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Review

Cardiovascular and Respiratory Health Effects of Fine Particulate Matters ($PM_{2.5}$): A Review on Time Series Studies

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Abstract: Ambient air pollution remains one of the most important risk factors for health outcomes. In recent years, there has been a growing number of research linking particulate matter (PM) exposure with adverse health effects, especially on cardiovascular and respiratory systems. The objective of this review is to examine the range and nature of studies on time series analysis of health outcomes affected by $PM_{2.5}$ across a broad research area. A literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping review framework through a strategic search of PubMed and ScienceDirect online databases for articles from January 2016 to January 2021. Articles were first screened by their titles and abstracts. Then two reviewers independently reviewed and evaluated the full text of the remaining articles for eligibility. Of the 407 potentially relevant studies, 138 articles were included for final analysis. There was an increasing trend in publications from 2016 to 2019 but a decreasing trend in the year 2020. Most studies were conducted in Eastern and South-Eastern Asia (69.6%), Europe and Northern America (14.5%) and Latin America and the Caribbean (8.7%), with the majority coming from high- and upper-middle-income countries (95.6%). The main methodology used was Generalized Additive Model (GAM) with Poisson distribution (74.6%). Morbidity was the most common health outcome studied (60.1%), with vulnerable groups (64.5%) often included. The association between $PM_{2.5}$ and health effects was stronger for respiratory diseases compared to cardiovascular diseases. In short-term studies (less than 7 years), respiratory diseases showed higher risks compared to cardiovascular. However, in long-term studies (7 years and more), cardiovascular showed higher risks.

Keywords: air pollution; $PM_{2.5}$; time series study; health effects; cardiovascular; respiratory

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1. Introduction

Air pollution, including gaseous pollutants, volatile organics and particulate matter (PM), is a leading environmental issue for our planet, ecosystems, and future. Human anthropogenic activities contribute to the release of gaseous pollutants and particles into the atmosphere, for example, in smog episodes which are generally caused by high concentrations of PM with an aerodynamic diameter of 2.5 µm or less ($PM_{2.5}$) [1]. Rapid development and urbanization globally are interconnected with air pollutants and climate change that have contributed to the global distribution of impacts and risks to both environment and human health [2]. Future trends of $PM_{2.5}$ and ozone pollutants emission across countries in Southeast Asia are predicted to be rising following the interaction of anthropogenic emissions with certain climate and meteorological conditions [3].

The pathogenicity of PM to cardiorespiratory systems is determined by their physical properties, such as size, composition, and solubility [4–6]. This is also influenced by the origins of PM, either natural and/or man-made, that differentiate the chemical properties such as water-soluble ions and inorganic and organic compounds [6,7]. Furthermore, their ability to produce reactive oxygen would trigger inflammation in cardiorespiratory and other targeted organs [8–10]. PM with an aerodynamic diameter smaller than 10 µm (PM_{10}) can be inhaled through the lungs and have impacts on human health. However, fine $PM_{2.5}$, with relatively smaller diameters than PM_{10}, can pass through the upper respiratory filtration, allowing the particles to reach the lower respiratory tract. $PM_{2.5}$ also has a larger surface area per concentration to carry toxic substances. It will then accumulate and diffuse in the alveolar and could be distributed to other parts of the body through air exchange and cause systemic damage [11].

Many epidemiological studies in various geographical areas of the world, including multi-city studies, have shown significant associations between air pollution and adverse effects on human health, particularly affecting cardiovascular and respiratory systems [12–14]. Human exposure to PM air pollutants induces alveolar inflammation, contributes to metabolic diseases, and increases the risk of cardiovascular diseases [15,16]. Furthermore, exposure to air pollutants will worsen the conditions for those with pre-existing chronic cardiovascular and respiratory diseases and make them more susceptible to respiratory infection [17,18]. Both short- and long-term human exposure to $PM_{2.5}$ raised the risk of cardiovascular and respiratory disease and mortality [19,20], and these associations were evidently shown in the earlier study of Harvard Six Cities that $PM_{2.5}$ is one of the causative factors of non-accidental deaths [21].

Following trends for global emission and air pollution distribution, studies of air pollution and health effects have been advanced from simple descriptive studies to epidemiological approaches and then to regression models. Epidemiological approaches contribute to a better understanding of pollutants and disease distribution and identifying the causal relationship. Regression analysis, on the other hand, allows interpolating, modeling, and predicting the effects of air pollution on health. A time series design is the commonly used regression model in assessing ambient air pollutant exposure and health effects over time, and this approach is more precise in risk estimation compared to other regression analyses [22,23].

Scoping reviews have already been used to observe a variability of health-related issues and are useful for looking into a broad and different scope of evidence. Globally, there have been varied changes in ambient pollution in the past two decades, with most cities showing rising levels of $PM_{2.5}$, especially in populous regions such as the Middle East, sub-Saharan Africa, and South Asia [24]. Existing reviews have systematically reviewed the literature from earlier years on the association between air pollution and health outcomes in broader topics [25–28]. However, reviews on time series analysis and specific health outcomes of cardiovascular and respiratory following exposure to $PM_{2.5}$ were less explored. To fill the gaps in the literature, we conducted a comprehensive scoping review of the literature with a focus on the particular topic of $PM_{2.5}$ air pollution and health effects related to cardiovascular and respiratory disease. The purposes of this review were as follows: (1) to examine the range and nature of studies on time series analysis design on health outcomes affected by $PM_{2.5}$ across the broad research area, (2) to summarize the publication characteristics, and (3) to identify the gaps and potential future research.

2. Materials and Methods

This review is part of an ongoing study on the cardiovascular and respiratory health impacts of $PM_{2.5}$ by the Institute for Medical Research, Ministry of Health Malaysia (NMRR-18-233-39743). It is being conducted to determine the distribution of published scientific articles on time series regression of $PM_{2.5}$ and health effects by geographic regions, with a focus on cardiovascular and respiratory disorders leading to hospital visits, admissions, and death. Our methodology framework was based on the 6 main steps of the scoping review, which include the process of linking the objectives and identified research questions, identifying and selecting relevant studies, charting data, collating and reporting results, and consulting with experts [29,30].

2.1. Stage 1: Identifying the Research Question

Although many studies had been conducted on air pollution, most were focused on PM_{10} and gaseous pollutants. Therefore, as mentioned above, this scoping review will concentrate on $PM_{2.5}$.

2.2. Stage 2: Identifying Relevant Studies

This review included primary research articles published in peer-reviewed journals. Only studies with relevant English-language articles conducted using time series design were included. This was to ensure that only articles with similar study designs were selected and compared. The following observational study designs were excluded: case-control, cohort, cross-sectional, panel (including randomized, crossover design), experimental, and case-crossover studies. Review papers such as systematic reviews, meta-analyses, scoping reviews, and critical reviews were also excluded, as well as conference proceedings and narrative reviews.

2.3. Stage 3: Study Selection

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for scoping review framework [29,30]. A search strategy was run on the 2 main available databases at the National Institute of Health (NIH) Malaysia, which were PubMed and Science Direct. The articles included primary epidemiological studies that utilized time series design. There were 3 important steps in identifying all relevant articles:

1. Search strategy for identifying only articles published in English. Keywords used Boolean operators (OR, AND) during the search process;
    - cardiovascular OR CVD, respiratory, cardiorespiratory, AND;
    - $PM_{2.5}$ OR particulate matter $_{2.5}$, AND;
    - time series.
2. All articles were restricted to those that have been published from January 2016 to January 2021 to limit the search to recent publications within the previous 5 years;
3. To avoid duplications and biases, the researchers reviewed together each of the articles to screen titles and abstracts from the databases for eligibility. In the next step, two reviewers independently reviewed and evaluated the full-text articles. Only primary research articles were evaluated to confirm inclusion based on the methodology used on the exposure and association assessment criteria.

2.4. Stage 4: Charting the Data

Data extracted from selected articles were entered into a database using MS Excel Spreadsheet and SPSS software ver. 22, so that the following relevant data could be recorded and charted as well as presented according to the variables of interest.

2.5. Stage 5: Collating, Reporting, and Summarizing the Results

Key information on the study characteristics that were charted during the review processes is listed below:

- Authors names;
- Year of publication;
- Duration and year of study;
- Study location by country and continent;
- Cardiovascular and respiratory diseases;
- International Statistical Classification of Diseases and Related Health Problems (ICD);
- Health endpoints (either mortality, hospital admissions, hospital visits, or emergency visits);
- Types of susceptible groups (either children, adults, the elderly, or not specified);
- The most frequent design used in time series analysis are the Generalized Additive Model (GAM), Generalized Linear Model (GLM), and Negative Binomial (NB);

- The descriptive of RRs associated with each disease.

Finally, the scoping review results were tabulated in order to find research gaps to either enable meaningful future research or obtain good pointers for policymaking.

2.6. Stage 6: Consultation with Experts

The authors of this study were priorly trained in scoping reviews by experts from Institute for Public Health Malaysia. The training provided guidance on scoping, systematic, and narrative review studies. The authors are also experts in the field of public health, environmental epidemiology and biostatistics.

3. Results

The first step in this review was searching for articles published in online databases, focusing on the effects of $PM_{2.5}$ on health. The search started in February 2021, using four different keyword combinations, of which a total of 407 potentially relevant articles were identified from the PubMed and Science Direct databases. A total of 140 articles were found to be duplicated and were then removed, leaving only 267 remaining articles. A total of 102 articles were omitted after screening through the titles and abstracts as they were not pertinent to the objective of the study, and 27 more articles were excluded after a full-text review for various reasons, bringing the total number of articles included in this scoping at 138 (Figure 1 and Table S1).

A total of 138 articles were included in this review on $PM_{2.5}$-related health effects for the 5-years period from January 2016 to January 2021 (Figure 2). The year 2019 had the largest count of articles published (*n* = 41), while the year 2016 had the lowest (*n* = 14), excluding the year 2021, which only contained the month of January. The selected time series studies of $PM_{2.5}$ on cardiovascular and respiratory health outcomes were published from almost all the geographic regions around the world. The majority of $PM_{2.5}$ time series and health effects studies selected were conducted in the Eastern and South-Eastern Asia region (69.6%), followed by Europe and Northern America (14.5%), and Latin America and the Caribbean (8.7%). Nine articles were published from other regions: Central & Southern Asia (*n* = 4), Northern Africa & Western Asia (*n* = 3), and Oceania (*n* = 2). One multi-country study was conducted in multiple regions on six continents; however, most of the cities were mainly located in East Asia, Europe, and North America, with a smaller number of cities in Latin America and Africa [31].

The included income groups are based on the World Bank Gross National Income (GNI) Economies, with about three-quarters of the human population currently living in countries defined as lower- or upper-middle-income economies [32]. We found that most of the studies (71.0%) have been conducted in upper-middle-income economies, mainly in Brazil, China, Colombia, Thailand, and Turkiye [Figure 3a]. This was followed by 34 (24.6%) articles from the high-income economies involving eleven countries. There were fewer selected articles from the lower-middle-income economies (3.6%), with only two countries involved (Iran and Vietnam). There was no published article on a time series study of $PM_{2.5}$ with cardiovascular and respiratory effects found for low-income economies.

Figure 3b provides the general characteristics of epidemiologic time series studies by country. China has the highest number (*n* = 83) of studies selected, which shows that epidemiologic studies of both acute and chronic effects of $PM_{2.5}$ have been well conducted there. This was followed by the United States and Brazil, with 10 published articles selected from each country. Four articles each were selected from Poland, South Korea, and Iran. There was minimal publication from other countries, with only one published article being included: Finland, Germany, Turkiye, Singapore, and Vietnam. While the majority of time series studies echoed the concerns of only a particular country, an article reported on the association of PM pollution with cardiovascular and respiratory mortality from 652 cities in 24 countries [31].

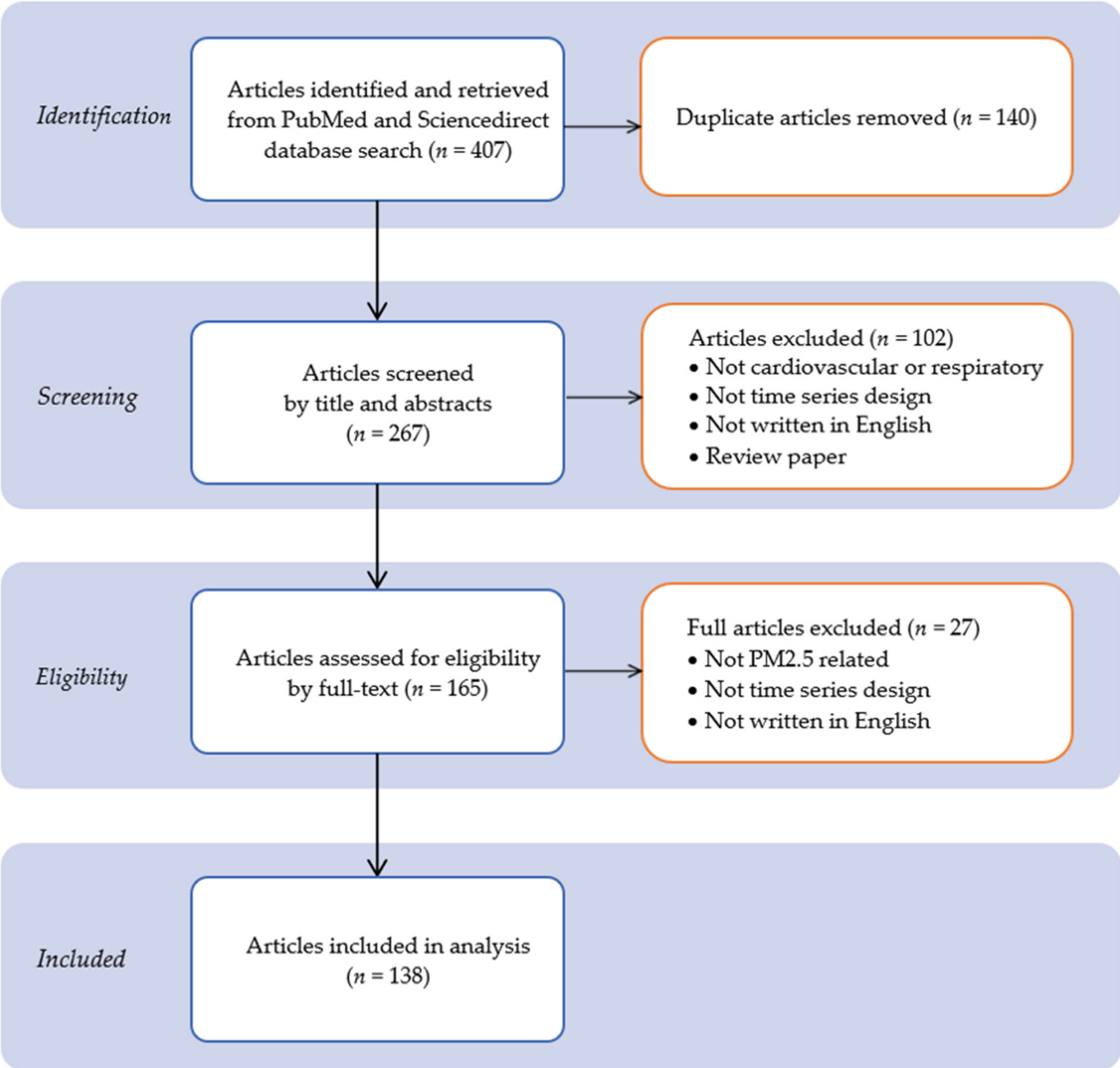

Figure 1. Flowchart for the article extraction process of time series studies on $PM_{2.5}$ and health effects.

Studies on time series of $PM_{2.5}$ with cardiovascular and respiratory health effects were interdisciplinary research areas and published in various international journals. More than half of the articles (63.8%) were frequently published in these top 9 journals (Figure 4). The Environmental Science and Pollution Research (ESPR) cumulatively published the highest number of related articles in the 5 years from 2016 to 2021 (n = 21), followed by the International Journal of Environmental Research and Public Health (IJERPH; n = 15) and Science of the Total Environment (STOTEN; n = 14). Other frequently published journals were on the multi-disciplinary application between the environment and health, including the BMC Public Health, Ecotoxicology and Environmental Safety, Environmental Health Perspectives (EHP), Chemosphere, and Environmental Research. The rest of the articles were published less frequently in another 38 journals that focused on environmental sciences (i.e., pollution and toxicology, hygiene, and safety) and health (i.e., public health, medical and clinical).

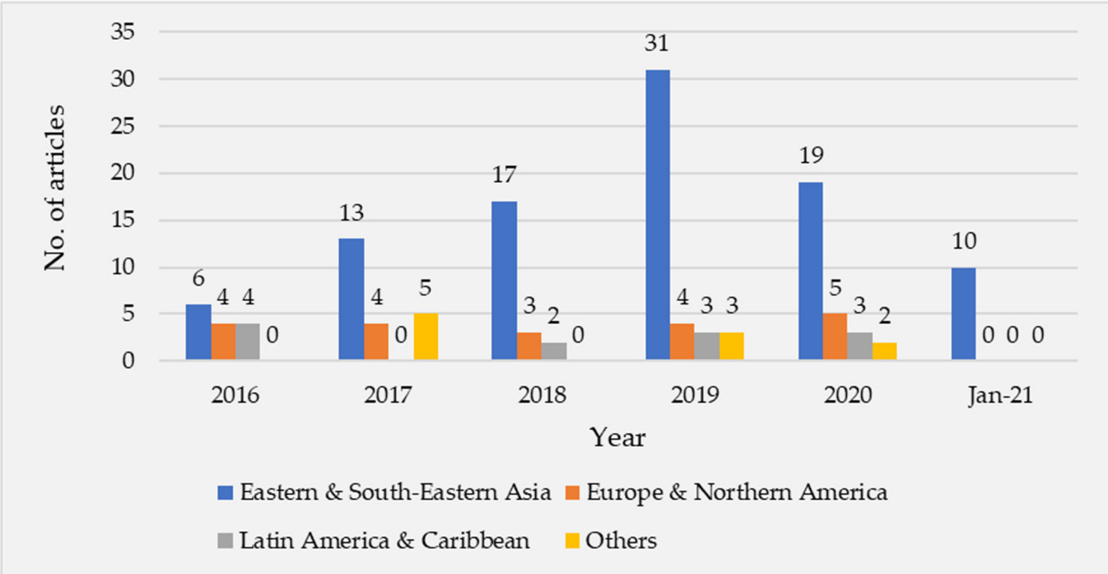

Figure 2. Distribution of time series studies of $PM_{2.5}$ with cardiovascular and respiratory health effects by geographic regions.

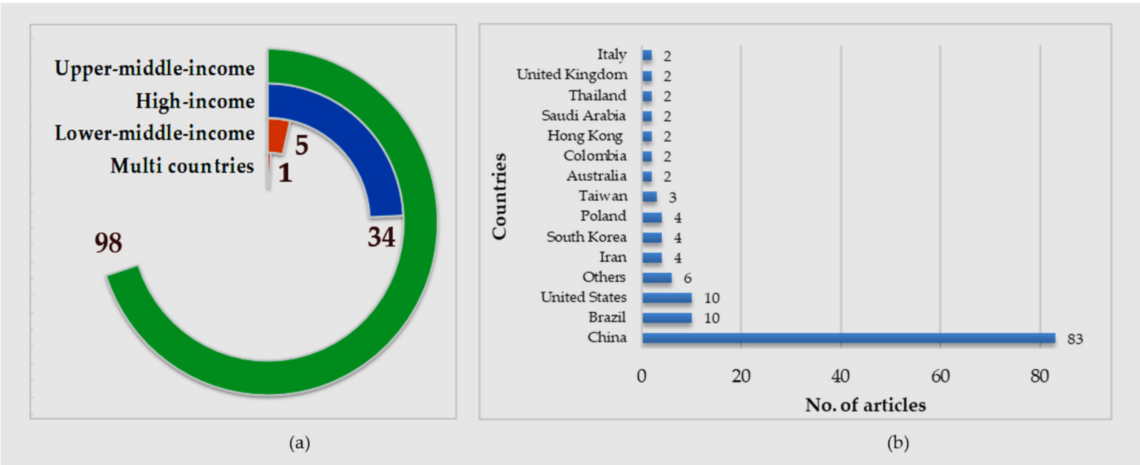

Figure 3. Frequency of time series studies of $PM_{2.5}$ with health effects by (**a**) income groups and (**b**) countries. Notes: Based on GNI per capita in USD by the World Bank Gross National Income (GNI) Economies [31]: High-income > 12,695, Upper-middle income = 4096–12,695, Lower-middle income = 1046–4095.

Time series studies require a group of data observations over an interval of time, and longer exposure to $PM_{2.5}$ of more than 12 months is expected to have cumulative cardiovascular and respiratory health effects. There were six time series studies conducted for a minimum period of 1 year, while there was only one study conducted for the maximum duration of 30 years (Table 1). However, we reviewed the relation of climate change detection based on meteorological time series data, and a study on visual analytics indicated that 7 years of duration would show notable and consistent warming tendencies [33]. Our review showed more than three-quarters of studies (80.4%) had analyzed $PM_{2.5}$ effects on cardiovascular and respiratory health outcomes by collecting data for less than 7 years (Table 1).

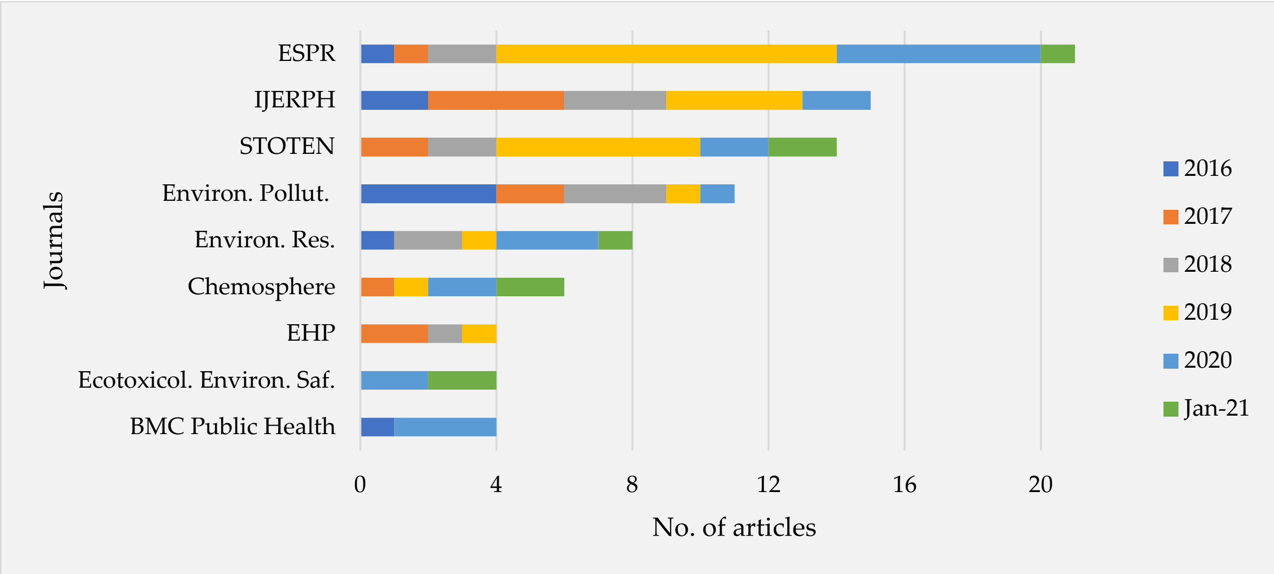

Figure 4. Main journals for selected articles on time series study of $PM_{2.5}$ with cardiovascular and respiratory health effects from January 2016 to January 2021. Notes: ESPR = Environmental Science and Pollution Research, IJERPH = International Journal of Environmental Research and Public Health, STOTEN = Science of the Total Environment, Environ. Res. = Environmental Research, Environ. Pollut. = Environmental Pollution, EHP = Environmental Health Perspectives, Ecotoxicol. Environ. Saf. = Ecotoxicology and Environmental Safety, BMC = BioMed Central.

Table 1. Methodology for time series studies of $PM_{2.5}$ and health effects.

Categories	N (%)
Study duration	
Less than 7 years	111 (80.4)
7 years and more	27 (19.6)
Type of time series analysis	
GAM and Poisson	103 (74.6)
GLM and Poisson	24 (17.4)
Negative Binomial	2 (1.4)
Others	9 (6.5)
ICD codes	
ICD-10	98 (71.0)
ICD-9	11 (8.0)
Both ICD	5 (3.6)
No classification	24 (17.4)

A widely used approach for time-series analysis of air pollution and health involves a semi-parametric Poisson regression with daily mortality or morbidity counts as the outcome [34]. There are two main approaches commonly used to estimate the effects associated with exposure to air pollution while accounting for smooth fluctuations in mortality that confound estimates of the effects of air pollution. One is the semi-parametric Poisson regression comprised of a Generalized Linear Model (GLM) with parametric splines, for example, natural cubic splines [35]. The other is the Generalized Additive Model (GAM) with nonparametric splines such as smoothing splines or locally weighted smoothers [36]. The GAM with Poisson regression was the main statistical methodology (74.6%) used in the analysis of selected articles, followed by the GLM and Poisson (17.4%). The estimation procedure in both analyses requires iterative approximations to find the optimal estimates. The difference is that the GLM emphasizes estimation and inference for the parameters of the model, while the GAM focuses on exploring the relationship between the dependent variable and the independent variables through visualization techniques.

The other time series methodologies were less explored in establishing the relationship. Only two studies used the Negative Binomial analysis. At the same time, nine other studies used different time series methodologies, such as the Bayesian Hierarchical Model, Inverse Probability Weighting, and Generalized Estimating Equation (GEE). These methods were not popularly used in regression time series studies, especially in finding the risk estimates of air pollution.

The ICD description of the 10th Revision (ICD-10) and/or the 9th Revision (ICD-9) was used in the majority (*n* = 114) of the studies. The ICD-10 (71.0%) was mostly utilized to classify cardiovascular and respiratory diseases compared to the ICD-9 (8.0%). The ICD-10 and ICD-9 codes for overall cardiovascular diseases known as circulatory system diseases are I00–I99 and 390–459, respectively. Fifty-seven percent of studies on this topic were conducted using these codes. The remaining were conducted on various specific cardiovascular diseases such as ischemic heart disease (IHD; ICD-10: I20–I25; ICD-9: 410–414), cerebral vascular disease (ICD-10: I60–I69) and Acute Myocardial Infarction (AMI; I20–I22) and congestive heart failure (ICD-9: 429). As for overall respiratory diseases, J00–J99 and 460–519 are the ICD-10 and ICD-9 codes, respectively, of the disease. More studies were conducted on specific ICD-10 or ICD-9 codes such as pneumonia (ICD-10: J00–J18; ICD-9: 480–488), asthma (ICD-10: J45–J46; ICD-9: 493), chronic obstructive pulmonary disease (COPD; ICD-10: J40–J44; ICD-9: 491–492), acute upper respiratory infection (AURI) (J00–J06), acute lower respiratory infection (ALRI; J20–J22), and rhinitis (J31). Less than five percent of the studies utilized the combinations of both ICDs. The remaining 24 studies used general classification based on symptom (i.e., wheezing) or diagnosis (i.e., asthma, chest infection, myocardial infarction, congestive heart failure, ischemic stroke, etc.).

The majority of the studies (64.5%) looked at specific age groups, namely children and the elderly, who were the most vulnerable (Table 2). The children's age group ranged from ages 0 to 18 years old. While most of the studies utilized 65 years old and above as the elderly group, others did not specify the cut-off point of age that they used. We found that single health outcomes of cardiovascular and respiratory in relation to $PM_{2.5}$ were commonly used (71.7%) as compared to combined health outcomes (29.3%). The most commonly used health outcomes were clinic/or ED visits (30.4%), followed by mortality only (29.7%) and hospital admissions only (29.7%). While fewer studies investigated the combined health outcomes (10.1%), the combination of admissions and clinic/or ED visits were conducted frequently (10 studies) as compared to other combinations. Nearly half (44.8%) of studies conducted among the elderly (only) were investigating the mortality outcomes. All studies among children (only) looked into morbidity outcomes of clinic or ED visits (64.7%) and admission (35.3%).

Table 2. Time series study of $PM_{2.5}$ and health effects based on age groups vulnerability.

Outcomes	**Children (Only) (*n* = 17)**	**Elderly (Only) (*n* = 58)**	**Children & Elderly (*n* = 14)**	**All Ages (*n* = 49)**
Health outcomes				
Mortality	0	26	0	15
Hospital admission	6	16	6	13
Clinic or ED visits	11	11	6	14
Combined	0	5	2	7
Disease				
Cardiovascular	0	21	1	15
Respiratory	17	18	8	19
Combined	0	19	5	15

From the 138 studies, nearly half (44.9%) focused solely on respiratory disease, and 39 (28.3%) were on the combination of both cardiovascular and respiratory diseases (Table 2). While the study on cardiovascular disease only made up the remaining (26.8%). All studies conducted among children (only) explored respiratory disease outcomes. At the same time, studies on cardiovascular, respiratory, and both disease outcomes were well distributed in the elderly (only) and all age groups.

Long-term time series studies of 7 years and more were frequently conducted in Europe & Northern America (44.4%) and Eastern & South-Eastern Asia (33.3%) compared to other regions (Table 3). The United States conducted most of the studies (*n* = 9), followed by China (*n* = 4), and two studies in each Australia and South Korea. Most of the long-term studies (40.7%) investigated both cardiovascular and respiratory diseases. However, studies on single health effects of cardiovascular disease (n = 10) were higher compared to respiratory disease (*n* = 6). More than half of long-term studies explored the vulnerable groups, with 11 studies observing the association between younger and older age groups and seven studies on gender. Only one study reported the findings on the association between poverty with $PM_{2.5}$ and respiratory hospital admissions.

The summary statistics of relative risks (RRs) reported by types of diseases are mainly the average of mean, quartiles, minimum and maximum values from all the selected articles (Table 4). The reported statistics of RRs by diseases are useful in estimating the burden of the disease and are tabulated by the duration of the study (short-term and long-term durations). Studies with less than 7 years' duration were classified as short-term, while studies lasting longer than or equal to 7 years were classified as long-term. In short-term studies, respiratory diseases showed higher RRs in mainly all the statistics compared to cardiovascular. However, in long-term studies, cardiovascular showed higher RRs. Smaller standard deviations in long-term duration for both diseases showed better precision estimates.

Table 3. Highlights of long-term time series studies (≥7 years) on $PM_{2.5}$ and health effects (*n* = 27).

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Eastern & South-Eastern Asia						
Chai et al., 2019 [37]	Lanzhou, China	10 years (2007–2016)	Hospital visits	RD (ICD-10: J00–J99)	• $PM_{2.5}$ concentrations were associated with an increase in the daily outpatient visits for RD. • A lag effect was observed, and this effect was the strongest on day 1. With each 10 μg/m^3 increase in $PM_{2.5}$, the daily outpatient visits for respiratory diseases increased by 0.53% (95% CI: 0.22–0.84%).	Each 10-μg/m^3 increase in $PM_{2.5}$ had a cumulative effect on RD visits • Age: Children aged ≤ 18 years showed maximum on day 14 (RR = 1.0213, 95% CI: 1.0128–1.0299). • Gender: Risk changes in males RR = 1.0053 (95% CI: 1.0022–1.0085) and females RR = 1.0053 (95% CI: 1.0020–1.0086)
Chen et al., 2021 [38]	Nanjing, China	16 years (2004–2019	Hospital admission	CVD (ICD-10: I00–I99), IHD (ICD-10: I20–I25), and CBVD (ICD-10: I60–I69).	Cumulative effect estimates for $PM_{2.5}$ on IHD mortality were elevated and statistically significant within 27 (2.11%; 95% CI: 0.12–.27%) and 22 (2.63%; 95% CI: 0.39–4.91%) days	• NA
Xu et al., 2019 [39]	Heifei, China	11 years (2007–2016)	Mortality	CVD (ICD-10: I00–I99), IHD (ICD-10: I20–I25), and CBVD (ICD-10: I60–I69)	• CVD deaths are significantly higher with seasonal changes during winter compared to summer. • Greatest impact for $PM_{2.5}$ was at lag 1 with ER of 0.84% (95% CI: 0.04–1.65%) and lag 0–5 with 3.14% (95% CI: 0.03–6.36%).	• Gender: Females suffered more adverse effects of $PM_{2.5}$, ER = 5.06% (95% CI 0.03–10.34%) at lag 0–5. • Age: $PM_{2.5}$ increased risk of CVD mortality on age < 65 years ER = 15.18% (95% CI: 2.31–29.66%) at lag 0–7.

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Lin et al., 2016 [40]	Hong Kong	14 years (1998–2011)	Mortality	RD (ICD-10: J00–J99)	A positive but non-significant synergistic interaction between daily mean and variation on RD and pneumonia mortality	• NA
Lin et al., 2017 [41]	Hong Kong	11 years (2001–2011)	Mortality	CVD (ICD-9: 390–459 or ICD-10: I00–I99) RD (ICD-9: 460–519 or ICD-10: J00–J99)	$PM_{2.5}$ was significantly associated with mortality; the highest increase in daily mean $PM_{2.5}$ at lag03 corresponded to ER of 2.77% (95% CI: 1.50–4.05%) increase in CVD mortality and 2.07% (95% CI: 0.49–3.67%) increase in RD mortality.	• NA
Yap et al., 2019 [42]	Singapore	13 years (2001–2013)	Mortality	CVD (ICD-9390–459) and (ICD-10 I00–I99) Non-accidental deaths (ICD-9000–799) and (ICD-10: A00–R99)	An increase of 10 μg/m^3 in $PM_{2.5}$ was associated with significant increases in non-accidental mortality ER: 0.660%; 95% CI: 0.204–1.118%) and CVD mortality (ER: 0.883%; 95% CI: 0.121–1.621%).	• Elderly: significant CVD mortality in elderly ≥65 years but not in those <65 years were seen in the acute phase of lag 0–5 days. However, the effects turned protective at a cumulative lag of 30 days.
Kwon et al., 2019 [43]	Seoul, South Korea	9 years (2007–2015)	Hospital admission	CVD: Atrial fibrillation (AF) and a primary diagnosis of CVD (ICD-10: I00–I99),	A 10-μg/m^3 increase in ambient $PM_{2.5}$ showed significantly increased admissions RR = 1.045; (95% CI: 1.002–1.089) at lag 3	• Gender: Effects of $PM_{2.5}$ was prominent in men (1.08; 95% CI: 1.02–1.14) at lag 3 • Age: Non-elderly aged <65 years (RR = 1.11; 95% CI: 1.04–1.20)

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Oh et al., 2020 [44]	South Korea (seven metropolitan cities)	8 years (2008–2016)	Hospital admission	ALRI	A 10 μg/m^3 increase in the 7-day moving average of $PM_{2.5}$ was associated with a 1.20% (95% CI: 0.71–1.71) increase in ALRI hospitalization	• Age: Study conducted among children aged 0–5 years • Gender: Association $PM_{2.5}$ with ALRI admission higher in boys (1.31%, 95% CI: 0.75–1.86) compared to girls (1.02%, 95% CI: 0.45–1.58)
Qiu et al., 2020 [45]	Taipei, Taiwan	8 years (2010–2017)	Hospital admission	RD (ICD-10: J00–J99), pneumonia (ICD-10: J12–J18), COPD (ICD-10: J40–J44), asthma (ICD-10: J45–J46)	A strong association of $PM_{2.5}$ with all-RD and asthma admissions; percentage change for RD in association with an IQR increased at different lags (Lag02 and Lag03)	• NA
Oceania						
Guo et al., 2020 [46]	Hazelwood, Australia	7 years (2009–2015)	EDV and hospital admission	CVD (ICD-10: I00–I99); CBVD (ICD-10: I61–I69), IHD (I ICD-10: 20–I25) RD (ICD-10: J00–J99); COPD (J41–J44), asthma (J45–J46).	• For each 10 mg/m^3 increase of $PM_{2.5}$ in lag (0–7) days, the risk of ED visit was significantly increased by 14% for RD, 22% for COPD with asthma, and 39% for COPD alone. • Risk of admissions was significantly increased by 28% for COPD and asthma	• NA

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Salimi et al., 2017 [47]	Sydney, Australia	11 years (2004–2015)	EAD	RD & CVD: breathing problems, chest pain, cardiac or respiratory arrest, and death, stroke or CBVD	• Each increase of 10 μg/m^3 in $PM_{2.5}$ were positively associated with same-day EAD for breathing problems (RR = 1.03, 95% CI: 1.02–1.04), arrest (RR = 1.03, 95% CI: 1.00–1.06), chest pain (RR = 1.01 CI: 1.00–1.02)	• NA
Europe & Northern America						
Strosnider et al., 2019 [48]	United States (17 states)	15 years (2000–2014)	EDV	RD (ICD-9: 460–519)	• Each 10-mg/m^3 increase in $PM_{2.5}$ on Lag (0–6) increased the risk for RD; RR = 1.020 (CI: 1.017–1.023).	• Children: RRs between all RD and $PM_{2.5}$ was higher among children than adults
Krall et al., 2017 [49]	United States (Atlanta, Birmingham, St. Louis, Dallas)	11 years (1999–2009)	EDV	RD: pneumonia (ICD-9: 480–486), COPD (ICD-9: 491, 492, 496), URI (ICD-9: 460–465, 466.0, 477), and asthma and/or wheeze (ICD-9: 493, 786.07)	• The associations for $PM_{2.5}$ with RD visits were frequently positive and significant across cities, but the lag of greatest association varied between cities • An IQR increase in lag 2 for $PM_{2.5}$ associated with increased risk (RR) 1.006 (95% CI: 1.003–1.010) in Atlanta, 1.008 (95% CI: 0.996–1.019) in Birmingham, 1.007 (95% CI: 0.999–1.016) in St. Louis, 1.001 (95% CI: 0.989–1.013) in Dallas	• NA

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Ye et al., 2018 [50]	Atlanta, United States	16 years (1998–2013)	EDV	CVD: IHD (ICD-9: 410–414), cardiac dysrhythmias (ICD-9: 427), CHF (ICD-9: 428), or CBVD (ICD-9: 433–437, 443–445, 451–453).	• RR for CVD was positive for $PM_{2.5}$ exposure [RR 1.0112 (95% CI: 0.990–1.0214)] • RR for CVD was also positive for $PM_{2.5}$ components (OC, EC, NO_3, Si, Ca, Fe, Zn, and water-soluble Fe)	• NA
Ebisu et al., 2019 [51]	California, United States	8 years (2002–2009)	Hospital admission	CVD: (ICD-9: 390–459) RD: (ICD-9: 460–519)	Exposure to an increase in $PM_{2.5}$ vehicular emissions associated with increased risk for CVD admission and RD hospitalizations in specific groups	Each IQR increase in $PM_{2.5}$ emissions is associated with: • Age: Elderly (≥65 years) increased risk of CVD admission 1.32% (95% CI: 0.16–2.49) at lag 0 • Children: increased risk of RD hospitalizations (0–18 years) 3.58% (95% CI: 0.90–6.33) at lag 2
Blomberg et al., 2019 [52]	United States (108 cities)	14 years (1999–2013)	Mortality	CVD (ICD-10: I01–I59) RD (ICD-10: J00–J99)	• A 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 2.97% (95% CI: 2.16–3.79) increase in CVD mortality in the spring, as compared with a 1.26% (95% CI: 0.57–1.95) increase in the fall. • RD mortality was found to have higher estimates of risk compared to CVD across all seasons.	• NA

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Hsu et al., 2017 [53]	New York, United States	16 years (1991–2006)	Hospital admission	CVD: CRHD (ICD-9: 393–396), hypertension (401–405), IHD (410–414), cardiac dysrhythmias (427), heart failure (428), and other CVD (430–434, 436–438)	• $PM_{2.5}$ was positively associated with CVD hospitalizations; each 10-µg/m^3 increment in $PM_{2.5}$ concentration accounted for a 1.37% increase in CVD (95% CI: 0.90%–1.84%) • $PM_{2.5}$ effect was strongest in winter, with an additional 2.06% (95% CI: 1.33–2.80%) increase in CVD.	• NA
Bi et al., 2020 [54]	Los Angeles, United States	12 years (2005–2016)	EDV and hospital admission	CVD (ICD-10: I20–I79) RD (ICD-10: J45–J46)	• In 2013–2016, the risk of CVD in ED visits associated with a 10 g/m^3 rise in 4-day $PM_{2.5}$ (lag 0–3) was greater (RR = 1.020, 95% CI: 1.010–1.030) compared to 2005–2008 (RR = 1.003, 95% CI: 0.996–1.010) • Risk estimates for asthma were higher in 2005–2008 (RR = 1.018, 95% CI: 1.006–1.029) but decreased in the following decades	• Specific age groups

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Qiu et al., 2020 [55]	New England, United States	13 years (2000–2012)	Hospital admission	CVD specific on AMI, CHF and IS	• Each 10 μg/m^3 increase in lag0–lag5 cumulative $PM_{2.5}$ exposure on average increased admissions rate by 4.3% (95% CI: 2.2–6.4%) AMI, 3.9% (95% CI: 2.4–5.5%) CHF, 2.6% (95% CI: 0.4–4.7%) IS	Each 10 μg/m^3 increase in $PM_{2.5}$ associated with: • Gender: Females had a higher risk of CHF admissions than males (p = 0.040) • Comorbidity: Diabetic elderly had higher risks of AMI admissions compared to non-diabetic (p = 0.010)
Yitshak-Sade et al., 2018 [56]	New England, United States	11 years (2001–2011)	Hospital admission	CVD (ICD 9: 390–429) or ischemic stroke (ICD 9: 432–435) RD (ICD 9: 460–519)	• An IQR (2.3 μg/m^3) increase of $PM_{2.5}$ exposure increased admissions by 4.09% (95% CI: 3.31–4.87) for RD and 6.58% (95% CI: 5.90–7.26) for CVD • Effect of $PM_{2.5}$ exposure on CVD admissions was stronger on colder days (0.56%, 95% CI: 0.21–0.91) compared to hotter days (−0.30%, 95% CI: −0.57–−0.03; p < 0.001)	• Elderly (≥65 years)

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Pearce et al., 2018 [57]	South Carolina, United States	12 years (2002–2013)	EDV and hospital admission	CVD: URI (ICD-9: 460–466, 477; CHF (ICD-9: 428); IHD (ICD-9: 410–414) RD: Asthma (ICD-9: 493, 786.07)	• A significant positive association between asthma with $PM_{2.5}$ (lag 2, 3), with the largest RR of 1.8% (95% CI: = 1.1–2.2%). • $PM_{2.5}$ was also significant with URI and IHD but not for CHF.	• NA
Solimini and Renzi, 2017 [58]	Rome, Italy	14 years (2001–2014)	EDV	Atrial fibrillation (AF) with ICD-9: 427.31	• For each 10 $\mu g/m^3$ increase of $PM_{2.5}$ at lag 0–1 day, the effect estimates for AF was 2.95%; 95% CI: 1.35–4.67%) at immediate lags, and 3.43%; 95% CI: 0.42–6.66% for extended lag	• Age: Elderly ≥75 years showed the percent increase in the risk of AF admission per 10 $\mu g/m^3$ increase of $PM_{2.5}$ was 5.01% (95% CI: 2.59–7.74) • Gender: significant association between $PM_{2.5}$, EDV for AF, and females was at immediate lag (3.51%; 95% CI: 1.29–5.90%).
Kuźma et al., 2020 [59]	Bialystok, Poland	10 years (2008–2017)	Mortality	CVD (ICD-10: I01–I59)	• $PM_{2.5}$ was discovered to have no effect on CVD daily mortality, except for the subgroup (males)	• Gender: Each 10-$\mu g/m^3$ increased of $PM_{2.5}$ increased risk for CVD mortality in males; RR = 1.07 (95% CI: 1.02–1.12); p = 0.01

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Kollanus et al., 2016 [60]	Helsinki, Finland	10 years (2001–2010)	Hospital admission and mortality	CVD (ICD-10: I01–I59) RD (ICD-10: J00–J64, J65–J99)	• Each 10 mg/m^3 increase in $PM_{2.5}$ is associated with increased CVD mortality, with a percentage change of 12.4%, 95% CI: 0.2–26.5%) at lag 3	• Age: Each 10 mg/m^3 increase in $PM_{2.5}$ is associated with increased CVD mortality in the elderly (≥65 years; 13.8%, 95% CI: 0.6%–30.4%) at a lag 0 and (11.8%, 95% CI: 2.2–27.7%) at lag 3
Central & Southern Asia						
Borsi et al., 2020 [61]	Ahvaz, Iran	11 years (2008–2018)	Hospital admission	CVD: deep venous thrombosis (DVT)	• There was a significant relation between exposure to $PM_{2.5}$ and DVT admissions; RR = 1.003 (95% CI: 1.000–1.005) at lag 0	Each 10 µg/m^3 increase in $PM_{2.5}$, increased risk of DVT admissions: • Gender: Females, RR = 1.004 (95% CI: 1.001–1.008) at lag 0 and lag 7 • Age: ≤60 years, RR = 1.005 (95% CI: 1.002–1.009)

Table 3. *Cont.*

Author (Reference)	Location	Study Period	Health Outcome	Diseases (ICD Classification)	Key Findings	Vulnerable Groups
Latin America & Caribbean						
Tapia et al., 2020 [62]	Lima, Peru	7 years (2010–2016)	Hospital visit	CVD (ICD-10: I20–I25, I63–I67) RD (ICD-10: J0–J45, J00–J06, J09–J22, J30–J45)	• ER visits for RD increased by 4% (95% CI: 0–5%) for each IQR increment in $PM_{2.5}$. Visits for ischemic heart disease (adults, 18–64 years) were 11% (1, 24%), while visits for stroke were 10% (3–18%).	• Poverty: Districts with higher poverty showed significant associations between $PM_{2.5}$ and RD visits
Multiple Countries						
Liu et al., 2019 [31]	Multi countries (652 cities, 24 countries)	30 years (1986–2015)	Mortality	CVD (I00–I99), and RD (J00–J99)	• Average daily all-cause mortality increased by 0.44% (95% CI: 0.39–0.50), daily CVD mortality increased by 0.36% (95% CI: 0.30–0.43), and daily RD mortality increased by 0.47% (95% CI: 0.35–0.58) for every 10 g/m^3 increase in the 2-day moving average of PM10 concentration	• NA

Notes: PM2.5 = particulate matter with aerodynamic diameter ≤2.5 µm, CVD = cardiovascular disease, RD = respiratory diseases, COPD = chronic obstructive pulmonary disease, AMI = Acute myocardial infarction, CHF = congestive heart failure, IHD = ischemic heart disease, IS = ischemic stroke, CRHD = chronic rheumatic heart disease CBVD = cerebrovascular disease, ALRI = acute lower respiratory infection, URI = upper respiratory infections, IS = ischemic stroke (IS), DVT = deep venous thrombosis, ICD= International Classification of Diseases, ED = emergency department, EAD = Emergency ambulance dispatches, EDV = Emergency department visits, ER = excess risk, RR = Relative risk, CI = Confidence Interval, IQR = interquartile range, NA = non-applicable.

Table 4. Highest Relative Risks (RRs) by cardiovascular and respiratory diseases.

Diseases Outcomes	Short-Term (Less than 7 Years)						Long-Term (7 Years & above)					
	Mean (SD)	Q1	Q2 (Median)	Q3	Min	Max	Mean (SD)	Q1	Q2 (Median)	Q3	Min	Max
Cardiovascular	1.0378 (0.066)	1.0073	1.0239	1.0485	0.8200	1.2880	1.0503 (0.0603)	1.0149	1.0297	1.0582	1.0050	1.2700
Respiratory	1.0493 (0.0751)	1.0082	1.0169	1.0723	0.9132	1.3800	1.0391 (0.0382)	1.0139	1.0355	1.0407	1.0074	1.1580

4. Discussion

Our review provided an overview of current literature using time series designs to look for the association between $PM_{2.5}$ with specific health outcomes of cardiovascular and respiratory diseases. We adhered to the methodology outlined for scoping review articles by using the six main principles of Arksey and O'Malley (2005) [29]. The guiding principle ensured that our methods were transparent and free from potential bias. There were a few identified strengths of the included studies, which have similar study design and methodology and broad geographical coverage. We hope that it will aid us in identifying research gaps and distributing research findings to stakeholders, policymakers, practitioners, and academics for possibly valuable directions and future research.

The results of this study showed that China published the highest number of articles on $PM_{2.5}$ air pollution and cardiorespiratory health effects using time series designs. China is one of the countries that faced the worst air pollution problems in the world, possibly as a result of increasing industrialization and urbanization over the last two decades [63,64]. Coal is fuelling an increasing number of vehicles and industries, which are the principal contributors to the country's dangerously high levels of air pollution [65]. Although coal-related pollution has always been a source of concern in China, coal burning during the winter months causes levels of airborne contaminants to increase drastically. According to one study, 40% of the $PM_{2.5}$ in China's atmosphere can be attributed to both industrial and residential sources of coal burning [66]. China had exceptionally severe and persistent haze pollution in the first quarter of 2013, affecting an area of more than 1.3 million km^2 and nearly 800 million people [67]. The annual average $PM_{2.5}$ and PM_{10} concentrations were 141 $\mu g/m^3$ and 303 $\mu g/m^3$, respectively [68]. Nearly half a million deaths in the country were related to $PM_{2.5}$ exposure from a combination of coal burning at power plants, factories, and homes burning coal for heat and fuel.

$PM_{2.5}$ levels are strongly related to meteorological variables such as temperature, relative humidity, and wind conditions, and the meteorological variations over the last 30 years related to the increment of the $PM_{2.5}$ levels [69]. Data records of at least 30 years are considered appropriate to fully capture the variability of air pollution or other meteorological parameters that are associated with climate change [33]. However, daily data of 7 years and above was also enough to show notable and consistent changes. The majority of the studies (79.3%) in this review were conducted in a short period of time, which was less than seven years duration with daily data. As a result, the risks associated with health impacts have been considered to be short-term effects. There were many reasons why short-term studies were mainly conducted compared to long-duration studies. One of the main reasons was the ability to capture good data for daily environmental and health data. Many developing countries in various regions have taken action to address air pollution over the past decade. This action was prompted by the development of monitoring systems to document air pollution concentrations, particularly $PM_{2.5}$ and with growing public awareness of high levels of pollutants in everyday life.

Our findings demonstrated that for long-term studies durations, the RRs were higher related to cardiovascular compared to respiratory diseases. This finding is consistent with results from other studies [70]. Many large prospective cohort studies and fine meta-analyses have further provided us with clear answers on the correlation between longer-term particulates exposure, particularly $PM_{2.5}$ and cardiovascular mortality [71].

Furthermore, the majority of the studies on cardiovascular were conducted among the elderly, while most of the studies on respiratory diseases were conducted among children. Therefore, short-term durations were more appropriate for respiratory diseases.

The results from this study showed that about three-quarters of the studies utilized the GAM in data analysis, and the GLM was used in a few studies. The GAM with non-parametric splines and GLM with parametric splines are the statistical methods commonly employed for time-series analysis [35,36]. These regression methods account for variations in time-varying confounders like the season, weather factors, and other trends while estimating the relationship between short-term changes in air pollution and short-term changes in mortality. These results were consistent with what was reported by Bell et al. (2004), that of more than 80 time-series studies on PM and mortality published since 1996, approximately 70% used GAM methods [72]. This might be due to the fact that the GAM technique makes fewer rigid assumptions about temporal confounders and mortality effects and fulfill the default convergence criteria. Furthermore, the findings provided compelling evidence that short-term changes in even low levels of air pollution could be associated with short-term changes in mortality at a single location.

It should also be mentioned that $PM_{2.5}$ concentration is currently only being monitored in certain countries compared to the monitoring of PM_{10} concentration which has been established in many countries. Even though the importance of $PM_{2.5}$ in the determination of health effects has been established, it takes a certain level of investment to set up $PM_{2.5}$ monitors or sensors. The World Health Organization (WHO) reported that coverage of the ground measurements of $PM_{2.5}$ and $PM_{10,}$ respectively, are still not uniformly distributed around the world [73]. These monitoring stations were mainly located in high- and middle-income economies such as Europe and North America, India, and China. $PM_{2.5}$ measurements can directly be used to estimate health impact and are therefore of particular interest. Thus, some middle-income countries have recently started to measure $PM_{2.5}$; for example, Malaysia introduced new standards and guidelines for $PM_{2.5}$ monitoring in 2017 [74]. This has improved its air quality monitoring network by incorporating continuous PM2.5 measurement into the national environmental monitoring program [75]. In comparison to PM_{10}, monitoring $PM_{2.5}$ allows for a better representation of the actual situation regarding high particulate matter concentrations owing to combustion, such as biomass burning and automobile emissions. When $PM_{2.5}$ measurements are not available, PM_{10} measurements are used to estimate $PM_{2.5}$. Due to that, there were studies that extrapolate $PM_{2.5}$ data using PM_{10} data that is available from monitoring stations or from Aerosol Optical Depth (AOD) data using a method that has been developed and validated [76].

Surprisingly, 95% of the selected studies on the relationship between air pollution and health outcomes originated from either high-income countries (24.3%) or upper-middle-income countries (70.7%). There was less research from lower-middle-income countries (4.3%) and none from low-income countries. Even though this review was looking for specific designs and methodologies, this clear discrepancy could possibly be due to inadequate environmental monitoring systems and public health surveillance programs. Less cohesive policies and inadequate scientific research may be another reason. This presents an issue in understanding the impact on low-income countries. It is reported that stroke incidence is largely associated with low and middle-income countries rather than with high-income countries [77]. One approach to overcome this is to conduct a stratified analysis by regional income to try and explore the economic factor.

The ICD is internationally recognized for the diagnostic classification of both morbidity and mortality. The ICD-10 was introduced as the 2010 version to replace the earlier version of ICD-9 that was adopted internationally in the early 1980s [78]. The ICD-10 was adopted later by more than 100 countries. However, it differed by modifications made according to the country's standard and specific clinical coding [79]. In this review, more than three-quarters of both cardiovascular and respiratory health outcomes used ICD codes. Even though health outcomes were classified using the same ICD codes, the different ways codes were used in mortality, admission, and ED visits were suggested to affect the comparability of specific categories of diseases, including cardiovascular and respiratory health effects [28,80]. With the latest version of ICD-11, which allows the systematic surveillance of mortality and morbidity data, both ICD-10 and ICD-11 classification adoption should be considered to ensure consistency of health outcomes [26].

The understanding of individual and population vulnerability to $PM_{2.5}$ exposure will support the policy in reducing pollution. Our review attempted to look into the health effects of $PM_{2.5}$ on cardiovascular and respiratory systems across different vulnerabilities such as gender, age groups, poorer and comorbidities. However, only age group was considered in more than half of the reviewed articles (60.8%). High levels of $PM_{2.5}$ exposure negatively affected the cardiovascular and respiratory systems of children and the elderly, with specific ages below 15 years old and more than 65 years old, respectively [81,82]. The other reviewed articles did not focus on any particular vulnerable group.

More time series studies designed to look into the effects of air pollution on these vulnerable groups should be conducted. The effects on healthy people and those with chronic diseases need to be studied separately, as people with co-morbidities and chronic illnesses were more susceptible to air pollution. Prospective cohort studies have shown the association of long-term exposure to air pollution with chronic illnesses-related mortality [83]. Other subgroups that need to be analyzed separately includes people with outdoor occupations, athletes, infants and children, older adults and those with poor socioeconomic background.

5. Conclusions

There were numerous time series studies of $PM_{2.5}$ on cardiovascular and respiratory health outcomes internationally in the last five years (2016–2021), mainly from the Eastern and South-Eastern Asia region. There was an unequal distribution of the epidemiologic studies of both acute and chronic effects of $PM_{2.5}$ as they were well conducted in both upper-middle- and high-income economies. The GAM with Poisson regression analysis was the main methodology used in the analysis. The single health outcomes of cardiovascular or respiratory disease were often employed, with mortality being the most prevalent health outcome. Most studies focused solely on respiratory diseases, with many of them looking at the vulnerable groups and utilizing ICD-10 in both diseases. The findings also showed that short-term studies showed higher risks for respiratory diseases, while long-term studies showed higher risks for cardiovascular diseases. To provide more insights on the global burden of diseases related to $PM_{2.5}$ pollution, more studies are needed to explore the impacts in lower incomes countries and other vulnerable populations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/atmos14050856/s1, Table S1: List of 138 accepted articles for scoping review on time series studies of $PM_{2.5}$ and health effects. References [84–191] have been cited in the Supplementary Materials.

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