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Association of Long-Term Exposure to Fine Particulate Matter and Cardio-Metabolic Diseases in Low- and Middle-Income Countries: A Systematic Review

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Abstract: Background: Numerous epidemiological studies indicated high levels of particulate matter less than 2.5 μm diameter (PM2.5) as a major cardiovascular risk factor. Most of the studies have been conducted in high-income countries (HICs), where average levels of PM2.5 are far less compared to low- and middle-income countries (LMICs), and their socio-economic profile, disease burden, and PM speciation/composition are very different. We systematically reviewed the association of long-term exposure to PM2.5 and cardio-metabolic diseases (CMDs) in LMICs. Methods: Multiple databases were searched for English articles with date limits until March 2018. We included studies investigating the association of long-term exposure to PM2.5 (defined as an annual average/average measure for 3 more days of PM2.5 exposure) and CMDs, such as hospital admissions, prevalence, and deaths due to CMDs, conducted in LMICs as defined by World Bank. We excluded studies which employed exposure proxy measures, studies among specific occupational groups, and specific episodes of air pollution. Results: A total of 5567 unique articles were identified, of which only 17 articles were included for final review, and these studies were from Brazil, Bulgaria, China, India, and Mexico. Outcome assessed were hypertension, type 2 diabetes mellitus and insulin resistance, and cardiovascular disease (CVD)-related emergency room visits/admissions, death, and mortality. Largely a positive association between exposure to PM2.5 and CMDs was found, and CVD mortality with effect estimates ranging from 0.24% to 6.11% increased per 10 μg/m3 in PM2.5. CVD-related hospitalizations and emergency room visits increased by 0.3% to 19.6%. Risk factors like hypertension had an odds ratio of 1.14, and type 2 diabetes mellitus had an odds ratio ranging from 1.14–1.32. Diversity of exposure assessment and health outcomes limited the ability to perform a meta-analysis. Conclusion: Limited evidence on the association of long-term exposure to PM2.5 and CMDs in the LMICs context warrants cohort studies to establish the association.

Keywords: air pollution; cardio-metabolic diseases

1. Background

Cardiovascular disease (CVD) is the leading cause of death in nearly all countries around the globe [1], and chronic exposure to air pollution is an important risk factor for CVD. Based on numerous epidemiological studies, particulate matter with a diameter of less than 2.5 micrometers (PM2.5)
is considered to be the main culprit for these adverse cardiovascular effects [2–4]. Evidence from systematic reviews and meta-analyses suggests a strong association between short-term exposure to elevated PM$_{2.5}$ and hospital admissions, myocardial infarction, stroke, and heart failure [5–8]. Even in countries where current international air quality standards are met (i.e., the World Health Organization (WHO) standards of 10 µg/m$^3$ annual mean concentration or 25 µg/m$^3$ 24-hour mean concentration) [2,9–12], small increases in PM$_{2.5}$ are associated with increased risk of stroke [13].

More recent evidence suggests that chronic, i.e., long-term exposure to elevated PM$_{2.5}$ also contributes substantially to cardio-metabolic diseases (CMDs) [4,14]. A meta-analysis from European and North American studies reported that the association between PM$_{2.5}$ and type 2 diabetes mellitus (T2DM) increased the risk by 10% for every 10 µg/m$^3$ increase in PM$_{2.5}$ [15], which was similar to a meta-analysis conducted in 2014 that found an 11% increase in T2DM risk per 10 µg/m$^3$ increase in PM$_{2.5}$ among five identified studies [16]. Similarly, a systematic review conducted in 2015 identified five studies on long-term PM$_{2.5}$ exposure and hypertension risk, and meta-analysis revealed a small albeit statistically non-significant effect summary odds ratio (OR) = 1.06 (95% confidence interval (CI), 0.98, 1.15) [17]. All of these reviews included only developed countries (US, Canada, and Europe).

Thus, while an association between PM$_{2.5}$ and CMD has been demonstrated by epidemiological studies conducted in developed countries, where the annual average PM$_{2.5}$ concentrations are near the WHO standard, scientific evidence from low- and middle-income countries (LMICs) is extremely limited [18]. This is concerning given substantially higher exposure levels in LMICs due to rapid industrialization and inadequate enforcement of environmental regulations [19]. Moreover, differences in the sources and composition of ambient air pollution, diet, and chronic disease status limit the generalizability of findings from developed countries [20]. To further define the current state of the science in LMICs, we conducted a systematic literature review of the association between long-term exposure to PM$_{2.5}$ and CMDs in LMICs.

**Objective**

To systematically compile evidence for the association between long-term exposure to PM$_{2.5}$ and CMDs in LMICs.

**2. Materials and Methods**

We performed this study in three stages: database search, title and abstract screening, and full-text review and extraction. First, we searched the following databases: Medline and Embase (from January 1, 1948 to March 6, 2018), Cumulative Index to Nursing and Allied Health Literature, SCOPUS, Cochrane database, and Web of Science. We restricted our search to articles published in English, and we only considered peer-reviewed original articles. Detailed search terms are provided in Appendix A.

**3. Definitions**

For the purpose of this review, we defined CMDs as a clustering of disorders (hypertension, lipid disorders, hyperinsulinemia, and glucose intolerance) that together lead to CVD and T2DM [21,22]. We focused specifically on long-term exposure to PM$_{2.5}$, defined as an annual average or average measure of more than 3 days of PM$_{2.5}$ exposure. We chose to focus on long-term exposure, given that the diseases of interest (CMDs) are chronic diseases that develop over long periods of time.

**3.1. Inclusion and Exclusion Criteria**

We included studies that:

1. Were original research published in peer-reviewed journals up to March 6, 2018.
2. Were conducted in an LMIC according to current World Bank classification [23].
(3) Quantified the association between exposure to PM$_{2.5}$ and at least one CMD, including CVD, T2DM, lipid disorders, hypertension, hyperinsulinemia, and glucose intolerance, and related hospitalizations.

(4) Involved long-term exposure to PM$_{2.5}$ (annual average or more than 3 days).

We excluded studies that:

(1) Were conducted only among the population aged less than 18 years.
(2) Used proxy measures to assess the exposure to PM$_{2.5}$ (e.g., proximity to major roads).
(3) Focused on a specific population (e.g., patients with previous CVD events or T2DM).

3.2. Selection of Studies

The search strategy followed the PICO-population, intervention/exposure, comparator (there was no comparator in our review) and outcomes process [24]: population-general population from LMICs, intervention/exposure- long-term exposure to PM$_{2.5}$, and outcomes - CMDs. Titles and abstracts were screened by three researchers (S.J., G.K.W., and M.M.). A full-text review was then performed independently by three researchers (S.J., G.K.W., and M.M). Disagreements were resolved by discussion in a small working group (S.J., G.K.W., M.M., and L.M.J.). Studies were then appraised for quality using the Cochrane Risk of Bias tool [25]. Each study was assessed for the following: selection bias, assessment of exposure and outcome, and adjustment for confounders. The studies were classified into three groups: high-quality (low risk of bias), medium-quality (unclear), and low-quality (high risk of bias). Two reviewers (S.J. and G.K.W.) independently appraised the studies, and disagreements were resolved in a consensus meeting. Only high-quality studies were included in this review.

3.3. Data Extraction

Data were extracted using a standardized extraction table that was piloted for two articles. Data extraction was performed by one researcher (S.J.) and was checked for accuracy by a small working group (G.K.W., M.M., and L.M.J.). The data extraction included study characteristics (author, year of publication, year of data collection, region, country, sampling method, sample size, location, setting), demographics (sex and age distribution), air pollution exposure information (method of measurement, length of exposure, and average measure), CMDs (prevalence/admissions/mortality, source of information), and results.

4. Results

4.1. Study Selection Process

We identified 10,861 articles in the database search, of which 5,291 were excluded as duplicates (Figure 1). Title and abstracts were screened, and 45 studies were identified for full-text review. Twenty-eight articles were excluded mainly because they were not original research ($n = 8$), did not assess PM$_{2.5}$ ($n = 3$), assessed short-term PM$_{2.5}$ exposure ($n = 11$), did not measure an association ($n = 1$), used proxy measures of PM$_{2.5}$ exposure ($n = 1$), or were in patients with a pre-existing condition ($n = 4$). The final review included 17 studies (Tables 1 and 2).
Figure 1. PRISMA flowchart [26].
Table 1. Study characteristics, exposure, outcome, and primary results of included studies (n = 11, listed alphabetically) measuring PM$_{2.5}$ exposure less than the annual average.

| Citation | Place of Study | Study Period | Study Design | Study Population (Age, Gender) | Sample Size | Particulate Matter Measuring Less Than 2.5 µm (PM$_{2.5}$) Measurement Method | Mean PM$_{2.5}$ µg/m$^3$ | Exposure Association to Outcome (No. of Days Exposure Data-Available) | Outcomes (Source) | Results |
|----------|----------------|--------------|--------------|--------------------------------|-------------|------------------------------------------------------------------------------|----------------|------------------------------------------------------------------|-----------------|---------|
| [27]     | Mexico City    | 1993–1995    | Time-series study | Residents aged 65 years and above | 4129 | Monitoring station with 24-hour integrated particle mass | 27 | 4 days (941 days)                                      | Daily mortality (Electronic records) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ was associated with a 3.4% (95% confidence interval (CI) 0.67, 6.18) increase in cardiovascular disease (CVD) mortality |
| [28]     | Plovdiv, Bulgaria | 2014       | Cross-sectional survey | General population aged 18 years and above | 513 | Official municipality source | 66.8 | Not Available (NA) (150 days)                                      | Type 2 diabetes mellitus (T2DM) prevalence (survey) | T2DM was positively associated with PM$_{2.5}$: Odds Ratio (OR) 1.32 (95% CI 0.28, 6.24) comparing top quartile (25.0–66.8 µg/m$^3$) to bottom quartile (0.0–25.0 µg/m$^3$) |
| [29]     | São José dos Campos, Brazil | 2010–2011 | Time-series study | Daily hospital admissions in elderly people (60 years and above) | 1765 | Gent Stacked Filter-like sampler; Companhia Ambiental do Estado de São Paulo—CETESB monitoring station | 4.4 | 5 days (350 days)                                      | CVD hospital admissions (Health Services Information Database) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ increased the risk of CVD hospitalization by 19.6% (95% CI 6.4, 34.6) |
| [30]     | Six cities of the Pearl River Delta region, China | 2013–2015 | Cross-sectional survey | Deaths registered | 316,305 | Monitoring stations in each of the six cities: Guangzhou, Shenzhen, Zhuhai, Dongguan, Foshan, and Jiangmen | 35.1 to 47.9 | 4 days (886 days)                                      | CVD Mortality (Guangdong Provincial Center for Disease Control and Prevention) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ concentration was associated with 2.19% (95% CI 1.80, 2.59) increase in CVD mortality |
| [31]     | Guangzhou, China | 2007–2011 | Time-series study | General population | 33,721 | Panyu Meteorological Center, South China Institute of Environmental Sciences & GRIMM Aerosol Spectrometer | 41.4 | 4 days (1079 days)                                      | CVD mortality (Guangdong Provincial Center for Disease Control and Prevention) | An inter-quartile range (IQR) increase in PM$_{2.5}$ (31.5 µg/m$^3$) was associated with excess risk of CVD mortality by 6.11% (95% CI 1.76, 10.64) |
| Citation | Place of Study | Study Period | Study Design | Study Population (Age, Gender) | Sample Size | Particulate Matter Measuring Less Than 2.5 µm (PM$_{2.5}$) Measurement Method | Mean PM$_{2.5}$ µg/m$^3$ | Exposure Association to Outcome (No. of Days Exposure Data-Available) | Outcomes (Source) | Results |
|----------|----------------|--------------|--------------|--------------------------------|-------------|-----------------------------------------------|----------------|------------------------------------------------|-----------------|---------|
| [32]     | Beijing, China | 2004–2006    | Time-series study | Emergency room visits (ERV) | 13,026      | Twin Differential Mobility Particle Sizer and Aerodynamic Particle Sizer | 109.8          | 11 days (1035 days) | CVD ERV (Emergency Department of Hospital) | An IQR increase in PM$_{2.5}$ (43.0 µg/m$^3$) was associated with 0.3% (95% CI (-)2.4, 3.0) and (-)0.1 (95% CI 3.4, 3.3) total and severe CVD ERV, respectively |
| [33]     | Beijing, China | 2008–2011    | Time-stratified case-crossover study | Death registered | 145,477 | U.S. embassy | 95.7          | 40 days (1046 days) | CVD/ Cerebrovascular disease (CBD)/Ischemic Heart Disease (IHD) (Death Registry of Chinese Center for Disease Control and Prevention) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ was associated with an increased risk of CVD mortality of 0.24% (95% CI 0.11, 0.39), CBD mortality of 0.23% (95% CI 0.03, 0.42), and IHD mortality of 0.22% (95% CI 0.12, 0.54) |
| [34]     | São José do Rio Preto, Brazil | 2011–2012 | Time-series study | Hospitalizations registered | 4505 | Coupled Chemistry Aerosol-Tracer Transport model to the Brazilian developments on the Regional Atmospheric Modeling System (CCATT BRAMS model) | 23.8          | 5 days (365 days) | CVD hospitalization (Unified Health System) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ was associated with a 15% increased relative risk (RR) for CVD hospitalization with SE of 0.007% |
| [35]     | Shenyang, China | 2006–2008    | Time-series study | General population | 32 | Continuous monitoring system at Shenyang Regional Meteorological Center; Ambient Dust Monitor 365 | 95.9          | 3 days (730 days) | Cause specific mortality (Liaoning Provinical Center for Disease Control and Prevention) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ was associated with a 0.42% (95% CI 0.10, 0.73) increase in CVD mortality |
| [36]     | Cuiabá and Varzea Grande, State of Mato Grosso, Brazil | 2009–2011 | Time-series study | General population aged 45 years and above | 17.7 | Method developed and validated for the Brazilian Amazon and Cerrado | 17.7          | 10 days (983 days) | Daily mortality and hospitalization (Mortality Information System and Hospital Information System) | Every 10 µg/m$^3$ increase in PM$_{2.5}$ was associated with a 2.64% (95% CI 0.53, 4.06) increase in risk of CVD hospitalizations and 3.57% (95% CI 0.82, 6.38) increase in CVD mortality |
| Citation | Place of Study | Study Period | Study Design          | Study Population (Age, Gender) | Sample Size | Particulate Matter Measuring Less Than 2.5 µm (PM$_{2.5}$) Measurement Method | Mean PM$_{2.5}$ µg/m$^3$ | Exposure Association to Outcome (No. of Days Exposure Data-Available) | Outcomes (Source) | Results                                                                 |
|----------|----------------|--------------|-----------------------|--------------------------------|-------------|--------------------------------------------------------------------------------|--------------------------|------------------------------------------------------------------|------------------|------------------------------------------------------------------------|
| [37]     | Chongqing, China | 1995         | Cross-sectional survey | Deaths registered            | 47          | 24-hour samples collected from two roadside sites from representative areas of differing principal social activities | 147                      | 5 days (213 days)                                                  | Daily mortality (Chongqing Anti-Epidemic Station) | Every 100 µg/m$^3$ increase in PM$_{2.5}$ was associated with 1.09% (95% CI 0.95,1.20) increase in CVD mortality |

CI-confidence interval; CVD-cardiovascular disease; PM-Particulate matter; NA-not available; T2DM-type 2 diabetes mellitus; OR-odds ratio; IQR-inter-quartile range; IHD-ischemic heart disease; CBD-cerebrovascular disease; RR-relative risk.
Table 2. Study characteristics, exposure, outcome, and primary results of included studies (n = 6, listed alphabetically) measuring PM$_{2.5}$ exposure as annual average or more.

| Citation | Place of Study | Study Period | Study Design | Study Population (Age, Gender) | Sample Size | PM$_{2.5}$ Measurement Method | Mean PM$_{2.5}$ µg/m$^3$ | Exposure Association to Outcome (No. of Days Exposure Data-Available) | Outcomes (Source) | Results |
|----------|----------------|--------------|--------------|---------------------------------|-------------|-------------------------------|-------------------------|-------------------------------------------------------------------|------------------|---------|
| [38]     | Varanasi, India | 2001–2015 | Time-series study | General population | 5700 | MODIS onboard NASA-EOS AQUA and TERRA satellites | 136.9 | 13 years (13 years) | Premature mortality from ischemic heart disease (IHD), Stroke (Premature deaths) | The estimated premature deaths per year from ambient PM$_{2.5}$ exposure in Varanasi: IHD 1600 (95% CI 600, 2200), Stroke 1000 (95% CI 500, 1400) |
| [39]     | Shanghai and seven provinces of Guangdong, Hubei, Jilin, Shaanxi, Shandong, Yunnan, and Zhejiang, China | 2007–2010 | Cross-sectional survey | General population aged 50 years and above | 12,665 | van Donkelaar and co-workers to estimate the outdoor PM$_{2.5}$ concentrations | 33.7 | 3 years (3 years) | Hypertension (World Health Organisation (WHO) Study on global aging and adult health) | Odds ratio (OR) for hypertension: 1.14 (95% CI 1.07, 1.22) for every 10 µg/m$^3$ increase in PM$_{2.5}$ |
| [40]     | National, China | 2011–2012 | Cross-sectional survey | General population aged ≥45 years | 11,847 | Satellite-based spatial statistical model | 72.6 | 1 year (303 days) | Type 2 diabetes mellitus (T2DM) prevalence, blood glucose, and HemoglobinA1c (HbA1c) (survey) | An inter-quartile range (IQR) increase in PM$_{2.5}$ (41.1 µg/m$^3$) was associated with increased T2DM prevalence ratio( PR):1.14 (95% CI 1.08, 1.20), elevated levels of fasting glucose by 0.26 mmol/L (95% CI 0.19, 0.32), and HbA1c by 0.08% (95% CI 0.06, 0.10) |
| [41]     | National, China | 2015 | Cross-sectional survey | General population aged 20–49 years | 10,843,140 | Hybrid geophysical statistical approach | 47.1 | 3 years (3 years) | Tachycardia and Resting heart rate (Survey) | OR for tachycardia: 1.018 (95% CI 1.017, 1.020) and a 0.07 (95% CI 0.073, 0.079) bpm elevation in the resting heart rate for every 10 µg/m$^3$ increase in PM$_{2.5}$ |
Table 2. Cont.

| Citation | Place of Study | Study Period | Study Design | Study Population (Age, Gender) | Sample Size | PM$_{2.5}$ Measurement Method | Mean PM$_{2.5}$ $\mu$g/m$^3$ | Exposure Association to Outcome (No. of Days Exposure Data-Available) | Outcomes (Source) | Results |
|----------|----------------|--------------|--------------|-------------------------------|-------------|--------------------------------|----------------------------|---------------------------------------------------------------|------------------|---------|
| [42]     | Liaoning, China | 2009         | Cross-sectional survey | General population aged 18–74 years | 15,477      | Satellite-based spatial statistical model | 82.0                      | 3 years (3 years) | Prevalence of diabetes, fasting glucose, 2-hour glucose, and 2-hour insulin (Survey) | An IQR increase in PM$_{2.5}$ (26 $\mu$g/m$^3$) was significantly associated with increased diabetes: OR 1.14 (95% CI 1.03, 1.25) |
| [43]     | National, China | 2000–2005    | Cohort study | Males 40 years and above | 189,793     | Combination of satellite-derived and chemical transport model estimates calibrated to surface measurements | 43.7                      | 6 years (6 years) | CVD Mortality (Survey) | Hazard ratio (HR) for CVD mortality was 1.09 (95% CI 1.08, 1.10) for every 10 $\mu$g/m$^3$ increase in PM$_{2.5}$ |
The following study designs were used in the included studies: seven were cross-sectional studies, eight were time-series studies, one was a time-stratified case-crossover study, and one was a cohort study. The included studies were conducted in the following countries: Brazil (n = 3), Bulgaria (n = 1), China (n = 11), India (n = 1), and Mexico (n = 1). Only two studies were conducted before 2008, and the rest were conducted after 2008 (past 10 years) on the studied outcomes.

4.2. Study Characteristics: Exposure and Outcomes

The most common methods of exposure assessment used in these studies were modeled estimates from hybrid space-time models, which use a combination of satellite remote sensing, meteorology, and land use as predictors (n = 8); data from nearby monitoring stations (n = 4); both direct measurements of PM$_{2.5}$ and data from monitoring stations (n = 3) and direct measurement using personal monitors (n = 2). We could not perform meta-analyses due to the heterogeneity of PM$_{2.5}$ measurement methods across studies. The average concentration of PM$_{2.5}$ reported in all of the Chinese studies was 73.85 \(\mu g/m^3\) ranging from 33.7 \(\mu g/m^3\) to 147 \(\mu g/m^3\). PM$_{2.5}$ concentrations reported by studies conducted in India (2015), Brazil (2010–2012), Bulgaria (2014), and Mexico (1995) were 136.9 \(\mu g/m^3\), 4.4 to 23.8 \(\mu g/m^3\), 66.8 \(\mu g/m^3\), and 27 \(\mu g/m^3\), respectively. With respect to CMD outcomes reported in the included studies, three studies evaluated hospital admission and emergency room visits (ERV); nine studies evaluated CVD mortality; five studies evaluated CVD risk factors, including T2DM. Table 1 summarizes 11 studies which evaluated shorter PM$_{2.5}$ exposure windows (3 days up to 40 days), and Table 2 summarizes six studies which evaluated longer PM$_{2.5}$ exposure windows (annual average up to 13-year average). The exposure association to outcome grouped the included studies into two categories, namely studies measuring less than annual averages of exposure and studies measuring an annual average of exposure with an exact number of days of exposure assessment mentioned in the Tables 1 and 2.

4.3. Mortality Outcomes

Of the nine studies that evaluated CVD mortality [27,31,33,35–38,43,44], eight (91%) reported significant effects of long-term PM$_{2.5}$ exposure. Of these studies, six were conducted in China, and one study each was carried out in Mexico, India, and Brazil. For every 10 \(\mu g/m^3\) increase in PM$_{2.5}$, CVD mortality increased, ranging from 0.24% (95% CI 0.05, 0.43) on 40th day after exposure to 6.11% (95% CI 1.76, 10.64) per interquartile (IQR) increase (31.5 \(\mu g/m^3\)) in PM$_{2.5}$ at moving averages for the previous 3 days [31,33].

The national prospective cohort study conducted in China, which included 189,793 men aged 40 years and above, reported a hazard ratio (HR) for CVD mortality for every 10 \(\mu g/m^3\) increase in PM$_{2.5}$ of 1.09 (95% CI 1.08, 1.10) for a 6-year time period [43]. A time-series study from Guangzhou with a sample size of 33,721 adults reported that the excess risk (ER) of CVD mortality was 6.11% (95% CI 1.76, 10.64) per IQR increase in PM$_{2.5}$ at moving averages for the previous 3 days [31]. A study of 145,477 adults aged 45 years and above conducted in Beijing reported the estimated percentage increase in the risk of death for every 10 \(\mu g/m^3\) increase in PM$_{2.5}$. They found that the risk of CVD mortality rose by 0.24% (95% CI 0.05, 0.43), cerebrovascular disease (CBD) mortality by 0.23% (95% CI 0.0, 0.50), and ischemic heart disease (IHD) mortality by 0.22% (95% CI 0.06, 0.50) over 0–5 days [33]. For every 10 \(\mu g/m^3\) increase in PM$_{2.5}$, a study in Shenyang, China found an increase in CVD mortality of 0.42% (95% CI 0.10, 0.73) [35]. In contrast, a study conducted in Chongqing, China found no association between CVD mortality and PM$_{2.5}$ [37].

The only Mexican study reported that for every 10 \(\mu g/m^3\) increase in PM$_{2.5}$, there was a 3.4% (95% CI 0.67, 6.18) increase in CVD mortality [27]. The only study from India reported a burden of 5700 (95% CI 2800, 7500) annual premature deaths (0.16% of the population) attributable to PM$_{2.5}$ exposure, of which 29% and 18% were IHD and stroke, respectively. The estimated premature deaths per year from ambient PM$_{2.5}$ exposure in Varanasi, India by IHD was 1600 (95% CI 600, 2200) and stroke was 1000 (95% CI 500, 1400) [38]. A Brazilian study reported that every 10 \(\mu g/m^3\) increase in PM$_{2.5}$ resulted in a relative risk (RR) of 1.81% (95% CI 0.03, 3.61) for CVD mortality [36].
4.4. Hospital Admissions and Emergency Room Visits

There were four studies [29,32,34,36], one from China and three from Brazil that evaluated hospital admissions and ERV. All reported significant effects of long-term PM$_{2.5}$ exposure.

In Brazil, the RR was 2.64 (95% CI 1.60, 3.69) for hospitalizations related to PM$_{2.5}$ over a period of 10 days [36]. Another study in Brazil reported a significant increase in the risk of hospitalization for circulatory system diseases of 19.6% (95% CI 6.4, 34.6) per 10 µg/m$^3$ increase in PM$_{2.5}$ 5 days after exposure [29]. The third study in Brazil similarly reported a 15% (SE 0.07%) increase in the risk of hospitalization for CVD per 10 µg/m$^3$ increase in PM$_{2.5}$ concentration 5 days after exposure [34].

The only Chinese study found that an IQR increase in PM$_{2.5}$ (43.0 µg/m$^3$) was associated with 0.3% (95% CI (-)2.4, 3.0) total CVD ERV for 11-day moving average [32].

4.5. CVD Risk Factors

Of the five studies that evaluated CVD risk factors [28,39–42], including T2DM, all reported significant effects of long-term PM$_{2.5}$ exposure. Four of these studies were conducted in China, and one study was conducted in Bulgaria. The following CVD risk factors were assessed by studies included in this review: hypertension ($n=1$), tachycardia and resting heart rate ($n=1$), insulin resistance and T2DM ($n=3$).

A study conducted in China among adults aged 50 years and above found that for every 10 µg/m$^3$ increase in PM$_{2.5}$ over a 3-year period, the adjusted OR for hypertension was 1.14 (95% CI 1.07, 1.22). Each 10 µg/m$^3$ increase in ambient PM$_{2.5}$ was associated with a 1.04 mmHg (95% CI 0.31, 1.78) increase in diastolic blood pressure and a 1.30 mmHg (95% CI 0.04, 3.56) increase in systolic blood pressure [39]. A cross-sectional survey among adults between 20 and 49 years, also from China over a 3-year period, reported, for every 10 µg/m$^3$ increase in PM$_{2.5}$, that the OR for tachycardia was 1.018 (95% CI 1.017, 1.020) and resting heart rate increased by 0.076 bpm (95% CI 0.073, 0.079) [41]. Another Chinese study found that PM$_{2.5}$ was significantly associated with increased diabetes by OR: 1.14 (95% CI 1.03, 1.25) per IQR increase (26 µg/m$^3$) in PM$_{2.5}$ over a 3-year period [42].

A study in China among adults aged 45 years and above reported that an annual average IQR increase (41.1 µg/m$^3$) in PM$_{2.5}$ was significantly associated with increased T2DM prevalence, PR= 1.14 (95% CI 1.08, 1.20), elevated levels of fasting glucose by 0.26 mmol/L (95% CI 0.19, 0.32), and elevated HbA1c by 0.08% (95% CI 0.06, 0.10) [40]. A study from Bulgaria reported that PM$_{2.5}$ was positively associated with T2DM, OR 1.32 (95% CI 0.28, 6.24) [28].

5. Discussion

We identified just 17 studies conducted in LMICs with the link between long-term PM$_{2.5}$ exposure and CMD, and most of the studies (65% of studies) were in China. This is concerning because LMICs carry the greatest burden of both CMD and air pollution, and most of the studies we reviewed reported significant increases in CVD mortality with increasing PM$_{2.5}$ levels. The Global Burden of Disease (GBD) in 2015 and Global Health observatory data repository reported that the population-weighted mean exposure to PM$_{2.5}$ in China, India, Brazil, Mexico, and Bulgaria were 58.4 µg/m$^3$ (95% CI 58.1, 58.7), 74.3 µg/m$^3$ (95% CI 73.9, 74.8), 11.4 µg/m$^3$ (95% CI 11.2, 11.5), 20.1 µg/m$^3$ (95% CI 16.7, 27.2), and 18.8 µg/m$^3$ (95% CI 18.3, 20.6), respectively. In our review, all the included studies indicated higher levels of PM$_{2.5}$ than reported by the GBD except for one study from Brazil [29], which reported slightly lower estimates. In this review, PM$_{2.5}$ estimates reported by Chinese studies ranged from 33.7 to 147 µg/m$^3$; Indian PM$_{2.5}$ estimates ranged from 94.4 to 136.9 µg/m$^3$; Brazilian PM$_{2.5}$ estimates ranged from 4.4 to 23.8 µg/m$^3$; Mexican PM$_{2.5}$ estimates was 27.0 µg/m$^3$, and Bulgarian study reported 66.8 µg/m$^3$, all of which were much higher than the values reported by the GBD study [4]. Therefore, the GBD estimates may be underestimating CVD deaths attributable to PM$_{2.5}$ in the countries of focus. Similarly, a global review and meta-regression analysis also observed much lower levels of PM$_{2.5}$ in China compared to our estimates [45]. Most (70%) of the research studies included in this review were
conducted in major cities and industrial centers in China, including Beijing, Chongqing, Guangzhou, Liaoning, Pearl River Delta region, Shanghai, and Shenyang, which may at least partially explain this deviation from the GBD estimates. Satellite-based estimates must be used cautiously and following shortcomings must be kept in mind: underestimation of ground measurements in locations with higher concentrations like East Asia, South Asia, North Africa, and Sub-Saharan Africa [46].

The duration of exposure ascertainment to outcome varied from a 3-day average to a 13-year average. The effect estimates varied with duration of exposure—longer exposure periods associated with smaller effect estimates. We observed differences among the effect estimates for cardiovascular mortality for annual averages or longer duration and less than annual averages. In our review, we observed that the effect estimates were smaller when the exposure window was longer, which needs further investigation. This was similar to a global meta-analysis of cohort studies, which also found that the effect estimates decreased with increasing concentrations [45].

This review was focused on CMDs as we currently lack literature on the effects of long-term exposure to PM2.5 on CMDs in LMIC settings. Globally, 17.1% of IHD mortality and 14.2% of CBD mortality in 2015 was attributable to PM2.5 as reported by GBD [7]. A prospective European cohort study found an increased risk of stroke associated with a 5 μg/m³ increase in PM2.5 with a hazard ratio of 1.19 (95% CI 0.88, 1.62) [13]. In our review, Luo et al. from their Beijing study reported that every 10 μg/m³ increase in PM2.5 was associated with an increased risk of CBD mortality of 0.23% (95% CI (-)0.03, 0.50) [33].

Across all of the included studies, the results ranged from 0.24% [33] to 6.11% [31] increase in CVD mortality for every 10 μg/m³ increase in PM2.5. While this effect estimate is relatively small, the ubiquitous nature of the exposure is likely to result in a large population-attributable disease burden. This range of values was higher than a recent meta-regression analysis of 53 studies, that found the percent increase at mean exposure of 10 μg/m³ PM2.5 associated with a 1.46% (95% CI 1.25, 1.67) increase in CVD mortality [45]. Similarly, a review of European epidemiological studies reported that the relative risk of CVD mortality was 1.11 (95% CI 1.07, 1.15) for a quartile increase in PM2.5 [47]. Another global review also noted that cardiorespiratory mortality was increased by 2.29% (95% CI 1.36, 3.85) per 10 μg/m³ increase in PM2.5 [48]. The effect estimates depended on the type of exposure assessment method as using ground-level monitors produced estimates 44–46% lower than that of hybrid space-time model [45]. Most of the studies reviewed here utilized secondary data from stationary monitoring stations (seven studies) or were modeled estimates (eight studies), which might not accurately reflect personal exposures. The only Indian study reported that premature mortality per year in the city of Varanasi from IHD was 1600 (95% CI 600, 2200) and stroke was 1000 (95% CI 500, 1400) after exposure to PM2.5 that could be saved [38]. There were no Indian studies measuring the impact of ambient air pollution on cardio-metabolic health outcomes, which needs focus in the future studies, given the fact that air pollution levels are alarmingly high, especially in the Indo-Gangetic plain [49].

A strong association between PM2.5 and CVD hospital admissions was observed. A pooled estimate from European countries reported that relative risk of cardiovascular hospitalizations increased by 1.8% (95% CI 0.1, 3.4) per IQR increase in PM2.5 (12.4 μg/m³) [50]. Results from a global review and meta-analysis showed that hospital admissions due to cardiorespiratory diseases were increased by 1.64% (95% CI 1.06, 2.53) per 10 μg/m³ increase in PM2.5 [48], which was much lower than the studies from Brazil identified in this review that reported a 15–19.6% increase in CVD hospitalizations [29,34]. On the contrary, a Chinese study observed that total and severe CVD ERVs increased by 0.3% (95% CI (-)2.4, 3.0) and decreased by 0.1% (95% CI 3.4, 3.3) for an IQR increase in PM2.5 by 43.0 μg/m³ in 11-day moving average, respectively, which indicated delayed association [32]. The varying effect estimates could be attributed to the population included and the exposure assessment method used in these studies.

Long-term exposure showed the strongest associations with hypertension. In a meta-analysis, there was a statistically insignificant increase in hypertension risk (OR = 1.065, 95% CI 0.985–1.152)
with each 10 µg/m³ increment in PM$_{2.5}$ [17]. We found very similar results from the Chinese study by Lin et al. who reported an increased risk of hypertension by an OR = 1.14 (95% CI 1.07, 1.22) with each 10 µg/m³ increment in PM$_{2.5}$ [39]. A meta-analysis among cohort studies reported a positive association for T2DM and relative risk of 1.25 (95% CI 1.10, 1.43) for every 10 µg/m³ increase in PM$_{2.5}$. Another review of European and North American studies reported that the pooled relative risk estimate for T2DM per 10 µg/m³ increase in PM$_{2.5}$ was 1.10 (95% CI 1.02, 1.18) [15]. The Chinese study from our review reported that for an IQR increase in PM$_{2.5}$, T2DM prevalence increased by PR = 1.14 (95% CI 1.08, 1.20) [40]. There were no studies conducted on lipid disorders with respect to air pollution exposure.

In this review, about two-thirds of the studies included were conducted in the last three years (2016–2018) indicating that this area is gaining more focus recently. A prospective cohort study design is considered the gold standard, but only one study, which was conducted in China, used a cohort design [43]. Further studies examining personal exposure to PM$_{2.5}$ or statistically modeled estimates for PM$_{2.5}$ and CMDs in LMICs are in urgent need to help develop scientific literature.

This study is not without its limitations, firstly the heterogeneity of identified studies prohibited the use of meta-analytical methods to produce summary estimates of effect. We focused on long-term exposures considering that in LMICs, ambient air pollution is chronic exposure and effects may be larger for long-term exposures versus short-term exposures. From our review results, we cannot conclude this assumption, as we found that for a longer duration of exposure, the effect estimates were smaller, and further investigation is needed to confirm this. The second limitation is that we focused solely on one component of ambient air pollution, PM$_{2.5}$, yet individuals are exposed to complex mixtures. We chose to focus on PM$_{2.5}$ versus PM$_{10}$ because previous research has demonstrated a stronger effect on CVD due to the ability of PM$_{2.5}$ particles to travel to distant organs [14]. Moreover, most included studies used a single-pollutant model, but a few also measured other pollutants, including PM$_{10}$, PM$_{1}$, sulfur dioxide (SO$_2$), nitrogen dioxide (NO$_2$), nitrous oxide (NO), carbon monoxide (CO), ozone (O$_3$), black carbon, organic and elemental carbon, soluble ions, and noise and traffic pollution. We evaluated only the effect estimates of PM$_{2.5}$ here. The third limitation is the type of studies included in this review is very different and, hence, the effect sizes should be interpreted with caution. Future research should expand to include multipollutant models that take into account potential interactions between pollutants, as well as source-specific effects.

In conclusion, few studies have evaluated the association between long-term exposure to PM$_{2.5}$ and CMD outcomes in LMICs, and the majority of this literature has come from China. We did not identify a single study conducted in North and Sub-Saharan Africa, which is home to 17% of the world’s population. Considering that the vast majority of morbidity and mortality attributable to PM$_{2.5}$ is in LMICs, this represents a major environmental injustice. The global environmental health community must drive a strong research agenda relating to the CMD effects of PM$_{2.5}$ in these settings in order to provide context-specific evidence to policymakers in these countries.

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Abbreviations

CBD-Cerebrovascular Disease;  
CI-Confidence Interval;  
CMD-Cardio-Metabolic Diseases;  
CO-Carbon Monoxide;  
CVD-Cardiovascular Diseases;  
DBP-Diastolic Blood Pressure;  
DM/T2DM-Diabetes Mellitus/Type 2 Diabetes Mellitus;  
ER-Excess Risk; ERV-Emergency Room Visits;  
HbA1c-HemoglobinA1c;  
HIC-High Income Countries;  
HR-Hazard Ratio;  
IHD-Ischemic Heart Disease;  
IQR-Interquartile Range;  
LMIC-Low- and Middle-Income Countries;  
NO$_2$-Nitrogen Dioxide;  
NO-Nitrous Oxide;  
O$_3$-Ozone; OR-Odds Ratio;  
PM-Particulate Matter;  
RR-Relative Risk;  
SBP-Systolic Blood Pressure;  
SD-Standard Deviation;  
SO$_2$-Sulfur Dioxide;  
WHO-World Health Organization.

Appendix A.

Appendix A.1. Search Terms

Air pollution: "air pollution" or "particulate matter" or "air pollutants" or "ambient air pollution" or "Total suspended particles" or "particulate matter" or "soot"  
CMD: "diabetes" or "diabet*" or "IDDM" or "NIDDM" or "Cardiovascular*" or "Cardiovascular Diseases" or "Cardiovascular Abnormalities" or "Heart Arrest" or "Cardiac arrest*" or "Arterial Occlusive Diseases" or "Cerebrovascular Disorders" or "Hypertens*" or "Myocardial Ischemia" or "Prehypertens*" or "Angina*" or "Glucose Metabolism Disorders" or "Diabetes*" or "Prediabet*" or "Hyperglycem*" or "Glucose Intoleran*" or "Insulin Resist*" or "Lipoprotein*" or "Apolipoprotein*" or "Chylomicrons" or "Chylomicron Remnants" or "Cholesterol*" or "High-Density Lipoproteins, Pre-beta" or "Cardiac Death" or "Asphyxia" or "Brain Death" or "Death, Sudden" or "Death, Sudden, Cardiac" or "Sudden Cardiac Death" or "Sudden Cardiac Arrest" or "Cardiac Arrest, Sudden"  
Countries: Low- and Middle- Income Countries (Low income, lower middle income, upper middle-income countries) and “NOT” High Income Countries (see Table A1 for detailed search strategy).
Appendix A.2. Cochrane Risk of Bias Tool

Table A1. Low risk of bias.

| 1 | Borja-Aburto 1998 | Low | Low | Low | Low |
| 2 | Dzhambov 2016 | Low | Low | Low | Low |
| 3 | Ferreira 2016 | Low | Low | Low | Low |
| 4 | Jain 2017 | Low | Low | Low | Low |
| 5 | Lin 2016 | Low | Low | Low | Low |
| 6 | Lin 2016 | Low | Low | Low | Low |
| 7 | Lin 2017 | Low | Low | Low | Low |
| 8 | Liu 2013 | Low | Low | Low | Low |
| 9 | Liu 2016 | Low | Low | Low | Low |
| 10 | Luo 2016 | Low | Low | Low | Low |
| 11 | Mantovani 2016 | Low | Low | Low | Low |
| 12 | Meng 2013 | Low | Low | Low | Low |
| 13 | Rodrigues 2017 | Low | Low | Low | Low |
| 14 | Venners 2003 | Low | Low | Low | Low |
| 15 | Xie 2018 | Low | Low | Low | Low |
| 16 | Yang 2018 | Low | Low | Low | Low |
| 17 | Yin 2017 | Low | Low | Low | Low |

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