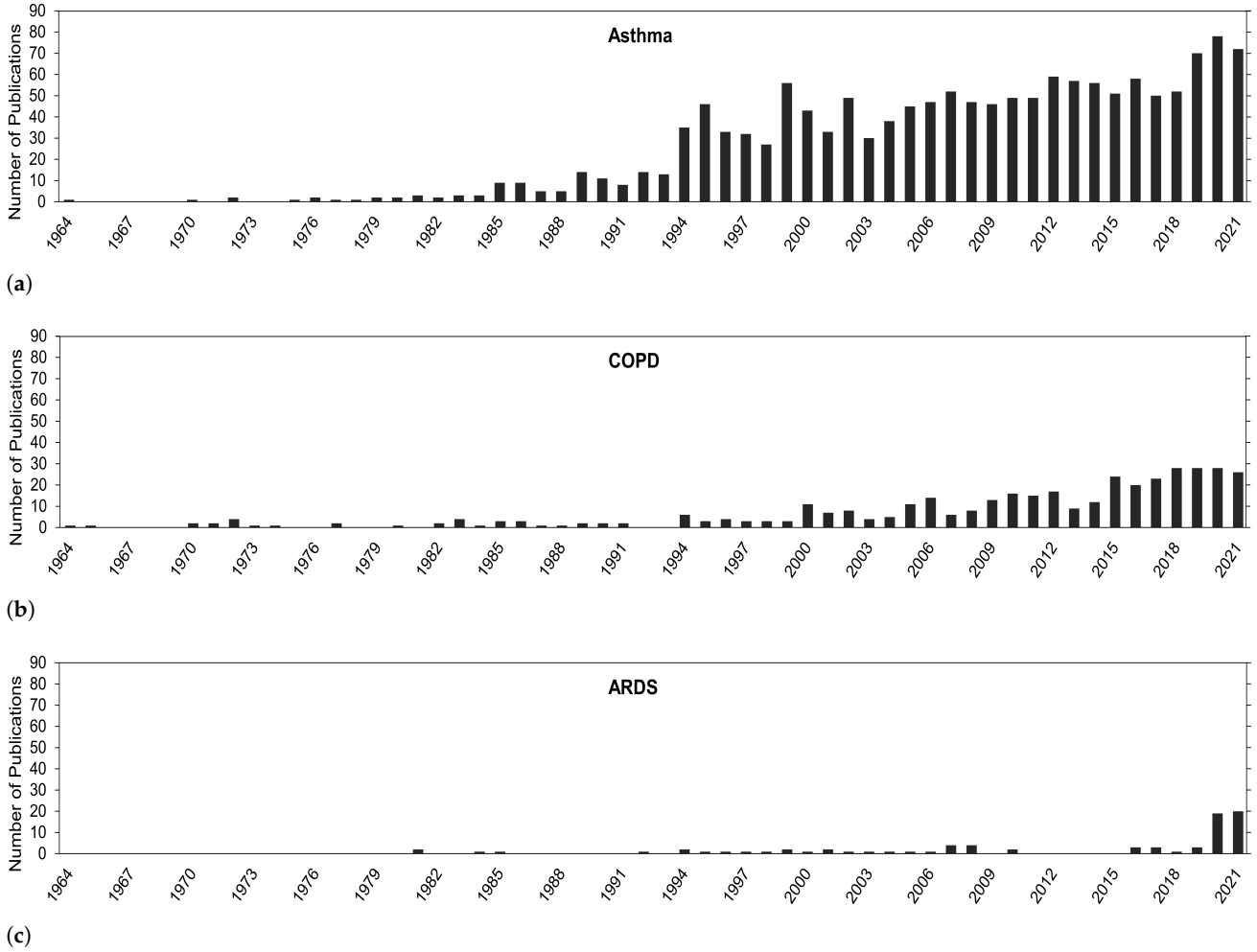

Figure 2. Number of publications for O_3 correlated with (**a**) asthma, (**b**) COPD, (**c**) and ARDS.

Despite the general increase in publications, the research on O_3 is lacking in comparison with other pollutants, as depicted in Figure 3. The use of O_3 is mostly for confounding hypothesis purposes in multi-pollutant models. Regardless, the overall trend is positive, and we expect to see more studies in this research field going forward.

Two forest plots were created to better understand if there is evidence that correlates O_3 with health deterioration, one for asthma seen in Figure 4 and another for COPD in Figure 5. To the right of the dotted line, values greater than 1 represent an increase in the risk of hospitalizations, emergency visits, or death due to the increase in O_3. The forest plots contain studies that show a significant association between O_3 and the respective health problem. Regarding asthma, 33 out of 40 studies have stated that O_3 presents a significant correlation. Similar results are observed for COPD with 14 out of 18 studies showing a significant correlation. In the case of ARDS, not shown in the plots due to small sample data, three out of four studies exhibit a significant association between O_3 and ARDS.

These plots demonstrate enough evidence to affirm that O_3 is responsible for health deterioration regarding asthma and COPD. This is in line with recent meta-analysis and shows that O_3 appears to play a non-negligible role in exacerbating these diseases [34,92].

In Figure 6, results are summarized by categorizing them as not significant, positively and negatively associated. Most of the studies in this review, 50 out of 59, show a positive significant increase in RR, HR, or OR for COPD, asthma and ARDS with the increase of O_3 concentrations. We make no statements if the studies made proper use of statistical procedures on the data presented. We reiterate that regardless of statistical procedure, the meaning of the statistics according to the data, or how it is presented, it still

demonstrates an association between an increase in harm to health caused by exposure to O_3.

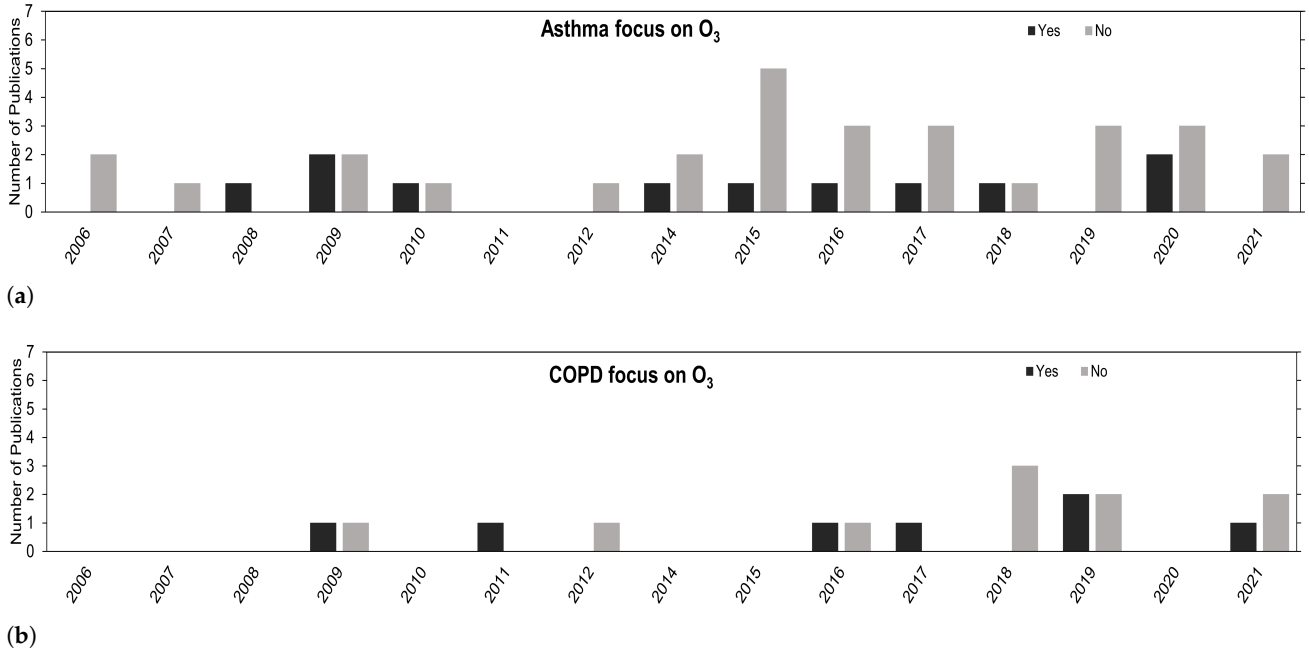

Figure 3. Number of publications over the years concerning (**a**) asthma and (**b**) COPD that have their focus on O_3 (Yes) or that focus on other air pollutants besides O_3 (No).

Most studies reveal significant increases in morbidity and mortality due to O_3. However, 11 studies report no significant association, and three studies report negative associations. Possible explanations would be datasets that are too small to make accurate statements or the fact that describing personal exposure to O_3 varies greatly depending on the type of exposure assessment, i.e., how many AQMS, satellites or type of chemical transport model used. This can range from high resolutions with low accuracy to low resolutions with high accuracy and every combination in between. Locality will always be a source of variability to overcome as we can never be completely sure that our data accurately represents the spatiotemporal exposure to pollutants perfectly, everywhere, and at all times [23,93]. Through this reasoning, Ling Ding et al. (2017) states that the difference in these results can be due to the spatial variation of chemical pollutants and delayed hospital visits in Chongqing [65]. In Zielisnki et al. (2018) the authors hypothesize that these dissonant results may be explicable by the nature of O_3 as a pollutant with a delayed secondary reactivity. A more in-depth explanation is given by Alves CA et al. (2010) which mentions that methyl ethers or esters in engine fuels are highly toxic, and closely related to alkyl nitritates. These are known to induce respiratory sensitivity in humans and could explain the paradoxical ozone associations. The existence of this nitrite pollutant that is rapidly destroyed by solar radiation is negatively correlated with O_3, possibly causing some discrepancies in results [46]. Despite the knowledge shared in these studies, and ultimately realizing that these issues vary from location to location, it was noticeable that O_3 was an afterthought in most other studies because no discussion was provided on why O_3 results have differed from current literature.

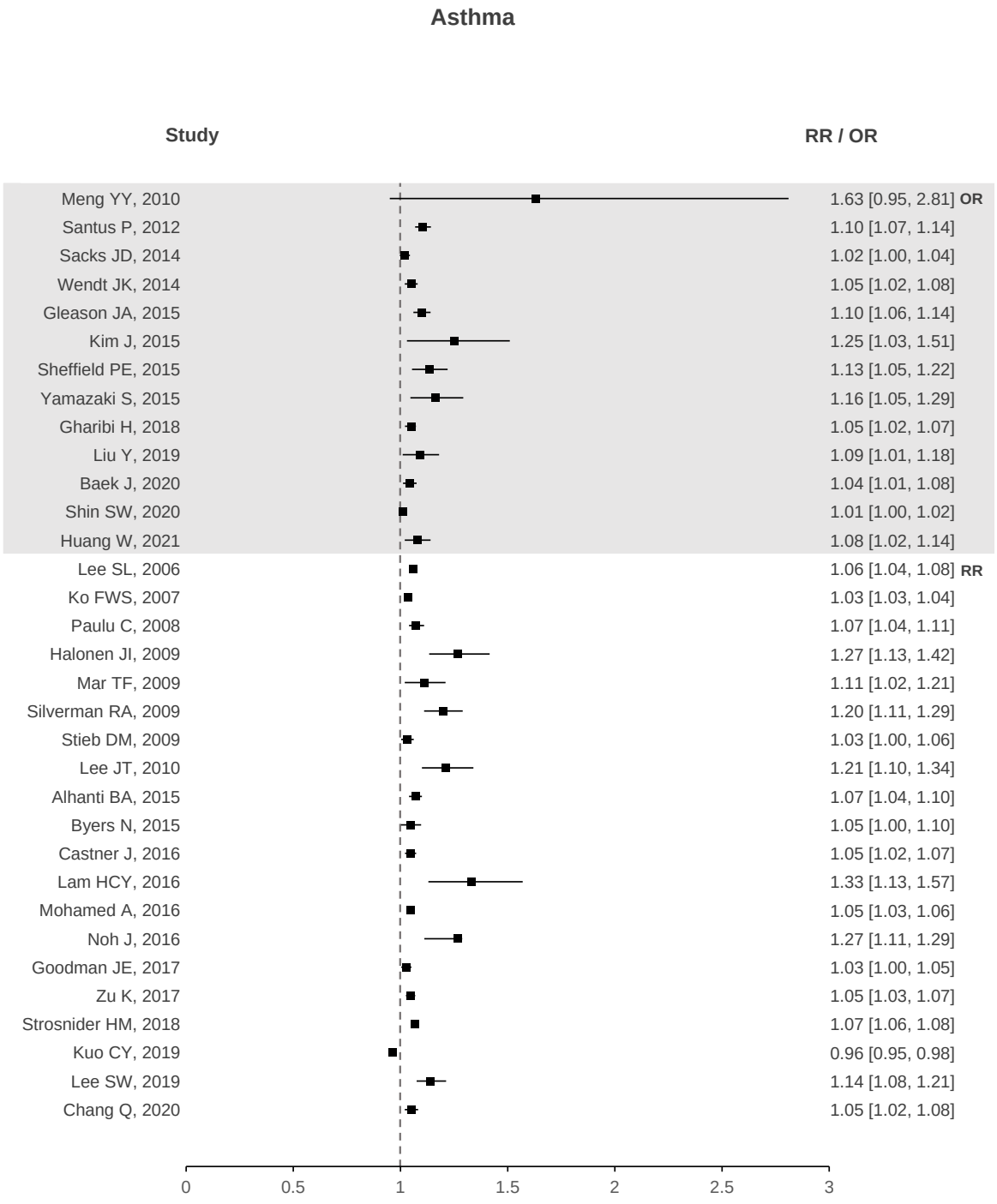

Figure 4. Asthma forest plots of O_3 increased risk results.

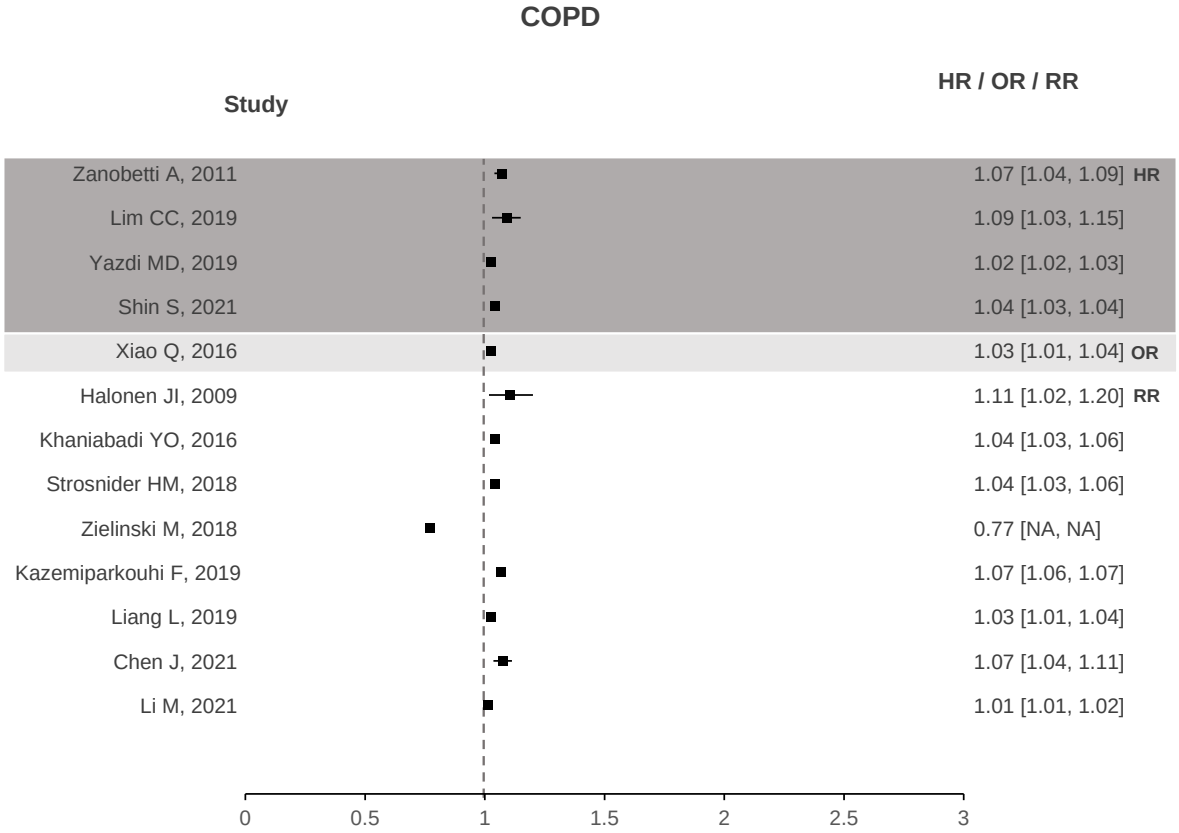

Figure 5. COPD forest plots of O_3 increased risk results.

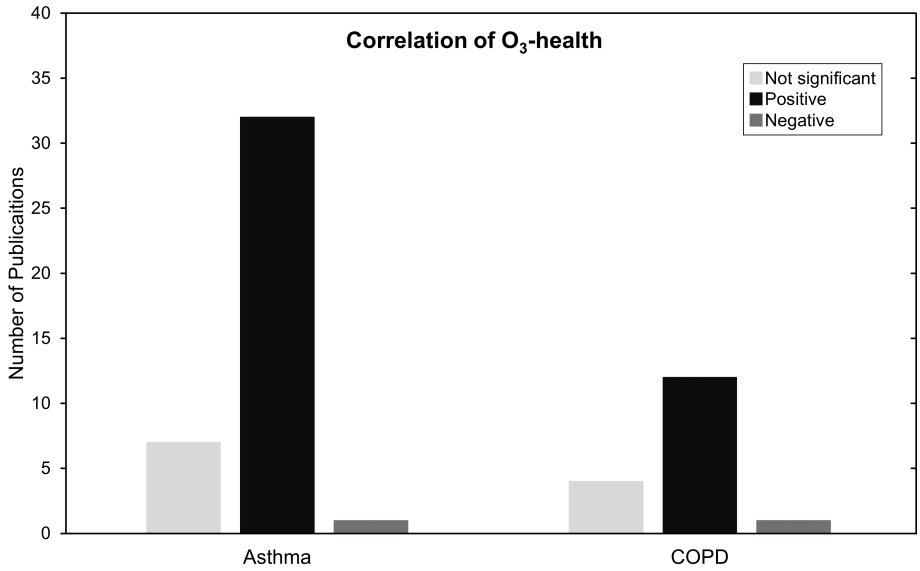

Figure 6. Summary of O_3 and asthma and COPD type of association. Negative, significant and not significant.

Table 2 contains an in-depth summary of the studies in this review. From these 59 studies, 27 datasets focused on hospital admissions, 20 on emergency department visits, eight on mortality, and 2 were observational studies. The remainder had datasets composed of combinations of these categories. There were 12 countries spanning three continents. They cover a total of 2630 locations which encompass states, counties, and cities. Although we cannot argue that these impacts are seen worldwide, the array of locations collected

point to nefarious O_3 effects being relatively widespread in considerably different cultural, topographic, and climacteric conditions.

One of the objectives was to try and understand where Portugal and Portuguese studies are situated in this research field. Unfortunately, there is a low amount of data in this scope. We decided to include four Portuguese studies that do not focus on a particular disease but instead look at respiratory diseases as a whole. In Strosnider et al., 2018 [72], it is said that defining respiratory diseases based on primary diagnosis and ICD-9 codes could potentially lead to misclassification; however, such misclassification would not affect the results for all respiratory diseases combined. Despite not being a full justification, the inclusion of these broader Portuguese studies serves to compare results regarding ozone and nefarious respiratory health impacts. The study conducted in Porto reported that an increase 10 $\mu g/m^3$ in the daily maximum 8-h moving average of O_3 is associated with a 1.015 (%CI 0.986–1.025) increase in respiratory mortality. In Lisbon, we have similar findings where an increase of the daily maximum 1-h average O_3 registered a RR of 1.048 for hospital admissions. The two remaining studies have either not reported their results, or found RR results to be not significant. Despite the low quantity of data regarding Portuguese studies, we could still argue that they are aligned with other studies in this review by looking at Table 2, and Figures 4 and 5.

Which age groups are the most affected? In Table 2, of the seven mortality studies, six were related to COPD, mainly affecting older people. In the HA and EV categories, 30 of 54 studies were related to asthma, affecting mainly younger people. By taking a closer look at the ages breakdown for the population most affected by these diseases, we refer to Figure 7. The most affected age group in the asthma category are adolescents, followed by children, or in other words, the population below the age of 18. Conversely, COPD seems to affect people above 65 years old (the elderly). For ARDS, its impacts affect almost anyone above 18 years old of age, but the sample is too relatively small to make factual statements.

Epidemiologically, asthma causes hyperresponsiveness and inflammation of the airways. Possible causes are genetic predispositions, differences in sex, medication exposure, or environmental risks factors such as O_3. Children and young adults are a vulnerable subpopulation to asthma due to their developing respiratory and immune systems. They spend more time outdoors and are usually more physically active, leading to higher ventilation rates and higher pollution exposures per body weight than adults [5,36]. The mechanisms by which O_3 contributes to harm may be related to affecting antioxidant activity, DNA repair, cell proliferation and apoptosis [9]. The elderly are also susceptible to harmful air pollution due to their vulnerable and waning respiratory system. This is aggravated by underlying health conditions. In Halonen et. al, 2009 [42], the author states that the irritating oxidative nature of O_3, readily reacts with compounds in the epithelial lining fluid in the airways. It is suggested that elderly people have decreased availability of antioxidants, and this may serve as an explanation for their reduced defense mechanisms against O_3 pollution. Lastly, ARDS causes difficulty in breathing as oxygen cannot enter the body. The negative contribution of pollutants damaging airways may exacerbate ARDS symptoms and cause health deterioration at all ages [64,94].

Next, to better understand seasonality we focused on studies that investigated and partitioned risk results by season. These data are summarized in Figure 8. For asthma, 23 studies analysed seasonality and 15 commented or presented their highest and most significant correlation during warm season. For COPD, all four studies that checked seasonality presented their highest most significant results in warm season. This is in line with current meta-analysis research [34,92] and can be explained by the proposed O_3 formation mechanism in the introduction section, especially by Equation (4). During the summertime, higher irradiation leads to favorable conditions for O_3 production, which exacerbates health impacts due to O_3 being available at higher concentrations in the air.

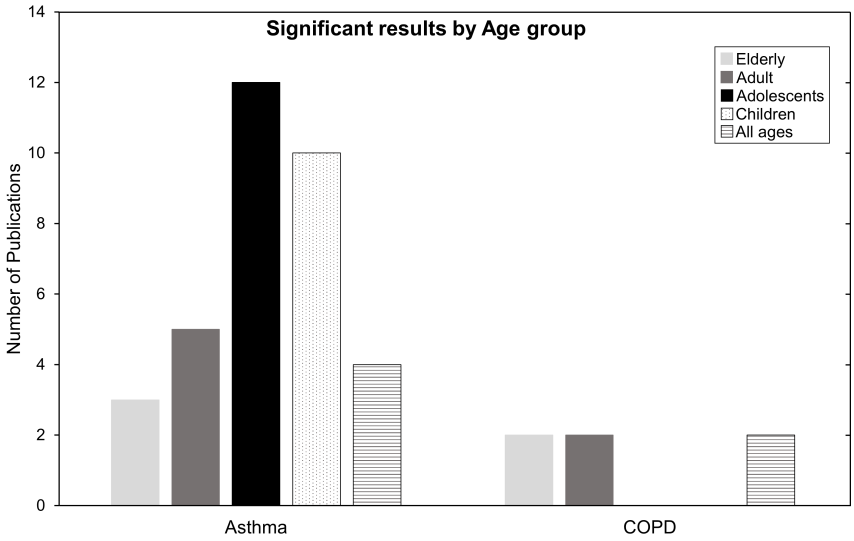

Figure 7. Number of publications categorized by age for Asthma and COPD. Children ages 0–12, adolescents ages 13–18, adults ages 19–64, and elderly ages 65+. Some publications have one or more age group and are therefore counted twice or more.

There are other possible explanations for this seasonality besides O_3 variation. Higher allergen concentrations in the air, or hot humid weather can cause the airways to narrow due to thermoregulatory functions, leading to symptoms similar to coughing, wheezing, or shortness of breath. Thermoregulatory responses which increase pulmonary ventilation and cardiac output might contribute to the observed increase in hospitalizations for respiratory infections. This is especially true for COPD as it is characterized by constant pulmonary and systemic inflammation [95,96].

Despite these explanations, four asthma studies presented high risk-related results in the cold season and another four found no association with season (Figure 8). A common explanation is the topographic variability between the locations in which these divergent seasonality results are obtained. In Qiu et al. (2018) [71] it is stated that Chengdu has a typical basin climate with characteristics of high humidity, static wind frequency and atmospheric stability subject to neutral weather in winter. This obstructs air pollutant transport and diffusion, form local circulation, and result in continuous heavy pollution weather, especially heavy PM accumulation. These topographic and climacteric conditions, as well as differences in health endpoints and modeling strategies, may contribute to this heterogeneity of findings [65,71].

Lastly, this review highlights some incongruities in exposure monitoring, with 17 of these studies not specifying how many AQMS were used to calculate O_3 exposure. The studies that fail to give this information, seen in Table 2, often mention the use of air-quality networks but do not specify how many AQMS were used. In rare occasions, a map of the network is provided, leaving the reader to interpret the AQMS quantity.

Seldom do studies specify when data were discarded. It is assumed in good faith that the data used had at least 75% valid points. Therefore, in 8 or 24 h of O_3 monitoring data, there are at least 6 or 18 h of valid data points, respectively, as per EPA guidelines [97]. Regardless, this should always be stated. Another issue that is open to interpretation is the type of 8-h measurements used and consequent calculations for the exposure assessment. Most studies use the daily maximum 8-h average; however, some make mention of the "maximum 8-h average", "highest 8-h average", "mean estimated 8-h average", or "daily 8-h maximum". Although some of these mean the same thing, some might not as the process is not extensively explained. This type of heterogeneity is unnecessary. The daily maximum 8-h average proposed by the EPA guidelines should be used [97]. An additional unnecessary divergence resides in the type of average O_3 time used, ranging from 1-, 8-, and 24-h maximums or averages. This can lead to disparities in the results. Three studies

in this review attempted to tackle this issue using different averaging times and comparing them. In Stieb et al., 2018 it is stated that associations of 8-h maximum ozone concentration with asthma and COPD visits were similar or smaller in magnitude than associations based on 24-h average concentration [45,64]. In the Xing Li et al. (2019) meta-analysis [34], significant and similar associations were found for O_3 1-h maximum and O_3 8-h maximum while marginal effects were identified for O_3 24-h average. Furthermore, other studies claim that 8-h averages show better sensitivity to actual maximum levels and provide better comparisons among AQMS [98].

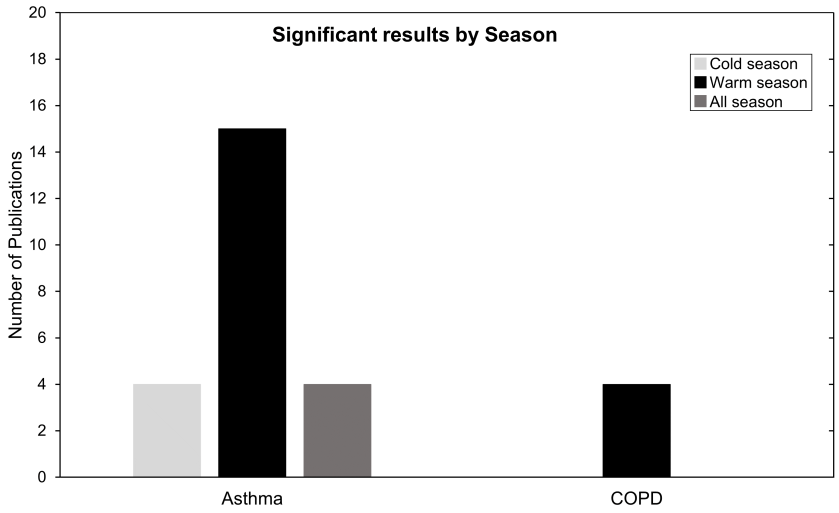

Figure 8. Number of publications categorized by season. Warm season (April until September) and cold season (October until March).

With respect to lag times, there is no standard approach and studies tend to test several different lag configurations and interpret the results. This is considered a non-problem because despite no particular care being taken on lag selection in this review, studies appeared not to vary significantly. The main takeaway in lag-related information seen in Table 2 was that fewer associations were found in day models [84]. This delayed effect of O_3 is recurrent, with most studies in this review reporting that lags between day 1 and day 3 are the most prevalent for the correlation of O_3 and health, yielding the strongest associations (Table 2).

It is noteworthy that 28 of the 59 studies used IQR as the risk-related increment. This leads to unnecessary heterogeneity making direct comparisons between results difficult. The IQR scaling type of analysis can be appropriate but can also have shortcomings when the index pollutant has high variability, and the co-pollutant does not. In those cases, the IQR hypothesis might not accurately depict the relationship between the two [99]. We are not fully assured why authors opted to use IQR-relative risk increments and if it made sense to use them according to their data. Nevertheless, homogenization should be sought by following the procedure stipulated by the Health Risks of Air Pollution in Europe (HRAPIE) report cited by the WHO [6]. This would make use of standardized risk-related increments of 10 ppb (20 $\mu g/m^3$) instead of IQR.

When addressing the short-term and long-term morbidity and mortality for asthma, COPD, and ARDS, it is apparent that the research is growing and evolving as our understanding of the correlation between air pollutants and health increases. Evidence suggests ozone has long-term health deterioration impacts in both asthma, COPD, and ARDS. In one of the most cited cohorts from Jerret et al. (2009) [13], it was demonstrated that an increase in O_3 concentration is associated with a significant increase in the risk of death from respiratory causes. Thus, we highlight some comments made by studies contained in this review that corroborate those statements. In Kazemiparkouhi et al. (2019) [74], there is strong evidence that O_3 exposure is associated with mortality from respiratory-related causes and

advises continued reevaluation of ambient pollution standards that are designed to protect the most vulnerable members of the population [86]. In Ware et al. (2016) the evidence points towards long-term O_3 exposure being associated with the development of ARDS in at-risk critically ill patients, particularly in trauma patients and current smokers. This O_3 exposure may represent a previously unrecognized environmental risk factor for ARDS [64]. Paulin et al. (2020) found that exposure to a higher concentration of 10-year historical ozone was associated with lower lung function, and more emphysema and air trapping on computerized tomography (CT) scan, even after accounting for smoking history. These findings support the role of ambient ozone exposure in COPD morbidity, the fourth leading cause of death in the United States, which is often attributed to tobacco exposure in developed countries [86]. However, there are still discrepancies that must be investigated, with a significant portion of studies not finding any associations. In Shin et al. (2021), it is argued that despite finding positive associations for incidences of COPD with exposures to air pollution, they did not obtain the same results for adult-onset asthma [91]. It is hard to make statements about the long-term impacts of O_3 because accurately depicting the personal exposure of a patient, or patients, is not technologically or logistically possible yet. We can understand how concentrations vary over an area, but to actually claim that this represents the patient personal exposure at all times, over a lifetime, is currently impossible. Therefore, continuous air-pollution monitoring is necessary.

5. Conclusions

This work aimed to historically review the relationship between ground-level ozone O_3 and health impacts, specifically respiratory diseases such as asthma, COPD, and ARDS. This review allows us to characterize current worldwide trends, compare them with Portuguese data, offer insight on possible shortcomings, and suggest improvements.

We will summarize the current body of research highlighted in this review by answering the proposed research questions:

RQ1: Is there research that correlates health deterioration with O_3? How has it been evolving throughout the years?

RQ2: If so, does this research show evidence of O_3 causing health deterioration?

RQ3: Is the evidence proven globally, or is it localized?

RQ4: Are there any Portuguese studies? How do they relate to existent studies elsewhere?

RQ5: According to the available evidence, which age groups are the most affected?

RQ6: How does seasonality impact O_3 and consequent health deterioration?

RQ7: Is the monitoring of the exposure to O_3 adequate? Where do we stand on studies regarding short-term and long-term morbidity and mortality for asthma and COPD?

RQ8: What are the research gaps and possible improvements?

This review states that:

RQ1: Yes, there is considerable research regarding asthma and COPD, but not ARDS. Asthma correlation with O_3 has the most publications, followed by COPD and ARDS. The number of publications in this field is trending upwards for all diseases, and it is expected to continue growing.

RQ2: Yes, in 64 datasets from 59 studies, 53 datasets have shown a significant statistical correlation between O_3 and health. Of these 53 correlations, 3 are negative associations. The remaining 50 are positive associations that correlate O_3 with health deterioration for all diseases in review.

RQ3: The studies in this review represent 12 countries, and while they span three continents and two of them are the largest economies in the world, USA and China, we cannot make the argument that these trends are worldwide, but we can attest they are relatively widespread.

RQ4: We found four Portuguese studies that investigate O_3-health correlations, but they are broader in nature. They investigate respiratory diseases as a whole, making it harder to pinpoint the exact effects of O_3 on morbidity and mortality for asthma, COPD or ARDS. Regardless, they still provide insight on O_3-health associations and seem aligned with worldwide trends in this review concerning respiratory diseases.

RQ5: For asthma, the most affected group by O_3 air pollution is people younger than 18. For COPD, the most affected group is the elderly above 65 years old. ARDS seems to affect anyone over 18, but the sample is too small to make finite arguments.

RQ6: Seasonality has been verified in this review. Roughly 70% of studies that checked for seasonality report summer as a period of particular concern and that it contributes to exacerbation of health deterioration. This follows the rationale that higher irradiation potentiates O_3 formation during the summer, creating conditions for higher concentrations of O_3 at ground level. For this same reason, several studies in this review have only used warm-season data. A clear example of this is seen in the four ARDS studies, which did not check for seasonality. Consequently, it is important to state that despite clear trends of summer seasonality, location can still play a crucial role and create conditions for divergent results in this regard. This was the case in four asthma studies that reported their most significant results during cold season.

RQ7: The exposure assessments are conducted with the best available data and is considered appropriate to characterize pollution concentrations over large areas. Unfortunately, current high resolutions accounting for AQMS, satellite, and chemical transport models remain limited and make it difficult to claim that it accurately describes people personal exposure, especially over a lifetime.

RQ8: Portuguese studies are lacking and should be encouraged. Greater precision and better data are now a possibility through the Portuguese open-source health database "*transparencia.sns.gov.pt*" created in 2016, and the continuous improvement of the QualAr air-monitoring network along with a newly installed H2020 Sharing Cities network. This review shows that current approaches provide evidence on the non-negligible role of ground-level O_3 on health deterioration but there is room for improvement. Increasing data collection by health institutions and applying denser AQMS networks will be paramount to better describe personal exposure and should help tackle long-term research. Suggested improvements for homogenization are: risk-related increments of 10 ppb should be used instead of IQR scaling; use of daily maximum 8-h averages whenever possible; and consistent reporting of how many AQMS, satellite and type of chemical transport models used. The topographic effect on concentrations and health deterioration should not be underestimated, and seasonality should always be checked.

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Abbreviations

The following abbreviations are used in this manuscript:

#	Number of data points
µ	Micron
APA	Portuguese Environment Agency
AQMS	Air-quality monitoring station
ARDS	Acute respiratory distress syndrome
Avg	Average
C	Celsius

CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computerized tomography
ED	Emergency department
EPA	European Environmental Agency
ER	Emergency room
EV	Emergency visits
g	Gram
HA	Hospital admissions
HO_2	Hydroperoxyl
HR	Hazard ratio
hv	light
ICD	International Classification of Diseases
ICEV	Internal combustion engine vehicle
ICU	Intensive care unit
IoT	Internet of things
IPCC	Intergovernmental Panel on Climate Change
IQR	Interquartile range
m	Meter
max	Maximum
NA	Not available
NAAQS	National Ambient Air-Quality Standards
NO	Nitrogen monoxide
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
NS	Not significant
°	Degree
O_3	Ground-level ozone
OR	Odds ratio
PM_{10}	Particulate matter
ppb	Parts per billion
ppbV	Parts per billion volume
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QualAr	Portuguese air-quality database
RQ	Research questions
RR	Relative risk
VOC	Volatile organic compounds
WE	Weekend effect
WHO	World Health Organization
wk	Week
yr	Year

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