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Associations Between the Chemical Constituents of Fine Particulate Matter and Human Health Outcomes: A Literature Review

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ASSOCIATIONS BETWEEN THE CHEMICAL CONSTITUENTS OF FINE PARTICULATE MATTER AND HUMAN HEALTH OUTCOMES: A LITERATURE REVIEW

by
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ABSTRACT

Exposure to fine particulate matter, $PM_{2.5}$, a component of air pollution, has known systemic effects on the human body. Research on the specific chemical constituents of $PM_{2.5}$ that impact human health is fairly new, however. This literature review aims to draw connections between the chemical constituents of $PM_{2.5}$ and their implications on human health. We conducted an online search for scholarly articles using a number of key-terms, and created a system to filter the search results. We focused on 69 articles pertaining to $PM_{2.5}$ and its effects on different health systems. We found positive associations of $PM_{2.5}$ components with human health endpoints in 97% of the studies. While $PM_{2.5}$ chemical constituent studies are less common than concentration based research, it is clear that conducting more research is necessary to better understand how $PM_{2.5}$ impacts human health.

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LIST OF ABBREVIATIONS

Fine Particulate Matter ($PM_{2.5}$)

Particulate Matter (PM)

Environmental Protection Agency (EPA)

Chronic Obstructive Pulmonary Disease (COPD)

Reactive Oxygen Species (ROS)

Dithiothreitol (DTT)

Polycyclic Aromatic Hydrocarbons (PAH)

Black Carbon (BC)

Elemental Carbon (EC)

Organic Carbon (OC)

Volatile Organic Compounds (VOC)

Force Expiratory Volume (FEV)

Fractional Exhaled Nitric Oxide (FeNO)

Blood Pressure (BP)

Heart Rate Variability (HRV)

Carotid Intima-Media Thickness (CIMT)

Coronary Artery Calcium (CAC)

Pulse Wave Velocity (PWV)

Aortic Augmentation index (AIx)

Tumor-Necrosis Factor Alpha (TNF-α)

Land-Use Regression (LUR)

Emergency Department (ED)

Cox Proportional-Hazards Model (CPHM)

1 Introduction

It is estimated that 7 million deaths occur globally every year due to air pollution exposure. Air pollution is a mixture of hazardous substances in the air resulting from man-made and naturally occurring emissions (NIEHS 2021). The particles that make up air pollution are solid and liquid droplets incorporated with gaseous substances (NRDC 2016). Energy use, power generation, coal-based power plants, manufacturing byproducts, chemical production fumes, and vehicle emissions are primary example sources of man-made air pollutants. Naturally occurring hazardous pollutants stem from wildfire smoke, volcanic eruptions, and decomposing organic material (NIEHS 2021). A major component of air pollution that has detrimental effects to human health is particulate matter.

1.1 Fine Particulate Matter

Particulate matter (PM) is a component of air pollution that negatively impacts human health. Particulate matter with an aerodynamic diameter smaller than 10 μm, has the greatest influence on human health outcomes. $PM_{2.5}$, has an aerodynamic diameter of 2.5 μm or less and is of public health concern and particular research interest due to its ability to exit the lungs and enter the bloodstream (US EPA 2018). Although it is small, $PM_{2.5}$ has a large enough surface area to carry droplets of solids and liquids that can be highly toxic. These microscopic materials are able to enter the respiratory tract via inhalation, then the bloodstream, and are ultimately found throughout the body (Xing et al. 2016). Some health issues that have been linked to $PM_{2.5}$ exposure include heart and respiratory irregularities, and individuals with preexisting thoracic conditions can experience elevated or aggravated symptoms (US EPA 2020). Because $PM_{2.5}$ can

enter the blood stream, health implications beyond respiratory and cardiovascular effects are possible as well.

The Environmental Protection Agency (EPA) has a defined standard of air quality under the Clean Air Act to regulate the quality of air in the United States and protect public health (EPA 2021). The act sets standards for the six criteria air pollutants, including PM. The remaining five common components of air pollution include lead, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide. Concentrations of the criteria air pollutants are monitored to regulate emissions and ensure that ambient levels are safe for the public. While the EPA monitors concentration of PM in ambient air under the Clean Air Act, the chemical composition of PM, and $PM_{2.5}$ especially, has become increasingly important to understanding the impact that it has on human health. It is widely accepted that PM has negative implications on health. Despite this, there is limited research on the specific components of PM that affect health. Within the last decade, this area of research has grown as more studies have begun to look beyond the overall concentrations of PM, and more in depth at the specific chemical constituents that affect human health.

$PM_{2.5}$ exists in our everyday environment, stemming from a number of different sources, which affects its chemical composition. While some $PM_{2.5}$ is directly emitted from sources such as fires and construction sites, most fine particulate matter is formed in the atmosphere (US EPA 2018). This occurs when emissions from power plants, automobiles, and other sources react with each other. In addition to outdoor sources, $PM_{2.5}$ can be emitted by household appliances, cleaning and personal care products. Processes, machines, or appliances that conduct combustion reactions can produce emissions that cause oxidative stress within the human body. This property

is a key point of research on how $PM_{2.5}$ is detrimental to human health. Specifically, oxidative stress has been linked to a number of age-related diseases. These include neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and cancer among other conditions (Liguori et al. 2016).

Oxidative stress in the body is caused by a disparity between present reactive oxygen species (ROS) and the body's ability to detoxify them. Detoxification can be in the form of directly detoxifying the reactive intermediates and products, or by repairing tissues and cells from damage that ROS can inflict (Mena S. et al. 2009). Quantifying the ability of $PM_{2.5}$ to induce oxidative stress is therefore essential to understanding the extent to which $PM_{2.5}$ can negatively impact health. This can be done by measuring oxidative potential from $PM_{2.5}$ collected on air filter samples through the dithiothreitol (DTT) assay. The rate of DTT consumption by the ROS associated with $PM_{2.5}$ is indicative of the reactivity of the species on the air filter (Charrier et al. 2013). The oxidative potential of $PM_{2.5}$ has been attributed to large amounts of organic compounds called polycyclic aromatic hydrocarbons (PAH). PAH molecules take part in the chemical reactions that generate radicals that induce damage in tissues. PAHs absorb to $PM_{2.5}$ (Bigagli and Lodovici, 2011).

In addition to measuring the oxidative potential of $PM_{2.5}$, the chemical composition of particulate matter is important to understanding the impact of ambient particulate matter on human health. Depending on the source of PM, different elements and chemicals attach to the surface of $PM_{2.5}$ (Zhang et al. 2018). These chemical constituents are able to enter the body

through inhalation along with fine particulate matter. Due to its small size and the ability of constituents to attach to its surface, inhalation of $PM_{2.5}$ brings foreign chemicals into the lungs. This includes ozone; sulfur dioxide; nitric oxide; other atmospheric gases; and transition metals like iron, lead, zinc, and mercury; amongst many others (Bigagli and Lodovici 2011).

Research on the chemical constituents of $PM_{2.5}$ most commonly includes analyses of different compound classes including elements, carbon, polyatomic ions, and gaseous pollutants. $PM_{2.5}$ studies that analyze elements frequently include the transition metals in their research as well as several alkali, alkaline and other metals. Commonly occurring metals in $PM_{2.5}$ include Pb, As, Cd, Cu, Zn, and Ni. While many metals are essential to human life, necessary intake is usually low and over-exposure can have toxic effects (Queensland 2021). Metals are naturally occurring in the air and other aspects of the environment, but industrial endeavors like mining, smelting, power generation, electronics, and combustion reactions create an excess presence of harmful metals in the air. These man-made endeavors also contribute to carbon emissions. Carbonaceous materials including black carbon (BC), elemental carbon (EC), and organic carbon (OC) are frequently occurring toxic components of $PM_{2.5}$. Carbon emissions primarily stem from the burning of fossil fuels like natural gas, oil, and coal (EPA 2021). These combustion reactions occur during power use and generation (electricity), manufacturing, and transportation for example. Polyatomic ions like sulfate, nitrate, and ammonium are considered secondary PM because they form from gaseous emissions (EPA 2004). Sulfates form from sulfur dioxide, nitrates form from nitrogen dioxide, and ammonium ions, from atmospheric ammonia, form in the atmosphere with sulfate and nitrates (EPA 2004). Industrial combustion processes create sulfur dioxide emissions; nitrogen oxide emissions stem from vehicles, industrial processes, and

power plants; agriculture is the primary source of atmospheric ammonia (EPA 2004). Sulfur dioxide and nitrogen dioxide are gaseous pollutants present in air pollution. While these pollutants are not $PM_{2.5}$ components, they help form secondary PM when reacting with sulfate and nitrate respectively. Ground-level ozone is another important aspect of air pollution, and it falls under the six criteria air pollutants along with sulfur dioxide and nitrogen dioxide. This form of ozone is a common emission of industrial combustion reactions (SJQ Air Pollution Control). Another compound class that is found in $PM_{2.5}$ is volatile organic compounds (VOC). VOCs include PAHs and they are primarily indoor emissions stemming from cleaning supplies, paint, office equipment, craft supplies like glue and permanent markers…etc (EPA 2021).

Approximately 9 out of 10 people breathe air containing pollution (WHO 2020). While it is widely understood that $PM_{2.5}$ is a component of air pollution that has significant impacts on human health, the specific components and their specific effects on health are less frequently studied. $PM_{2.5}$ research has historically focused around the concentration of $PM_{2.5}$ in air pollution measurements. Only within the last decade has research dedicated to studying the chemical constituents of $PM_{2.5}$ and their health implications become more common. The EPA has published a "Health Effects Notebook for Hazardous Air Pollutants," which contains fact sheets on a number of individual constituents (EPA 2021). Many constituents are not included in this publication of fact sheets, and many of the hazard summaries are vague or have no information on health implications. To better understand how and why high PM concentrations in air pollution are detrimental to human health, it is essential to conduct more research on the specific chemical constituents of $PM_{2.5}$ and their relation to health outcomes.

1.2 Methods for Studying Human Health Effects of $PM_{2.5}$ Components

Chemical constituents have differing effects throughout the human body because of the variability between bodily systems. Likewise, these effects are measured with various methods given the body system of focus. These areas of focus included respiratory health, cardiovascular health, mortality, birth outcomes, and systemic effects. Respiratory function is a common point of research in the physical implications of $PM_{2.5}$. Subcategorizations of respiratory function include pulmonary function, airway inflammation, presence of a wheeze, respiratory-related hospitalizations, and cancer. Pulmonary function is most commonly measured with a spirometry test, which measures the amount of air that the lungs are able to hold. Patients are required to inhale as much air as they can and then exhale it as hard and quickly as possible into the mouthpiece of a spirometry machine (American Lung Association 2020). This is also called the force expiratory volume (FEV). Airway inflammation is a common indicator of many underlying respiratory diseases. It is often measured with exhaled nitric oxide tests, which are also known as fractional exhaled nitric oxide (FeNO) tests. An FeNO test quantifies the amount of nitric oxide in patients' exhaled breath. Nitric oxide is released within the body as an immune response to inflammation (Mayo Clinic 2020). Its presence in exhaled breath is therefore an indicator of airway inflammation.

Cardiovascular health is described by many different measurement techniques. Blood pressure (BP), heart rate variability (HRV), carotid intima-media thickness (CIMT), and coronary artery calcium (CAC) are common measurements in determining cardiovascular function. BP is a measurement of pressure exerted by blood when the heart beats and when it is resting (NCBI 2019); HRV measures the time difference between heartbeats (Campos 2017);

CIMT tests determine the thickness of the intima and media layers within the carotid artery using ultrasound technology (Radiology 2019); coronary artery calcium, also known as plaque, is determined with an x-ray scan of the heart (Mayo Clinic 2019). Blood pressure measurements should fall below 120/80 mmHg. Chronic high blood pressure, also known as hypertension, greatly increases health risk for heart disease (CDC 2020). HRV is not the same as a heart rate or pulse measurement. While HRV measures variability in the time elapsed between successive heart beats, a pulse measurement counts the number of heart beats that occur within 60 seconds (NCBI 2013). A low HRV is indicative or poor cardiovascular health (Harvard 2017). A low resting heart rate indicates better cardiovascular health (Mayo Clinic 2020). CIMT tests detect the thickening of the arteries, which is indicative of a cardiovascular disease known as atherosclerosis (Darabian 2013). CAC tests measure calcium buildup in the heart, which is a risk factor for coronary disease. Additional measurements of cardiovascular integrity include arterial stiffness, pulse wave velocity (PWV), and aortic augmentation index (AIx). Because of their complexity, these techniques are not as commonly used in routine medical practice as the aforementioned methods (Segers et al. 2019). Spirometry is sometimes used in gauging cardiovascular health as well because a reduced FEV is a risk factor for cardiovascular disease and mortality (Brasil 2017).

Prenatal exposure to $PM_{2.5}$ and its implications on birth outcomes can be defined by pre-term births and newborn size. Births occurring before 37 weeks of gestation are considered to be premature (CDC 2020). Risk differences of pre-term birth can be assessed using live birth certificate data and statistical regression. Pre-term birth and low birth weight are indicative of adverse birth outcomes. The presences of inflammatory biomarkers such as cytokines,

fibrinogen, various interleukin proteins, tumor-necrosis factor alpha (TNF-α)…etc, are common indicators of systemic inflammation. Researchers can analyze participant blood samples for these biomarkers and determine if an immune response has occurred (Suhaimi & Jalaludin 2015). The presence of inflammatory biomarkers in human blood is indicative of systemic inflammation.

Regression models are commonly used methods in studying $PM_{2.5}$. Land-use regression (LUR) models are frequently utilized to assess $PM_{2.5}$ exposures in unmonitored locations using previous monitoring results (NCBI 2007). LUR models are useful in characterizing $PM_{2.5}$ exposure and health implications over specified area parameters. A number of variables can be analyzed with this statistical method. Multivariate studies frequently include data pertaining to mortality, hospitalizations, and Emergency Department (ED) visits. Poisson regressions are also used to study these variables in concordance with $PM_{2.5}$ exposures. Poisson regressions are used to examine associations between daily pollutant levels and health data for mortality or hospitalizations in large areas. This type of regression is useful in extrapolating environmental and health data acquired over multi-year time periods to analyze associations. The Cox proportional-hazards model (CPHM) is a frequently used regression method in mortality studies. It is used to investigate the association of participant survival time with predictor variables (STHDA).

1.3 Study Overview

With support from my advisor, I reviewed articles that studied the associations between $PM_{2.5}$ components and human health outcomes. I hypothesize that significant positive associations will be found between metals and carbonaceous compounds with all health endpoints that included these constituent classifications in their research. Concentrations of

$PM_{2.5}$ are frequently used for determining health associations however the more health relevant compounds present in $PM_{2.5}$ may provide better insight into human diseases than concentration measurements.

2 Methods

We primarily searched for published articles using Google Scholar and PubMed, as well as The University of Mississippi Library's One Search tool. Our search strategy focused on finding studies that linked $PM_{2.5}$ and its constituents to varying human health implications. All search terms included "fine particulate matter," and a body organ or system: "lungs," "cardiac," mortality," "birth outcomes," and "systemic." This was followed by various terms including "human," "participant," "cohort," "composition," "element," "carbon," and/or "organic." Our screening strategy was to find peer-reviewed articles in the English language only, with full-text versions available, the inclusion of $PM_{2.5}$ constituent measurements, and relevancy to certain health outcome categories. We did not use any restrictions on publication year. We narrowed our selection to the articles that pertained to the following categories: respiratory, cardiovascular, systemic, mortality, and birth outcomes. After reviewing the 107 articles found in the search, outcomes within these categories were further categorized. The articles were initially sorted by primary health endpoint based on title prior to additional sorting based on the abstract and methods of each article. Respiratory articles were organized into pulmonary function, wheeze, airway inflammation, respiratory hospitalizations, and lung cancer categories. Mortality articles were organized by respiratory and cardiovascular mortality. Cardiovascular health articles were categorized into acute/short-term responses or disease. Birth outcome articles were categorized under pre-term/low birth weight and systemic effects were categorized under systemic inflammation. Articles that did not clearly fit within these categorizations were eliminated. Despite filtering for full-text versions and $PM_{2.5}$ component analyses, some articles of the 107 total found in the first search did not have accessible full-text versions or didn't analyze

individual $PM_{2.5}$ components. These were eliminated from the 107 total in addition to articles that did not fit within the health endpoint categorizations. This screening process allowed us to organize articles that studied the commonly studied health implications of $PM_{2.5}$ constituents.

The analysis approach was to focus on the types of chemical constituents and whether or not they had positive or negative associations with health outcomes, the number of study participants or the studied area size/parameters, and the method(s) used.

3 Results

After refining our search results, a total of 107 articles were reviewed. As shown in ***Figure 1***, respiratory articles made up the majority of our search with 38 total articles. This is followed by 26 cardiovascular articles, 19 systemic, 15 mortality, and 9 birth outcome articles. After the screening process, we used 69 articles in the final analysis. We chose 27 respiratory articles, 18 mortality, 14 cardiovascular, 5 birth outcome, and 5 systemic inflammation studies. Several of the birth outcome studies utilized niche methods for specific variables and were therefore excluded from the final analysis. Many of the systemic focused articles that we found in our initial search were not cohesive to our study, so we eliminated the majority them during study analysis. ***Figure 2*** illustrates the number of remaining articles in each category following our screening process.

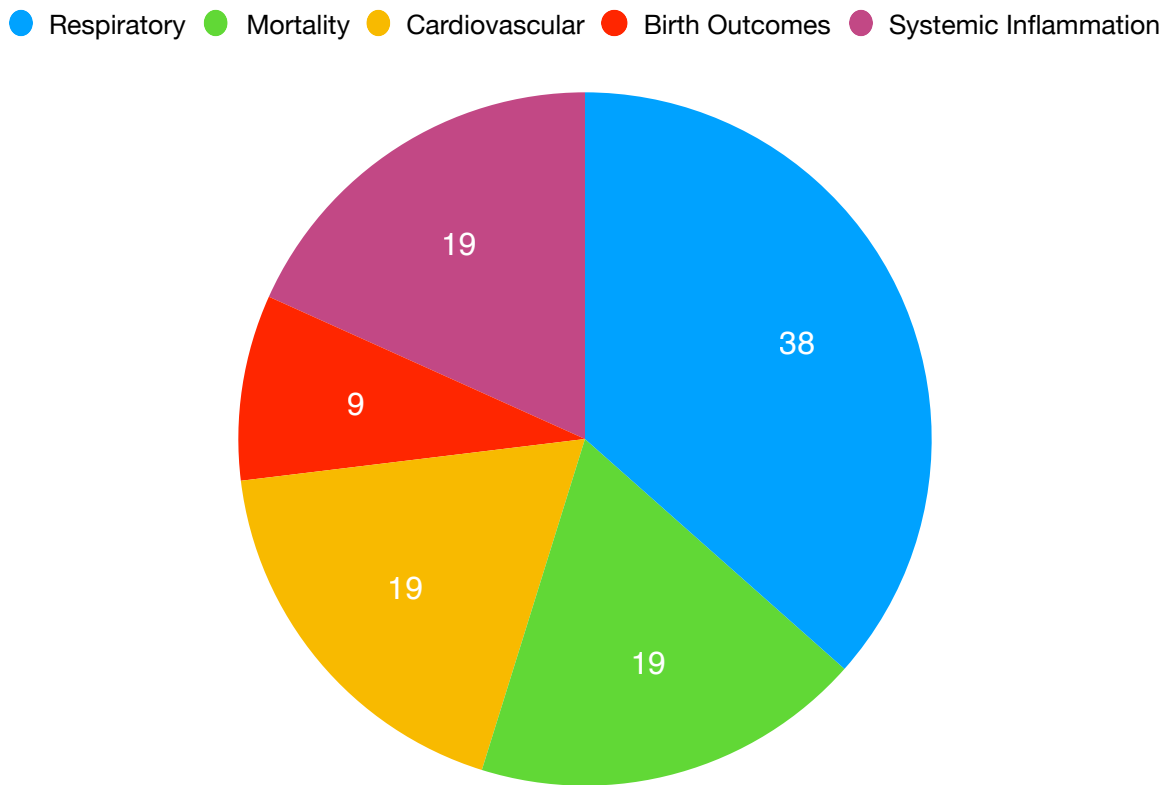

Figure 1. Total articles in each health endpoint category of the reviewed articles (Total = 107)

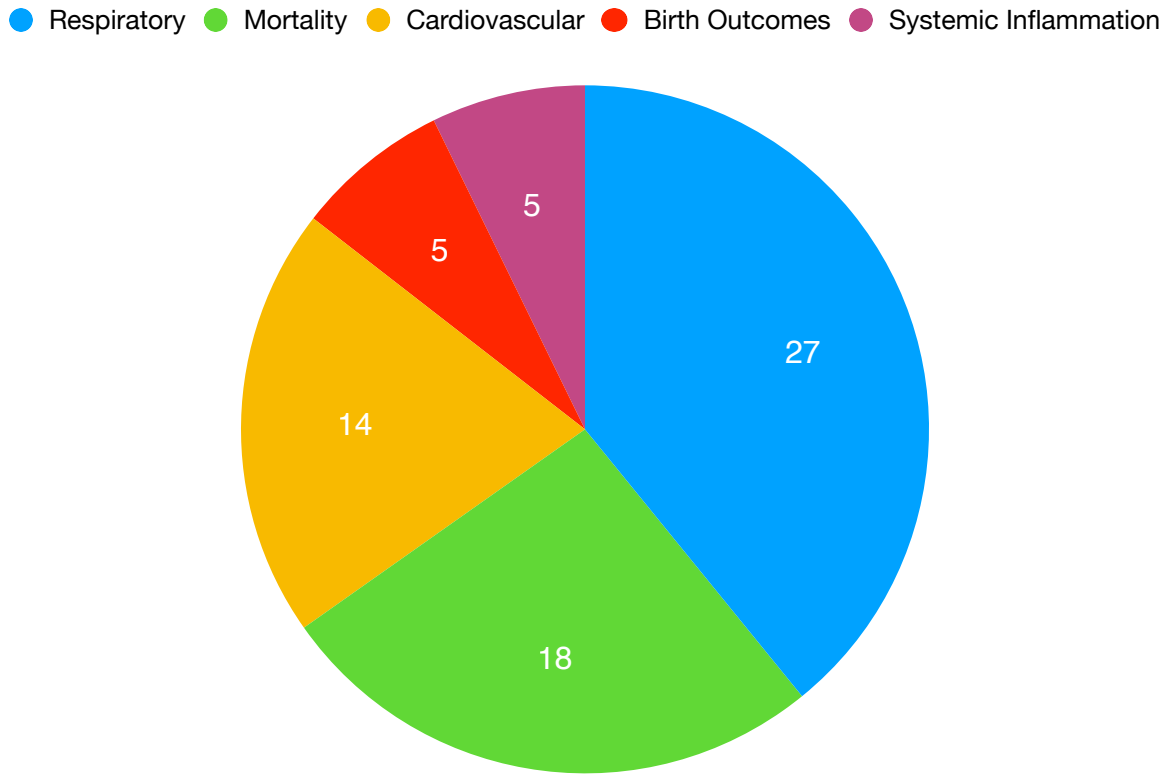

Figure 2. Remaining number of articles in each health endpoint category following the screening process (Total = 69)

3.1 $PM_{2.5}$ constituent associations with respiratory health

Table 1 presents the articles that studied $PM_{2.5}$ constituent effects on the respiratory system. All of the respiratory studies were conducted in urban areas including Chinese cities Beijing, Shanghai, and Wuhan and United States cities such as New York City, Los Angeles, Seattle, Baltimore, and Denver. The constituent effects were determined in terms of pulmonary function, the presence of a wheeze, inflammation, hospitalizations, and lung cancer. Pulmonary function was primarily measured via spirometry tests. Positive associations between $PM_{2.5}$ constituents and decreased pulmonary function were mostly found with the following elements and carbonaceous compounds: Cu, Pb, Zn, Ni, V, BC, and EC. Study 10 on almost 400 coke-factory workers found a positive association with polycyclic aromatic hydrocarbons and pulmonary function (Shen 2018). Study 13 measured oxidative potential with DTT assays (Yan 2019). The presence of a wheeze was determined through symptom questionnaires and positive associations were found with Ni, V, BC, and EC. The studies that analyzed airway inflammation measured exhaled nitric oxide. Positive associations were found primarily with the carbonaceous compounds BC, EC, and OC. The airway inflammation study that analyzed elemental constituents, found positive associations with metals like Fe, Zn, and Pb, in addition to EC and OC (Zhang 2019). Respiratory hospitalizations were measured with LUR. Positive associations were found for BC, EC, and OC. Ni and V were also found to have positive associations in the study that analyzed elemental constituents (Belli 2009). Elemental constituents were measured in the lung cancer study, which used 14 cohorts and hospital data. According to the study, Cu, Ni, and S were found to have positive associations with lung cancer (Raaschou-Nielsen 2016).

Table 1. Respiratory Studies

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
Pulmonary Function					
1	Elements, Gaseous pollutants	40 healthy university students, male	Spirometry	(+) Cl, Zn, Cu, V, Pb, Sn	Wu 2013
2	Elements, Carbon, Polyatomic ions	21 male college students	Spirometry	(+) Cu, Cd, As, Sn	Wu 2013
3	Carbon, Polyatomic ions	28 male COPD patients	Spirometry	(+) EC, SO_4^{2-}, NO_3^-	Chen 2017
4	Elements, Polyatomic ions	33 patients (23 women, 10 men)	Spirometry	(+) Na, Mg, NH_4^+	Bourotte 2007
5	Carbon, Gaseous pollutants	22 adults	Exhaled Nitric Oxide	No significant associations	Habre 2018
6	Elements Carbon	120 adults	Spirometry	(+) Si, Al, Ca, Ti	Baccarelli 2014
7	Elements	43 schoolchildren	Spirometry	(+) Al, Pb, Zn, Mn	Hong 2007
8	Elements, Carbon, Polyatomic ions, Gaseous pollutants	40 schoolchildren	Spirometry	(+) EC	Spira-Cohen 2011
9	Elements	163 homes (children)	Spirometry	(+) V	Jung 2017
10	VOCs	390 coke oven workers and 115 controls	Spirometry	(+) 5-6 ring PAHs	Shen 2018
11	Carbon	16 adults	Spirometry	(+) BC	Pan 2018

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
12	Carbon	614 mother-child pairs	Spirometry	(+) BC	Rice 2016
13	Elements, Gaseous pollutants	3701 participants	LUR	(+) OPDTT*	Yan 2019
14	Carbon, VOCs	37 healthy students	Spirometry	(+) OC	Huang 2019
15	Carbon, Gaseous pollutants	7071 participants	Spirometry	(+) BC, NO_x, O_3	Wang 2019
Wheeze					
1	Elements Carbon	725 women	Symptom Questionairres	(+) Ni, V, EC	Patel 2019
2	Carbon	408 children	Symptom Questionairres	(+) BC	Jung 2012
Airway Inflammation					
1	Elements Carbon	43 adults	Exhaled nitric oxide	(+) K, Fe, Zn, Ba, Cr, Se, Pb, EC, OC	Zhang 2019
2	Carbon, Polyatomic ions	32 adults	Exhaled nitric oxide	(+) EC	Shi 2016
3	Carbon, Polyatomic ions	30 COPD patients	Exhaled nitric oxide	(+) EC, OC, NO_3^-, NH_4^+	Chen 2015
4	Carbon, Gaseous pollutants	60 elderly patients	Exhaled nitric oxide	(+) BC, OC, NO_x	Delfino 2019
5	Carbon	129 children	Exhaled nitric oxide	(+) BC	Lovinsky-Desir 2019
6	Carbon	60 patients	Exhaled nitric oxide	(+) BC	Chen 2019
Respiratory Hospitilazations					
1	Elements, Carbon, Polyatomic ions	106 counties	LUR	(+) Ni, V, EC	Belli 2009

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
2	Carbon, Polyatomic ions	5 Denver counties	LUR	(+) EC, OC	Kim 2019
3	Carbon, Gaseous pollutants	467,994 adults	LUR	(+) BC	Gan 2019
Lung Cancer					
1	Elements	14 cohort studies	Hospital Data	(+) Cu, S, Ni	Raaschou-Nielsen 2016

* - Oxidative Potential DTT (OPDTT) — oxidative potential assessed by dithiothreitol assay

3.2 $PM_{2.5}$ constituent associations with mortality

Articles that studied $PM_{2.5}$ constituent effects on respiratory and cardiovascular mortality are presented in ***Table 2***. The studies were performed in urban areas including several metropolitan cities: Xi'an and Shanghai, China; United States metropolitan cities Houston, Seattle, Boston, Denver; Copenhagen, Denmark, and other urban European cities. The 13 respiratory mortality studies primarily used preexisting mortality data to determine constituent effects. In the studies where the amount of study participants was not clearly defined, Poisson regressions were used in combination with mortality data from the studied area. Many positive associations were found between the following constituents and respiratory mortality: (+) EC, OC, Ni, Cl, S, Zn, NH_4^+, NO_3^-, SO_4^{2-}. Positive associations were also found with BC, Si, Ca, Cu, O_3, and NO_2. The cardiovascular mortality studies also used mortality data in addition to regression models. The Poisson regression was used in Studies 2, 3 and 4. Studies 1 and 5 used the CPHM. Study 1 used LUR in addition to CPHM. The more frequent positive associations

found in the cardiovascular mortality studies were K, Cu, EC, OC, SO_4^{2-}. There were also positive associations with As, Pb, Fe, NO_3^-, and NH_4^+. Study 1 focused on elemental constituents, but found no significant associations with cardiovascular mortality (Wang 2014).

Table 2. Mortality Studies

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
Respiratory Mortality					
1	Elements, Carbon, Polyatomic inos	Approx. 5,000 women	Health and pollution data	(+) OC, SO_4^{2-}	Ostro 2010
2	Elements, Carbon, Polyatomic ions	47,838 deaths	Mortality data	(+) Cl, Ni, EC, OC, NH_4^+, NO_3^-	Cao 2012
3	Elements	291,816 participants	Mortality data	(+) S	Beelen 2015
4	Elements, Carbon, Gaseous Pollutants	Detroit, MI & Seattle, WA	Mortality data, Poisson regression	(+) Ni, EC, O_3	Zhou 2011
5	Elements, Carbon, Polyatomic ions	42,022 deaths	Mortality data	(+) Mg, Cl, NH_4^+	Son 2012
6	Elements, Carbon	75 US cities	Mortality data, Poisson regression	(+) Si, Ca, S	Dai 2014
7	Elements, Gaseous Pollutants, Polyatomic ions	8 Canadian cities	Mortality data, Poisson regression	(+) Ni, Zn	Burnett 2000
8	Carbon, Polyatomic Ions	Denver, CO metropolitan area	Mortality data, Regression	(+) EC, OC	Kim 2015
9	Elements, Polyatomic ions	333,317 deaths	Mortality data	(+) V, EC, OC, NH_4^+, SO_4^{2-}, NO_3^-	Zhang 2015
10	Elements, Carbon	101,884 women	Mortality data	(+) Cu, EC	Ostro 2015

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
11	Carbon, Gaseous pollutants	49, 564	CPHM	(+) BC, NO_2	Hvidtfeldt 2019
12	Elements, Carbon, Polyatomic ions, Gaseous pollutants	6 South Korean cities	Mortality data, Poisson regression	(+) Zn, Ni, V, EC, OC	Yoo 2019
13	Carbon, Polyatomic ions	25,185 deaths	Mortality data, Poisson regression	(+) EC, OC, NH_4^+, NO_3^-, SO_4^{2-}	Wang 2019
Cardiovascular Mortality					
1	Elements	322,291	Cohort analysis, LUR, CPHM	No significant associations	Wang 2014
2	Elements, Carbon, Polyatomic ions	California	Mortality data, Poisson regression	(+) K, Cu, Fe, EC, OC, NO_3^-, SO_4^{2-}	Ostro 2008
3	Elements, Carbon, Polyatomic ions	New York City, NY	Mortality data, Poisson regression	(+) EC, NO_3^-	Ito 2011
4	Elements, Carbon, Polyatomic ions	Shanghai, China	Mortality data, Poisson regression	(+) K, Cu, As, Pb, OC, SO_4^{2-}, NH_4^+	Wang 2020
5	Elements, Carbon	445,860 adults	CPHM	(+) EC	Thurston 2016

3.3 $PM_{2.5}$ constituent associations with cardiovascular health

The cardiovascular health studies and their significant constituent associations are shown in ***Table 3***. The studies were all conducted in urban areas with cities including Shanghai, and Beijing of China; New York City, Seattle, St. Louis, Los Angles, Chicago, Baltimore, Atlanta, and Boston of the United States. Studies demonstrating short-term exposure to $PM_{2.5}$ used blood pressure monitoring, HRV measurements, and spirometry. ED visits and poisson regressions

were used in studies 4 and 7. Across all acute/short term cardiovascular response studies, there were multiple positive associations with EC, OC, Ni, Cd, and NO_3^-. Positive associations with the following constituents were found one time out of all the short-term cardiovascular studies: As, Cr, Pb, Sr, Sn, V, Zn, NH_4^+, NO_2, SO_4^2, and CO. Study 1 found negative associations with Mg and Ca. Study 7 found a positive association with hydrocarbons (Lin 2017). In study 5 positive associations were found with Mg and Fe (Morishita 2015). Some cardiovascular disease studies used BP and HRV. Methods like CAC, CIMT, AIx, PWV that help gauge the presence or severity of cardiovascular disease were used in several studies. ED visits and Poisson regressions were used in Studies 1 and 4. Several positive associations were found with BC, EC, and OC. Only Studies 1, 2, 4 and 7 included elements in their constituent analysis. Positive associations with S were found in Studies 2 and 7, which both used CIMT and CAC measurements. Positive associations were found for Ni, Al, Fe, Ti, in Study 4 (Lu 2019). Study 1 did not find any elemental constituents with positive associations to cardiovascular disease (Sarnat 2015).

Table 3. Cardiovascular Health

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
Acute/Short-term Cardiovascular Responses					
1	Carbon, Polyatomic ions	28 COPD patients	BP	(+) EC, OC, NH_4^+, NO_3^-	Lin 2017
2	Elements, Carbon	24 COPD/ asthma patients	HRV, Spirometry	(+) Ni	Hsu 2011

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
3	Elements, Carbon, Polyatomic ions	78 participants	HRV	(+) As, Cd, Cr, Ni, EC, OC, NO_3^-, SO_4^{2-}	Hu 2020
4	Carbon, Gaseous pollutants	St. Louis, MO	ED visits, Poisson Regression	(+) EC, OC	Winquist 2014
5	Elements, Carbon	25 participants	BP, HRV	(+) Mg, Fe	Morishita 2015
6	Elements	59 participants	BP, HRV, Spirometry	(+) Ca, Cd, Pb, Sr, Sn, V, Zn	Cakmak 2014
7	Carbon, Gaseous pollutants	4,407,535 ED visits	ED visits, Poisson regression	(+) EC, OC, NO_2	Metzger 2004
Cardiovascular Disease					
1	Elements, Carbon, Gaseous pollutants	1,733,543 ED visits	ED visits, Poisson regression	(+) EC	Sarnat 2015
2	Elements, Carbon	6,814 participants	CIMT, CAC Exposure prediction modeling	(+) S, OC	Kim 2014
3	Carbon, Gaseous pollutants	6,795 participants	CAC	(+) NO_x	Kaufman 2016
4	Elements, Carbon, Polyatomic ions, Gaseous pollutants	31,749 ED visits	ED visits, Poisson regression	(+) Ni, Al, Fe, Ti, NO_3^-	Lu 2019
5	Carbon	65 non-smoking adults	BP, HRV, AIx	(+) BC	Brook 2016
6	Carbon	65 non-smoking adults	BP, HRV, AIx, PWV	(+) BC	Zhao 2014
7	Elements, Carbon	6,814 participants	CIMT, CAC	(+) S, EC, OC	Sun 2013

3.4 $PM_{2.5}$ constituent associations with birth outcomes

The studies analyzing constituent associations with birth outcomes are shown in ***Table 4***. These studies included large participant numbers and were conducted in mostly urban areas. Studies 1, 2, and 5 used newborn size as the parameter in determining associations. Studies 3 and 4 used pre-term birth risk and LUR. Studies 1, 2, and 5 found positive associations with Zn, and Studies 1 and 2 also found positive associations with Ni. Studies 2 and 5 found positive associations with EC. Other positive associations found in these three studies are: Si, Al, V, Fe, Ti, Mn, Br, Cu, SO_4^{2-}, NH_4^+. Studies 3 and 4 both found positive associations with EC. Study 3 also found a positive association with SO_4^{2-} (Rappazzo 2015). Study 4 analyzed PAHs and found positive associations with benzene and diesel in addition to OC, NH_4^+, and NO_3^- (Willhelm 2011).

Table 4. Birth Outcome Studies

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
Pre-term/Low birth weight					
1	Elements	34,923 single births	Newborn size	(+) Ni, Zn	Pedersen 2016
2	Elements, Carbon	76,788 infancts	Newborn size	(+) Si, Al, Zn, Ni, V, EC	Bell 2010
3	Carbon, Polyatomic ions	1,771,225 births	Pre-term birth risk differences, LUR	(+) EC, SO_4^{2-}	Rappazzo 2015

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
4	Carbon, Polyatomic ions, Gaseous pollutants, VOCs	241,415 births	Pre-term birth risk differences, LUR	(+) EC, OC, NH_4^+, NO_3^-, benzene	Willhelm 2011
5	Elements, Carbon, Polyatomic ions	646,296 births	Newborn size	(+) V, S, Fe, Ti, Mn, Br, Zn, Cu, EC, SO_4^{2-}, NH_4^+	Basu 2014

3.5 $PM_{2.5}$ constituent associations with systemic inflammation

Studies analyzing the associations of constitutes with systemic inflammation are shown in ***Table 5***. Blood samples were used to measure effects. Studies 1, 2 and 4 were conducted in Shanghai, China and Study 5 was done in Beijing. Study 3 was conducted in Boston, MA. Multiple positive associations were found with Si, Pb, Ti, EC, OC, and SO_4^{2-}. Other significant positive associations only found once across the studies are Cu, Ca, Cl, Co, Cd, Zn, Mg, Fe, Sn, Mo, Mg, BC, NO_3^-, and NH_4^+. Although all studies analyzed carbon constituents, Study 3 was the only study that found a positive association with BC (Garshick 2018).

Table 5. Systemic Inflammation Studies

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
Systemic Inflammation					
1	Elements Carbon	36 participants	Blood samples	(+) Pb, Si, Cu, Ca, Ti, EC	Lei 2020

Measurement & Study #	Constituents	Study Participants	Method	Associations to Components	Citation
2	Elements, Carbon, Polyatomic ions	28 participants	Blood samples	(+) EC, OC, NO_3^-, SO_4^{2-}, NH_4^+	Liu 2017
3	Carbon, Polyatomic ions, Gaseous pollutants	85 COPD patients	Blood samples	(+) BC	Garshick 2018
4	Elements, Carbon, Gaseous pollutants	40 adults	Blood samples	(+) Cl, K, Si, As, Pb, Se, SO_4^{2-}	Zhang 2020
5	Elements, Carbon, Gaseous pollutants	40 college students	Blood samples	(+) Mo, Sn, Zn, Mg, Fe, Ti, Co, Cd, OC	Wu 2012

3.6 Total positive associations with each component type in each health endpoint category

Respiratory studies that included the following 4 $PM_{2.5}$ chemical component types in their analyses found positive associations in: 10 out of 12 element analyses, 17 of 20 carbon analyses, 3 of 8 polyatomic ion analyses, and 2 of 7 gaseous pollutant analyses. For mortality studies that included these chemical components in their analyses, positive associations were found in: 12 of 15 element analyses; 13 of 14 carbon analyses; 8 of 11 polyatomic ions; 2 of 4 gaseous pollutants analyses. The following cardiovascular studies including these constituent types in their analyses found positive associations: 7 of 8 element analyses; 9 of 13 carbon analyses, 3 of 3 polyatomic ion analyses; 2 of 5 gaseous pollutant analyses. Birth outcome studies including the four different component types found positive associations in: 3 of 4 element analyses; 4 of 4 carbon analyses, 3 of 3 polyatomic ion analyses; 0 of 1 gaseous pollutant analyses. Systemic inflammation studies including the following component analyses

found positive associations: 3 of 4 element analyses; 4 of 5 carbon analyses, 2 of 2 polyatomic ion analyses; 0 of 3 gaseous pollutant analyses. The total numbers of studies for each health endpoint that included each type of component in their analyses is shown in ***Figure 3***. The number of papers out of these totals that found positive associations is shown in ***Figure 4***.

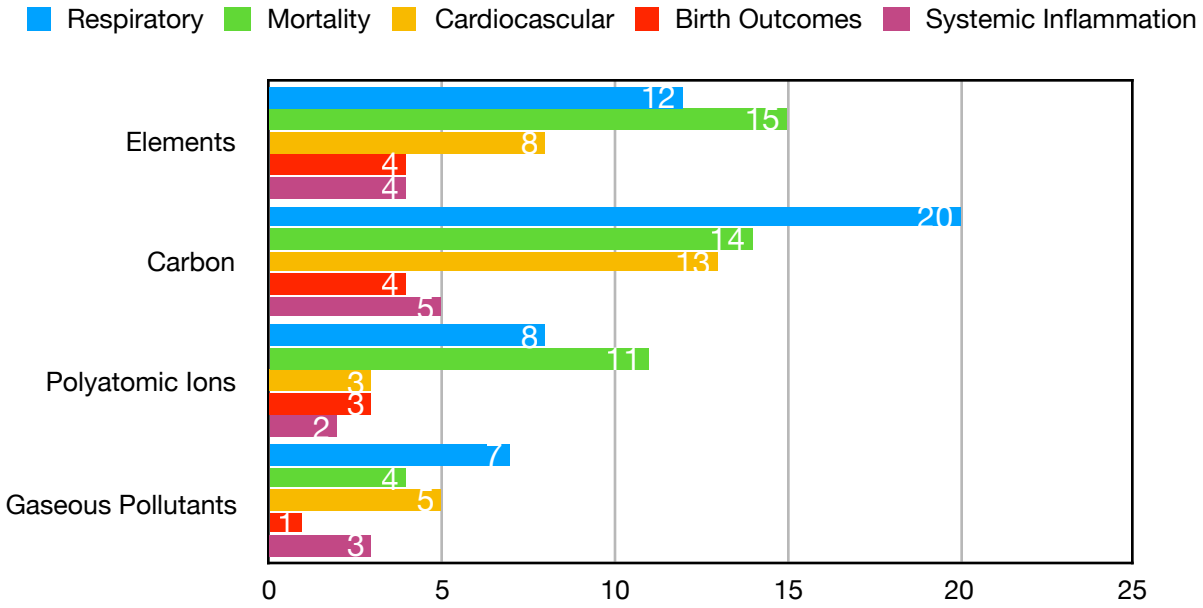

Figure 3. Total number of studies under each health endpoint that included each type of $PM_{2.5}$ component in their analyses (Total = 146)

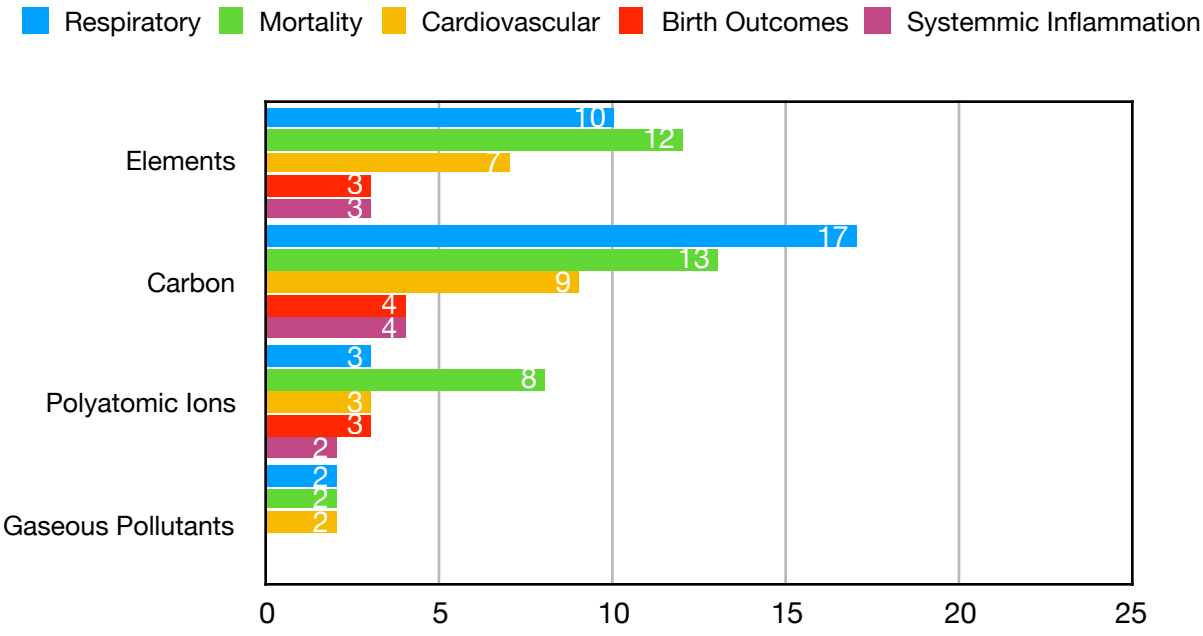

Figure 4. Total number of studies under each health endpoint that found positive associations with different $PM_{2.5}$ component types in their analyses (Total = 107)

4 Discussion

We reviewed articles that studied the associations of $PM_{2.5}$ chemical constituents and their impact on human health endpoints. The majority of the existing research on $PM_{2.5}$ and its connection to human health primarily focuses on $PM_{2.5}$ concentrations in air pollution. The aim of our study was to analyze articles that determined and measured the specific types of chemicals in $PM_{2.5}$ that affect health. Our results suggest that studying the chemical constituents of $PM_{2.5}$ could provide a better understanding of how it specifically impacts human health and disease. Positive associations of $PM_{2.5}$ components with health outcomes were found in 97% of the studies.

I hypothesized that all articles that included elements and carbon in their $PM_{2.5}$ analysis would find positive associations with their health endpoint of focus. This was not fully supported by our results, however, a significant majority of all articles that included these components in their research found positive associations. In total, 83% of the respiratory studies, 80% mortality studies, 75% cardiovascular, 75% birth outcome, and 75% of the systemic inflammation studies that included elements in their component analysis found positive associations with their respective health endpoints. Positive associations were found in 85% of the respiratory, 87% mortality, 69% cardiovascular, 100% birth outcomes, and 80% of the systemic inflammation articles that included carbon in their analysis. Although 100% of the studies did not report findings positive associations with elements and carbonaceous components as predicted, the vast majority of the studies did.

Of 69 total studies, 2 articles found no associations with $PM_{2.5}$ constituents and health endpoints. This 3% included 1 respiratory article and 1 mortality article. When measuring pulmonary function, no significant associations to chemical compounds were found in the 5th study of this section. Of the pulmonary function studies, Study 5 was the only one to use an exhaled nitric oxide test (Habre 2018). All but one other study used spirometry as the primary method in determining pulmonary function. The choice in method is likely the cause of Study 5's results, or lack thereof. In Cardiovascular Mortality Study 1, no significant associations were found (Wang 2014). This was likely due to a combination of method errors. Errors could include inaccurate $PM_{2.5}$ exposure measurement, and statistical analysis error. The researchers primarily attributed their lack of findings to applying a current LUR model at the time to older data (Wang 2014).

Some studies included component analyses that did not directly fall under the four component classifications used in this review. Study 10 in Pulmonary Function analyzed VOCs association with FEV measured by spirometry. Positive associations were found with 5 and 6-ring PAHs and pulmonary function (Shen 2018). Birth Outcomes Study 4 also included VOCs in its analysis. Positive associations were found between benzene and pre-term birth risk differences (Willhelm 2011). This study researched and included diesel fuel emissions in its LUR outside of Detroit, MI. Benzene is a common PAH and is found in diesel fuel as well as gasoline (IEA 2021). In Study 13 of Pulmonary Function, nitric oxides were included in the component analysis along with elements. DTT assays were used to analyze the oxidative potential of this component of air pollution. The study did not report findings on elemental associations, but

reported a positive association with oxidative potential DTT (Yan 2019). It concluded that oxidative potential assessed by DTT could be a useful metric in determining PM exposure.

Articles including polyatomic ions in their analyses mostly found positive associations with the polyatomic ions and their respective health endpoints of focus. 38% of respiratory articles, 73% mortality, 75% cardiovascular, 75% birth outcomes, and 100% of systemic inflammation articles found associations with polyatomic ions. Articles that included gaseous compounds in their analysis, however, did not find as many positive associations in comparison to studies that included elements, carbons, and/or polyatomic ions. Only 29% of the respiratory studies, 50% mortality, and 40% of the cardiovascular studies that looked for associations with gaseous pollutants found positive associations. No gaseous pollutant associations were found in the birth outcome and systemic inflammation studies. Gaseous pollutants like nitrogen dioxide, sulfur dioxide, and ozone are not direct components of $PM_{2.5}$. However, nitrate and sulfate can form from nitrogen dioxide and sulfur dioxide in the atmosphere, thus associating gaseous pollutants with $PM_{2.5}$ constituents. Researchers include these gaseous pollutants in their analyses because inhaled air is a complex mixture containing all air pollution components. By measuring gaseous pollutant associations with health endpoints, researchers can better determine the degree at which specific components are associated with specific health effects.

The chemical classes included in this analyses are relevant points of research because they are known to be hazardous to human health. The exact mechanisms of how and why elements, carbonaceous components, polyatomic ions, and gaseous pollutants impact our health when inhaled is less understood. While several of these components are harmful byproducts of man-made processes, some of these chemicals exist naturally in the environment and our body.

However, even chemicals necessary to life like those that we acquire from our diet and supplements, can have toxic effects on the body when inhaled. For instance, inhalation of airborne metals, which are commonly found in air pollution, can place acute stress on the respiratory and cardiovascular systems (Fortoul 2015). Continuous exposure to hazardous airborne particles can lead to illness and premature death. Some complications of exposure to these hazardous substances includes lung irritation, decreased immune response to infections, and worsening of pre-existing conditions like asthma and COPD amongst other adverse health effects (MPCA 2017).

Four studies that analyzed $PM_{2.5}$ total mass and/or concentration in addition to $PM_{2.5}$ component analysis, found more significant positive associations with individual constituents than overall concentration. Pulmonary Function Study 4 found positive associations with Na, Mg, and ammonium, and concludes that chemical constituents play a greater role in decreased respiratory health than $PM_{2.5}$ total mass (Bourotte 2007). Pulmonary Function Study 8 found significant positive associations with EC and concluded that carbonaceous $PM_{2.5}$ components, rather than total mass, have a greater negative impact on respiratory health (Spira-Cohen 2011). In Pulmonary Function Study 13, stronger and more consistent positive associations with oxidative potential DTT were found than with mass concentration (Yan 2019). Cardiovascular Mortality Study 5 found significant positive associations with EC and a 5 times greater risk of adverse health effects than total $PM_{2.5}$ mass in general (Thurston 2016). These conclusions support and emphasize the importance of analyzing the chemical constituents of $PM_{2.5}$ in health outcome studies.

Our findings suggest that studying the specific components of $PM_{2.5}$ and their associations with health endpoints could be lucrative. A better understanding of what chemicals in $PM_{2.5}$ contribute to adverse human health effects might provide better insight into protection efforts and medical treatments. While a number of environmental and public health protections are established by the EPA under the Clean Air Act, knowing the specifics of what chemicals influence which health outcomes and how, could better inform policy and medicine. Currently, lead is the only elemental $PM_{2.5}$ component that the EPA regulates (EPA 2021). A shift in research focus of $PM_{2.5}$ concentration and health effects to studying chemical constituents of $PM_{2.5}$ and their impact on human health is necessary to achieve this insight.

5 Conclusion

Almost all studies in our systematic review reported significant positive associations with chemical components of $PM_{2.5}$ and different health endpoints. Our findings demonstrate the importance of studying how $PM_{2.5}$ chemical constituents influence health outcomes. Conducting more research on how the specific makeup of $PM_{2.5}$ affects human health could better inform environmental and public health protection efforts, rather than researching $PM_{2.5}$ mass concentration implications alone.

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