


Review

Traffic-Related Particulate Matter and Cardiometabolic Syndrome: A Review

C. M. Sabbir Ahmed ^{1,2}, Huanhuan Jiang ², Jin Y. Chen ^{1,2} and Ying-Hsuan Lin ^{1,2,*} 

¹ Environmental Toxicology Graduate Program, University of California, Riverside, CA 92521, USA; cahme002@ucr.edu (C.M.S.A.); jchen137@ucr.edu (J.Y.C.)

² Department of Environmental Sciences, University of California, Riverside, CA 92521, USA; hjiang@ucr.edu

* Correspondence: ying-hsuan.lin@ucr.edu; Tel.: +1-951-827-3785

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Abstract: Traffic-related particulate matter (PM) is a major source of outdoor air pollution worldwide. It has been recently hypothesized to cause cardiometabolic syndrome, including cardiovascular dysfunction, obesity, and diabetes. The environmental and toxicological factors involved in the processes, and the detailed mechanisms remain to be explored. The objective of this study is to assess the current scientific evidence of traffic-related PM-induced cardiometabolic syndrome. We conducted a literature review by searching the keywords of “traffic related air pollution”, “particulate matter”, “human health”, and “metabolic syndrome” from 1980 to 2018. This resulted in 25 independent research studies for the final review. Both epidemiological and toxicological findings reveal consistent correlations between traffic-related PM exposure and the measured cardiometabolic health endpoints. Smaller sizes of PM, particularly ultrafine particles, are shown to be more harmful due to their greater concentrations, reactive compositions, longer lung retention, and bioavailability. The active components in traffic-related PM could be attributed to metals, black carbon, elemental carbon, polyaromatic hydrocarbons, and diesel exhaust particles. Existing evidence points out that the development of cardiometabolic symptoms can occur through chronic systemic inflammation and increased oxidative stress. The elderly (especially for women), children, genetically susceptible individuals, and people with pre-existing conditions are identified as vulnerable groups. To advance the characterization of the potential health risks of traffic-related PM, additional research is needed to investigate the detailed chemical compositions of PM constituents, atmospheric transformations, and the mode of action to induce adverse health effects. Furthermore, we recommend that future studies could explore the roles of genetic and epigenetic factors in influencing cardiometabolic health outcomes by integrating multi-omics approaches (e.g., genomics, epigenomics, and transcriptomics) to provide a comprehensive assessment of biological perturbations caused by traffic-related PM.

Keywords: traffic-related air pollution; particulate matter; health effects; cardiovascular disease; metabolic syndrome; diabetes; obesity

1. Introduction

Ambient air pollution is a major environmental cause of the global burden of diseases, leading to the development of chronic and acute respiratory diseases, lung cancer, cardiovascular diseases (CVD), metabolic syndrome, and cardiometabolic-associated health outcomes such as obesity and diabetes [1–3]. These health outcomes can be largely attributed to traffic emissions resulting from rapid urbanization and increased traffic loads within the past few decades [4,5]. Due to the incomplete combustion of fossil fuels, traffic emissions release a large amount of pollutants into the atmosphere, including carbon monoxide (CO), volatile organic compounds or poly aromatic hydrocarbons (PAHs), nitrogen oxides ($\text{NO}_x = \text{NO} + \text{NO}_2$), and particulate matter (PM) [6].

PM is a complex mixture made up of numerous organic and inorganic components. The chemical compositions of PM play an important role in controlling the environmental fate and toxicity. The sizes of particles are also directly linked to their atmospheric lifetimes, as well as their potential to cause adverse health effects through inhalation. In general, particles with aerodynamic diameters of greater than 10 μm have relatively short suspension half-lives, and they can be largely filtered out by the nose and upper airways [7]. Smaller particles, such as fine particles ($\text{PM}_{2.5}$, less than 2.5 μm in diameter) or ultrafine particles (UFP, less than 0.1 μm in diameter) can deposit deeply into the lungs, and they cannot be easily cleared up by the respiratory system [8,9]. These small particles may even directly penetrate the bloodstream to enter the circulation system [10] and reach various target organs (e.g., lung, heart, liver and brain) [8], which can trigger systemic health effects. It has been reported by the World Health Organization (WHO) that 4.2 million premature deaths occurred due to exposure to ambient $\text{PM}_{2.5}$ in 2016 [11]. Among all of the major emission sources, traffic-related PM could contribute to c. 25% of the ambient $\text{PM}_{2.5}$ globally, and up to 37% in regions with highly populated urban centers [12].

The chemical and physical properties of traffic-related PM vary, depending on the type of fuels, engine efficiency, and exhaust technologies [13–16]. Diesel and gasoline engine exhausts have been recognized as carcinogenic (Group 1 for diesel) and possibly carcinogenic (Group 2B for gasoline) to humans, by the International Agency for Research on Cancer [17,18]. Metals, PAHs (e.g., benzo[a]pyrene), and derivatives of PAHs (such as oxygenated PAHs and nitro-PAHs) have been constantly detected in exhaust PM from the operation of vehicles [16,19,20], and they are recognized as the major components that increase the risks of mutagenic or carcinogenic effects [21–23]. Recently, an increasing number of epidemiological studies have reported significant associations between exposure to PAHs or diesel exhaust mixture, and the health outcomes of β -cell dysfunction, insulin resistance, and increased blood pressure. A recent systematic review conducted by Meo et al. [24] highlighted the effects of long-term exposure to traffic-related PM on the increased risk of type 2 diabetes. Cardiometabolic syndrome is defined by a group of symptoms including hypertension, central obesity, insulin resistance, atherogenic dyslipidemia, low high-density lipoproteins, hypertriglyceridemia, impairment of glucose homeostasis, and elevated urinary albumin excretion [25,26]. The occurrences of these syndromes will eventually contribute to type 2 diabetes and cardiovascular events, and will largely increase the global costs of healthcare [27,28]. Considering traffic-related PM as a modifiable risk factor, understanding the underlying mechanisms of exposure-induced cardiometabolic syndrome is crucial to reducing the burden of diseases from obesity, diabetes, and cardiovascular morbidity.

The objective of this study is to provide an up-to-date overview on the associations between traffic-related PM and cardiometabolic syndrome, with a focus on cardiovascular health outcomes, metabolic dysfunction, obesity, and diabetes. We systematically reviewed the evidence from both epidemiological and toxicological research studies published over the past few decades. This study presents a snapshot of the current knowledge and limitations in available traffic-related PM and cardiometabolic research, and aims to bridge the gaps from sources to outcomes from a mechanistic perspective, on the cellular pathways and molecular mechanisms.

2. Methodology

We searched peer-reviewed journal articles on the topics of traffic-related PM and cardiometabolic health outcomes that had been published between 1 January 1980 and 20 June 2018. We included articles written in English only, and we considered all relevant original research papers, but excluded conference abstracts, unpublished data, and non-research publications, such as commentaries and review articles.

We reviewed literature that was indexed in four of the most commonly accessed databases for scientific journals: Google Scholar, Web of Science, PubMed, and JSTOR. In each database, we used a stepwise strategy to search the most relevant studies by entering the keywords in the following order: “Traffic-related air pollution”, “Particulate matter”, “Human health”, and “Metabolic syndrome”.

After applying the eligibility criteria, the key findings of our search results were summarized based on the study design, the characteristics of subject groups, the exposure metrics, and health outcomes. For epidemiological studies, we comprehensively reviewed the scientific findings on the associations between traffic-related PM and health outcomes, including metabolic syndrome, diabetes, obesity, CVD, and the associated morbidities and mortalities of these diseases. For controlled human exposure and toxicological studies, we described the methodologies of specific studies and the critical assessment of the effects of traffic-related PM exposure on the measured health endpoints. Finally, the limitations of these studies were identified, and the knowledge gaps were discussed.

3. Results

3.1. Search Results of Databases

The literature search from four databases identified a total of 19,646 papers. We excluded duplicates (i.e., identical papers obtained from multiple search engines), and removed papers that did not meet the inclusion criteria by reviewing the article titles and abstracts. After adding the final keyword of “metabolic syndrome”, we obtained a reduced number of articles from all databases (Table S1), with 244 from Google Scholar, three from Web of Science, 0 from PubMed, and four from JSTOR (Table S1). After reviewing the papers with the eligibility criteria, 25 independent studies were identified that were directly related to traffic-related PM and cardiometabolic health effects (Figure 1). Table 1 provides a summary of 25 studies included in the final review. Among 25 independent research papers, we found 18 articles on epidemiological studies, two articles on controlled human exposure, and five articles on toxicological studies. Details of the research findings in selected studies are provided in Table S2.

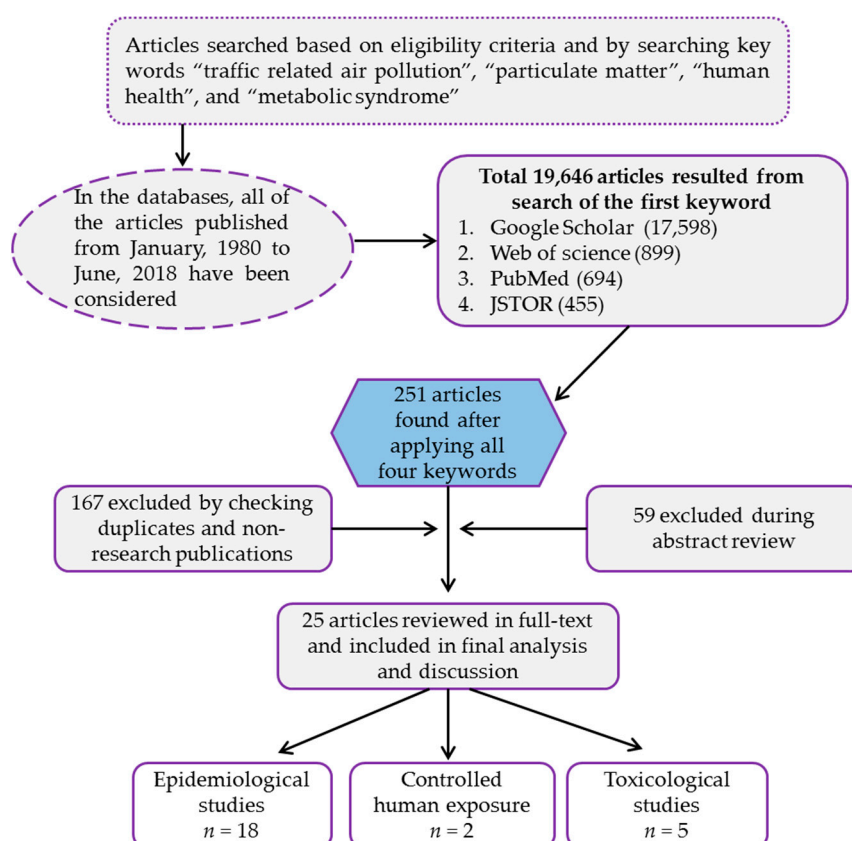


Figure 1. Flow chart of article selection based on the eligibility criteria.

Table 1. Summary of traffic-related PM and cardiometabolic health outcomes from 25 selected epidemiological, controlled human exposure, and toxicological research studies based on the eligibility criteria (more details in Table S2).

Health Outcomes	Reference	Location	Sample Size
Cardiovascular disease (CVD)-related outcomes: Cardiac rhythm inflammation coagulation, changes in heart rate variability, stroke, cardiac autonomic function coronary diseases, telomere length, and changes in white blood cells, neutrophils, monocytes, and inflammatory responses	Riediker et al., 2007 [29]	NC, USA	9
	Alexeeff et al., 2018 [30]	CA, USA	41,869
	Riediker et al., 2018 [31]	Western Switzerland	18
	Mazidi & Speakman, 2018 [32]	USA	26,349 (NHANES) ¹
			1,283,722 (BRFSS) ²
	Peretz et al., 2008 [33]	Seattle, WA, USA	27
	Wu et al., 2011 [34]	Beijing, China	14
	Gan et al., 2011 [35]	Vancouver, Canada	452,735
	Hou et al., 2012 [36]	Beijing, China	120
	Steenhof et al., 2014 [37]	Netherlands	31
Diabetes	Wagner et al., 2014 [38]	MI, USA	64
	Chen et al., 2013 [39]	ON, Canada	62,012
	Dijkema et al., 2011 [40]	Westfriesland, Netherlands	8018
	Ruckerl et al., 2014 [41]	Augsburg, Germany	274
Obesity	Hou et al., 2016 [42]	Wuhan Zhuhai, China	2730
	Ponticciello et al., 2015 [43]	Rome, Italy	150
Metabolic syndrome: insulin resistance, β -cell dysfunction, hypertension, blood pressure, hyperglycemia, atherosclerosis, systemic inflammation, and dysregulated insulin signaling	Hu et al., 2015 [44]	USA	1878 (NHANES) ¹
	Yang et al., 2017 [45]	Liaoning, China	24,845
	Chung et al., 2015 [46]	Boston, MA, USA	220
	Thiering et al., 2013 [47]	Munich and Wesel, Germany	397
	Brook et al., 2013 [1]	MI, USA	25
	Cosselman et al., 2012 [48]	Seattle, WA, USA	45
	Matsuda et al., 2013 [49]	Brazil	66
	Brocato et al., 2014 [50]	Jeddah, Saudi Arabia	9
	Xu et al., 2016 [51]	Beijing, China	N/A ³
	Wang et al., 2017 [52]	MD, USA	400

¹ NHANES: National Health and Nutritional Examination Survey; ² BRFSS: The Behavioral Risk Factor Surveillance System; ³ N/A: information not available.

The search results were grouped according to four time-periods (1980–1990, 1991–2000, 2001–2010, and 2011–2018) to show the temporal trend of research studies over the years (Table S1). Most studies identified in this review are in 2011–2018. The number of studies on traffic-related PM effects on metabolic syndrome in human health have increased dramatically during 2011–2018 (211 articles) compared to 2000–2010 (40 articles) and the earlier years, indicating the increasing attention to air pollution and metabolic syndrome in the last eight years. Traffic-related PM-induced metabolic health effects have posed an emerging issue, and have raised serious public health concerns.

3.2. Current Understanding of Cardiometabolic Syndrome Induced by Traffic-Related PM Exposure

Cardiometabolic complications are complex diseases that are influenced by a wide array of genetic, epigenetic, and environmental risk factors. Many of them are closely interrelated. In this review, we focus on the following cardiometabolic health outcomes: CVD, metabolic syndrome, diabetes, and obesity. We discussed evidence from epidemiological and toxicological studies, with a specific focus on identifying susceptible subpopulations and seeking a link between exposure metrics (e.g., exposure locations, time, concentrations, and chemical compositions) and the reported health outcomes.

3.2.1. Exposure Metrics

Spatial and temporal differences in research locations represent distinct emission patterns and surrounding environments, which may directly influence the exposure and health outcomes by modifying the physicochemical properties of pollutants. From epidemiological studies identified in this review, North America, East Asia, and Europe are the most frequently studied regions. PM concentrations and compositions could be highly variable in urban and rural settings. In addition, various sizes of PM have been reported in the studies on traffic-related PM, including PM₁₀, PM_{2.5–10}, PM_{2.5}, and UFP. The size distributions, number and mass concentrations have been considered as

important metrics for exposure assessment. Overall, particle number concentrations are related to size distributions. Smaller sizes of particles have higher number concentrations, greater surface areas, more redox reactive compounds, enhanced bioavailability, and longer retention time in the lung system [53]. Several size-segregated PM studies have indicated that UFPs are positively correlated with cardiovascular dysfunction [46,54,55]. The PM mass concentrations reported in the identified studies range from c. 4 to 127 $\mu\text{g}/\text{m}^3$ for epidemiological studies, c. 100 to 200 $\mu\text{g}/\text{m}^3$ for the controlled human exposure studies, and c. 17 to 600 $\mu\text{g}/\text{m}^3$ for toxicological studies, many of which exceed the WHO guidelines ($\text{PM}_{2.5}$: 25 $\mu\text{g}/\text{m}^3$ for the 24 h mean and 10 $\mu\text{g}/\text{m}^3$ for the annual mean; PM_{10} : 50 $\mu\text{g}/\text{m}^3$ for the 24 h mean and 20 $\mu\text{g}/\text{m}^3$ for the annual mean) but they may be representative of what polluted urban areas are typically encountered worldwide [56–58].

Several approaches have been used to estimate the exposure to traffic-related PM. The exposure concentrations of PM in the presented research studies were either retrieved from the ambient monitoring stations to infer the exposure at a community level or measured in situ to represent exposure concentrations at a personal level. Among 25 papers, only a limited number of studies have reported detailed PM chemical compositions. Common chemical species that are reported in traffic-related PM include black carbon (BC), organic carbon (OC), PAHs, elemental carbon (EC), and transition metals (e.g., Cu, Ni and V), and they are often accompanied with gaseous co-pollutants such as NO_x and CO. These chemical species have been widely used as markers for source apportionment of PM from vehicle emissions [59]. In identified toxicological studies, samples from concentrated PM collected from ambient or roadsides were often used for the exposure of model organisms [38,49–52].

In addition, proximity to roads has been commonly used as a surrogate measure to estimate traffic-related air pollution exposure [60]. In a cross-sectional diabetes screening study by Dijkema et al. [40], 8010 participants (aged 50 to 75 years), who lived in the semi-rural area of Westfriesland, Netherlands, were assessed between 1998 and 2000. Overall, there were no clear associations found between type 2 diabetes and traffic-related air pollution within a 250 m buffer in this study [40]. However, it was reported that women could be more susceptible than men in response to exposure to traffic emissions, although the associations were not significant [40]. As the exposure was characterized by the home addresses, misclassification could occur due to the lack of information on occupational or commuting exposure [40]. Also, unmeasured confounding factors such as lifestyle and personal socio-economic status (e.g., smoking status and prior cardiovascular disease) could have affected the data analysis [40].

3.2.2. Measured Health Endpoints

Of the examined health outcomes, CVD is the leading cause of deaths worldwide. Exposure to traffic-related PM may be a modifiable risk factor for the development of CVD, and it could be mechanistically linked to systemic inflammation and oxidative stress. For example, positive associations between exposure to traffic-related PM and altered cardiac autonomic function have been reported in young healthy adults [34]. In-vehicle exposure to $\text{PM}_{2.5}$ was linked to pathophysiologic changes that involve inflammation, coagulation, and cardiac rhythm [29]. Prehypertension and increased arterial blood pressures have also been observed in adults after exposure to traffic-related PM. These adverse health effects are more pronounced among females, the elderly, and in populations with genetic predispositions involved in the detoxification process of inflammation [29,30,45].

Heart rate variability, an index of autonomic balance [61], is an important marker for cardiometabolic syndrome [61,62]. It has been reported to be modified by traffic-related $\text{PM}_{2.5}$ in both epidemiological and toxicological studies. In the study on 18 healthy male Swiss highway maintenance workers that was conducted by Riediker et al. [31], a reduced standard deviation from normal to normal beat intervals (a marker of global autonomic activity) and the percentage of the interval differences exceeding 50 ms (a marker of parasympathetic activity) were observed after acute exposure to $\text{PM}_{2.5}$, especially during the working hours along the highway. This result indicated a reduction in

autonomic nervous activity that was induced by traffic-related PM [31,63]. Similarly, a toxicological study by Wagner et al. [38] reported enhanced and prolonged cardiac depression, including decreased heart rate variability and blood pressure, induced by traffic-related PM_{2.5} using a rat model.

The alteration of telomere length (TL) has been used as another biomarker of CVD [36]. As telomere sequences have a large amount of guanine residues, they are susceptible to being shortened by oxidative stress, which is a common pathway of CVD induction [64]. In a study by Hou et al. [36], ambient personal PM_{2.5} and EC (commonly found in traffic-related PM) in Beijing, China, were measured and correlated with the TL in blood samples from 120 truck drivers and 120 office workers. An increase of TL was attributed to exposure to personal PM_{2.5} and EC, either during working hours on the examination day, or 1–2 days prior to the examination, and truck drivers showed longer TL than office workers, indicating the participation of TL in sustaining the inflammatory mechanisms after short-term exposure to traffic-related PM [36]. However, they also suggested that long-term exposure to PM could shorten the TL after prolonged pro-oxidant exposures [36].

Another leading cause of global deaths is type 2 diabetes [65,66]. The incidents of diabetes are expected to increase rapidly worldwide [66]. Lifestyle, genetic, and environmental factors are notably associated with the prevalence of diabetes. In particular, exposure to air pollution has been linked to the increased risks of diabetes [67]. Chen et al. [39] reported a population-based cohort study in Ontario, Canada, which assessed the relationship between diabetes incidence and long-term exposure of PM_{2.5} from 62,012 data points. The results suggested that PM_{2.5} might contribute to the development of diabetes in population with ages of 35 years or older [39]. In addition to the evidence found in adults, a cohort study conducted by Thiering et al. [47] observed a clear association between long-term exposure to traffic-related PM and insulin resistance in 397 10-year old children in Germany.

3.2.3. Active Components within Traffic-Related PM

BC, metals, PAHs and their derivatives, diesel exhaust particles in traffic-related PM have been shown to be active components that lead to cardiometabolic health effects. Exposure to BC can promote the plasma levels of myeloperoxidase that can generate reactive oxygen and nitrogen species through lipid peroxidation, leading to inflammatory responses, oxidative stress, and the destabilization of the pre-existing atheromatous plaque and vessel occlusions, and endothelial dysfunction of vulnerable plaques [68–71]. The blood viscosity can also be elevated after exposure to BC, resulting in the onset of arterial thrombosis [71]. In a study conducted in Barcelona, Spain from 2005 to 2014, an association has been found between the BC (a median concentration of 1.4 µg/m³ since 2007) exposure and the onset of stroke and large-vessel atherosclerosis 1–3 days later based on the hospital admissions data [72]. Clear linear exposure-response relationships have also been identified between BC and coronary events, including hospitalization and mortality [35]. A study conducted in Rome, Italy by Ponticelli et al. [43] with 150 municipal police volunteers, reported that traffic police subjects were vulnerable to developed obesity, due to the exposure of traffic-related PAHs and metals. Peretz et al. [33] investigated the effects of exposure to diesel exhaust particles on 27 human subjects in Seattle, USA. Diesel exhaust particles are composed of a carbon core and a complex mixture of metals and organic materials [73]. With a short-term exposure of diesel exhaust at concentrations of 100 or 200 µg/m³, a vasoconstriction of conductance arteries and an acute endothelial responses have been observed in the studied subjects [33].

Notably, some discrepancies exist in the identified research studies regarding the role of BC in cardiometabolic health effects. There was no significant association between BC and diastolic blood pressure reported in the study of Chung et al. [46], which investigated 220 participants (mean age = 58.5 years) living near highway areas of Massachusetts. However, a positive association between particle number concentrations (as a measure of UFPs) and diastolic blood pressure was found, and this positive association was more pronounced among obese individuals than non-obese individuals [46].

3.2.4. Potential Underlying Mechanisms

Associations between exposure to traffic-related PM and health endpoints have been found from many epidemiological studies. Underlying cellular and molecular mechanisms remain to be explored. A few mechanisms have been proposed in the current literature.

First, exposure to traffic-related PM_{2.5} has been linked to the upregulation of the NF- κ B pathway, resulting in inflammatory responses and metabolic disorders [51]. Exposure-induced inflammatory responses were observed through the measurement of changes in white blood cell (WBC) counts [37]. Brocato et al. [50] reported that exposure of rats to PM₁₀ enhanced the expression of genes that were involved with inflammation, cholesterol and lipid metabolism, and atherosclerosis. Wang et al. [52] also concluded that that traffic-related PM_{2.5} exposure resulted in the dysregulation of insulin signaling, systemic inflammation, and an increased premature mortality in *Drosophila*. Second, the inhalation of traffic sourced PM_{2.5} can increase the level of proinflammatory cytokines and proinflammatory mediators that are closely related to blood coagulability and endothelial dysfunction [74,75]. Third, P_{2.5} exposure may stimulate the expression of RNAs that are related to systemic inflammation, endothelial dysfunction, and atherosclerosis [76]. Fourth, PM_{2.5} may interact with nociceptive or noradrenergic receptors to stimulate the sympathetic nervous system, and then elevate the circulating levels of the vasoconstrictor angiotensin II [48]. Fifth, exposure to traffic-related PM, such as diesel exhaust particles, may elevate the plasma concentration of endothelin 1, decreasing the blood flow to the heart and then cardiac events [77]. Another possible pathway is the increased production of C-reactive protein, an independent risk factor for CVD, after exposure to PM_{2.5} [78].

4. Discussion

Overall, through our literature review, there is clear evidence that exposure to traffic-related PM increases the risks of the development or exacerbation of cardiometabolic disorders in human populations. Our results are coherent with previous review studies that have comprehensively synthesized the existing knowledge on health effects of ambient air pollution, some of which have specifically focused on CVD and type 2 diabetes [34,40,79,80]. Our study further narrowed down the scope of the review to traffic-related PM, a major contributor to urban PM. We have sought to connect the detailed chemical compositions of traffic-related PM to the measured cardiometabolic health endpoints with mechanistic supports. The mechanisms behind metabolic syndrome are generally linked to systemic inflammation, and direct and indirect coagulation activation that is induced by the direct translocation of PM into the systemic circulation [3,9,81].

The chemical compositions of traffic-related PM are very complex and often not fully identified. To date, the metabolic health outcomes from EC, BC, PAHs, and metals have been widely studied and assessed, but the correlations between organic carbonaceous components (e.g., fuel-derived aldehydes, peroxides, and acids) and metabolic syndrome are still unclear. There is a study showing that an increase in blood pressure was strongly associated with an increase in ambient primary OC and UFPs in the Los Angeles basin, predominantly from traffic sources [82]. However, it should be noted that ambient OC is composed of numerous individual organic compounds, though it is constantly reported as one exposure metric. The physicochemical properties and functional groups of reactive organic constituents within PM could significantly modify the health effects of PM [83], which needs to be investigated further.

Figure 2 presents a conceptual diagram of the induction of cardiometabolic syndrome by traffic-related PM, which bridges the connections among the PM sources, exposure routes, and biological perturbations (at molecular and cellular levels). Inhalation exposure to traffic-related PM first induces inflammatory cytokines and chemokines (e.g., IL-6, TNF- α , and CCL2) [3,9,14,15,50,75] by the activation of the TLR2/4-NF- κ B signaling pathways, triggering the expression of cytokine genes [3,9]. These cytokines further cause systemic inflammation and oxidative stress, leading to the development of cardiometabolic disorders, including obesity and CVD. As different chemical

components in PM have different target sites, detecting detailed chemical compositions of traffic-related PM is crucial for deciphering the molecular mechanisms of cardiometabolic syndrome.

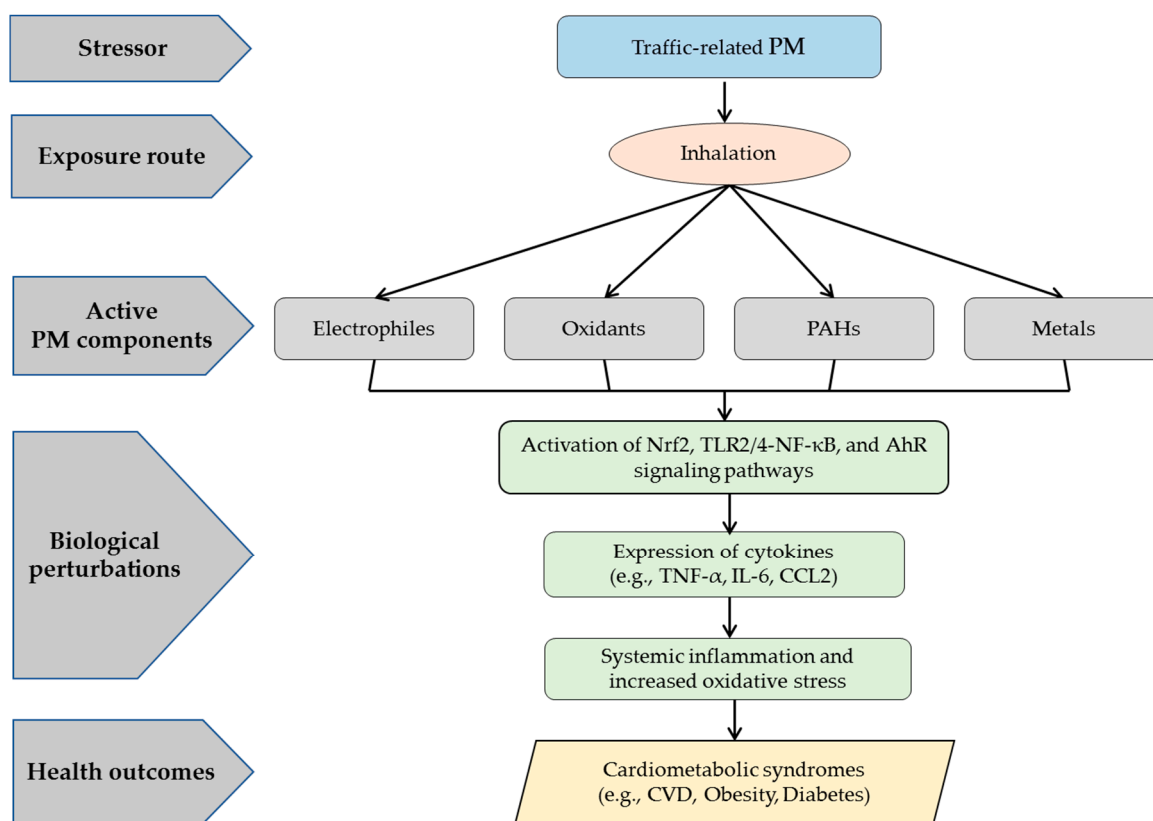


Figure 2. A conceptual diagram of traffic-related particulate matter (PM)-induced cardiometabolic syndrome-connecting sources, exposure, biological perturbations, and outcomes.

Despite significant progress in current research on traffic-related PM on cardiometabolic health outcomes, our understanding of environmental factors linked to diabetes is still limited. Common biochemical processes where hyperglycemia and free fatty acids induce oxidative stress, causing insulin resistance, β -cell dysfunction, and late diabetic complications (e.g., nephropathy, retinopathy, neuropathy, and macro- and microvascular damage) have been proposed [84]. It was hypothesized that free fatty acids and elevated glucose can activate the nuclear factor- κ B, p38 MAPK, and the NH_2 -terminal Jun kinases/stress-activated protein kinase stress pathways play a key role in developing late complications in type 1 and type 2 diabetes [84]. Various atmospheric particles including PAHs and nitro PAHs induce increased production of reactive oxygen species (ROS) and oxidative stress. Possible pathways that might be involved with adverse health effects of PAHs are:

- (1) Activation of peroxisome proliferator activated receptors (PPARs) [85] that are major regulators of lipid and glucose metabolism [86];
- (2) Imbalance between ROS production (e.g., peroxides, superoxides, and hydroxyl radicals) and antioxidant defenses, which may lead to alterations in insulin signaling pathways [87];
- (3) Induction of inflammation caused by PAHs that may lead to insulin resistance [88].

Current knowledge regarding the biological mechanisms of PAHs on perturbations of glucose metastasis that increase the risks of metabolic syndrome, remains unclear [44]. The current use of urinary hydroxyl PAHs is a robust biomarker in assessing health effects of PAHs, but the short life-time of PAHs in the human body can only indicate the instant responses of PAH exposure [42,44,89].

Also, studies have found that different types of PAHs (e.g., naphthalene and benzo[a]pyrene) contribute to different health effects, and more studies are needed to clarify the effects of different PAHs [44]. In addition, our current understanding of toxicological mechanisms points to systemic oxidative stress and inflammation-mediated cardiometabolic health effects. Recent studies indicate that particle-bound ROS may directly contribute to oxidative stress [90–92]. The role of PM-bound and PM-induced oxidative stress leading to the development or exacerbation of cardiometabolic syndrome needs to be further investigated.

In our review, we found that results were very pronounced in controlled human exposure studies with exposure to higher levels of traffic-related PM that far exceeded the WHO air quality guidelines. In the double-blinded and exposure crossover study by Cosselman et al. [48], 45 nonsmoking subjects (18–49 years) were exposed to 200 $\mu\text{g}/\text{m}^3$ of diesel exhaust for 120 minutes. A rapid and measurable increase in systolic blood pressure was observed in young nonsmokers. There was no significant effect on heart rate or diastolic blood pressure. The correlations between systolic blood pressure and exposure to traffic-related PM_{2.5} have also been reported previously by Brook et al. [93] and Langrish et al. [94]. Notably, it has been reported that even at low levels, traffic-related PM_{2.5} has been shown to dysregulate metabolic insulin sensitivity, and eventually contributed to the development of diabetes [1]. Long-term exposure at low dose levels should be further explored to establish the understanding of dose-response relationships for a better risk characterization.

Both genetic and epigenetic factors are important to the development of CVD and diabetes [95]. It is evident that genetic polymorphisms in detoxification enzymes could be a susceptibility factor leading to differential health effects upon exposure [96–98]. Epigenetic factors including chromatin remodeling, histone modification, DNA methylation, and non-coding RNA expression are also important [99]. Recently, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been used as effective biomarkers in the manifestation of diverse diseases [100]. Experimental data from in vitro and in vivo diabetic models have shown an altered profile of microRNA expression in insulin target tissues [100]. Overall, non-coding RNAs are critical in the pathogenesis and progression of metabolic disorders. Non-coding RNAs or their inhibitors may be potential targets during the treatment of cardiometabolic-associated health risks.

Some inconclusive results from different epidemiological or toxicological studies may be attributed to the variations of studied objects, sample sizes, exposure concentrations, dose levels, and genetic polymorphisms. In order to obtain more convincing results, sufficient samples, including populations with different genders from diverse backgrounds, should be considered. Also, any possible influential or confounding factors should be carefully examined to avoid biases. Most of the current toxicological studies focused on either the ambient traffic-related air pollutants or on primary exhaust from tailpipes of vehicles. There is a lack of toxicological information about aged or secondary PM derived from vehicle emissions. Potential synergistic effects from multi-pollutant exposure have not been characterized, either. Also, there are limited in vitro studies to investigate the pathways of traffic-related PM-induced health effects at a cellular level.

5. Conclusions

In this review, we aimed to obtain an overview to assess the current scientific evidence of traffic-related PM induced cardiometabolic syndrome by using the keywords “traffic related air pollution”, “particulate matter”, “human health”, and “metabolic syndrome” from 1980 to 2018. The initial literature searches from four databases identified a total of 19,646 papers. After adding all four keywords, reviewing the papers with the eligibility criteria, 25 independent studies were identified that were directly related to traffic-related PM and cardiometabolic health effects. Among 25 independent research papers, we found 18 articles on epidemiological studies, two articles on controlled human exposure, and five articles on toxicological studies.

From present review, we found consistent evidence of associations between exposure to traffic-related PM, and the development of metabolic syndrome in human populations, as supported by

laboratory experiments from both epidemiological and toxicological studies. The vulnerable groups are represented by the elderly (especially for women), children, and genetic susceptible individuals with a predisposition of genes that are involved in detoxification and inflammatory pathways. Our review also indicates that both genetic and epigenetic factors play a key role in traffic-related PM induced metabolic health burden. Considering that traffic-related PM is a modifiable risk factor, the reduction of PM from traffic sources may be translated to huge public health implications. Thus, connecting the dots between traffic-related PM compositions, environmental concentrations, the magnitude, frequency, and duration of exposure, and the molecular mechanisms and cellular pathways leading to pathogenesis, is crucial to bridge the source-to-health effects continuum.

Given that cardiometabolic syndrome is a multifactorial disorder, limitations existed in our search methodologies for the systematic review. In the processes of the literature search, we found that there was a scarcity of articles for specific areas, especially in toxicological studies. This may be due to the search keywords not being uniform across the disciplines. While the cardiometabolic syndrome covers vast areas including CVD (e.g., high blood pressure, heart rate variability, cardiac arrest, stroke, and myocardial dysfunction), obesity, diabetes (e.g., type 1 diabetes, type 2 diabetes, and gestational diabetes), hyper/hypoglycemia, and hypertension, not all of these research studies would use the term of “metabolic syndrome” in titles or abstracts. As a result, many relevant studies for each disease category could be missing because of the search terms within available databases. In addition, when collecting relevant papers from the databases using the four keywords, the search engines may miss the papers that are traffic-related, but that do not contain the exact keyword of “traffic-related air pollution”. The terms such as BC (an indicator of traffic-related PM) should also be included during the filtration. Nevertheless, our current review has provided a brief overview of the up-to-date understanding of the issues, and the results are coherent with prior studies.

Taken together, more studies are needed to understand the detailed chemical compositions, the spatial and temporal variations, the molecular mechanisms, and the action mode of traffic-related PM to advance the exposure assessment, and to improve the characterization of the potential health risks. For example, most studies identified in this review that showed strong associations, were based on short-term exposure to high levels of traffic-related PM. Though levels of ambient air pollution have declined over the past decades in many developing areas (e.g., North America and in Europe), it remains uncertain as to what extent the health effects of long-term exposure to low levels of traffic-related PM in general populations can be extrapolated from current research results. Further studies are required to elucidate this question. In addition, the recent developments of alternative fuels and engine technologies have been shown to change the physical and chemical characteristics of traffic-related PM emissions. Meanwhile, atmospheric transformations (e.g., the photochemical aging processes) of traffic emissions may significantly modify the chemical compositions and toxicity of traffic-related PM, which adds on another layer of complexity when assessing the health effects. Thus, studies focused on analyzing traffic-related PM emissions under various environmental conditions might be helpful, and speciation of organic PM compositions at the molecular level will contribute to a more accurate characterization of stressors. Moreover, future studies could also explore the role of genetic and epigenetic factors in influencing cardiometabolic syndrome by integrating the “-omics” approaches (e.g., genomics, epigenomics and transcriptomics) to provide a comprehensive assessment of biological perturbations caused by traffic-related PM, and to facilitate molecular diagnosis for systems understanding of adverse outcome pathways.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4433/9/9/0/s1>, Table S1: Results of databases with subsequent keywords “Traffic related air pollution”, “Particulate matter”, “Human health”, and “Metabolic syndrome”, grouped by various time intervals. Table S2: Summary of selected 25 articles on traffic-related PM and their impacts in the progression of cardiometabolic syndrome.

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References

1. Brook, R.D.; Xu, X.H.; Bard, R.L.; Dvonch, J.T.; Morishita, M.; Kaciroti, N.; Sun, Q.H.; Harkema, J.; Rajagopalan, S. Reduced metabolic insulin sensitivity following sub-acute exposures to low levels of ambient fine particulate matter air pollution. *Sci. Total Environ.* **2013**, *448*, 66–71. [[CrossRef](#)] [[PubMed](#)]
2. Du, Y.X.; Xu, X.H.; Chu, M.; Guo, Y.; Wang, J.H. Air particulate matter and cardiovascular disease: The epidemiological, biomedical and clinical evidence. *J. Thoracic Dis.* **2016**, *8*, E8–E19.
3. Wei, Y.J.; Zhang, J.F.; Li, Z.G.; Gow, A.; Chung, K.F.; Hu, M.; Sun, Z.S.; Zeng, L.M.; Zhu, T.; Jia, G.; et al. Chronic exposure to air pollution particles increases the risk of obesity and metabolic syndrome: Findings from a natural experiment in Beijing. *FASEB J.* **2016**, *30*, 2115–2122. [[CrossRef](#)] [[PubMed](#)]
4. Jakubiak-Lasocka, J.; Lasocki, J.; Siekmeier, R.; Chlopek, Z.; Pokorski, M. Impact of traffic-related air pollution on health. In *Environment Exposure to Pollutants*; Springer: Cham, Switzerland, 2015; Volume 834, pp. 21–29.
5. Libalova, H.; Rossner, P.; Vrbova, K.; Brzicova, T.; Sikorova, J.; Vojtisek-Lom, M.; Beranek, V.; Klema, J.; Ciganek, M.; Neca, J.; et al. Transcriptional response to organic compounds from diverse gasoline and biogasoline fuel emissions in human lung cells. *Toxicol. In Vitro* **2018**, *48*, 329–341. [[CrossRef](#)] [[PubMed](#)]
6. Zhang, K.; Batterman, S. Air pollution and health risks due to vehicle traffic. *Sci. Total Environ.* **2013**, *450*, 307–316. [[CrossRef](#)] [[PubMed](#)]
7. Anderson, J.O.; Thundiyil, J.G.; Stolbach, A. Clearing the air: A review of the effects of particulate matter air pollution on human health. *J. Med. Toxicol.* **2012**, *8*, 166–175. [[CrossRef](#)] [[PubMed](#)]
8. Xia, T.; Zhu, Y.F.; Mu, L.N.; Zhang, Z.F.; Liu, S.J. Pulmonary diseases induced by ambient ultrafine and engineered nanoparticles in twenty-first century. *Natl. Sci. Rev.* **2016**, *3*, 416–429. [[CrossRef](#)] [[PubMed](#)]
9. Franklin, B.A.; Brook, R.; Pope, C.A. Air pollution and cardiovascular disease. *Curr. Prob. Cardiol.* **2015**, *40*, 207–238. [[CrossRef](#)] [[PubMed](#)]
10. Hoet, P.H.M.; Brüske-Hohlfeld, I.; Salata, O.V. Nanoparticles—Known and unknown health risks. *J. Nanobiotechnol.* **2004**, *2*, 12. [[CrossRef](#)] [[PubMed](#)]
11. WHO (World Health Organization). *Ambient (Outdoor) Air Quality and Health*; Fact Sheet; WHO: Geneva, Switzerland, 2018.
12. Karagulian, F.; Belis, C.A.; Dora, C.F.C.; Prüss-Ustün, A.M.; Bonjour, S.; Adair-Rohani, H.; Amann, M. Contributions to cities' ambient particulate matter (PM): A systematic review of local source contributions at global level. *Atmos. Environ.* **2015**, *120*, 475–483. [[CrossRef](#)]
13. Karavalakis, G.; Short, D.; Vu, D.; Russell, R.; Hajbabaie, M.; Asa-Awuku, A.; Durbin, T.D. Evaluating the effects of aromatics content in gasoline on gaseous and particulate matter emissions from SI-PFI and SIDI vehicles. *Environ. Sci. Technol.* **2015**, *49*, 7021–7031. [[CrossRef](#)] [[PubMed](#)]
14. Bisig, C.; Roth, M.; Müller, L.; Comte, P.; Heeb, N.; Mayer, A.; Czerwinski, J.; Petri-Fink, A.; Rothen-Rutishauser, B. Hazard identification of exhausts from gasoline-ethanol fuel blends using a multi-cellular human lung model. *Environ. Res.* **2016**, *151*, 789–796. [[CrossRef](#)] [[PubMed](#)]
15. Roth, M.; Usemann, J.; Bisig, C.; Comte, P.; Czerwinski, J.; Mayer, A.C.R.; Beier, K.; Rothen-Rutishauser, B.; Latzin, P.; Müller, L. Effects of gasoline and ethanol-gasoline exhaust exposure on human bronchial epithelial and natural killer cells in vitro. *Toxicol. In Vitro* **2017**, *45*, 101–110. [[CrossRef](#)] [[PubMed](#)]
16. Yang, J.; Roth, P.; Durbin, T.D.; Johnson, K.C.; Cocker, D.R.; Asa-Awuku, A.; Brezny, R.; Geller, M.; Karavalakis, G. Gasoline particulate filters as an effective tool to reduce particulate and polycyclic aromatic hydrocarbon emissions from gasoline direct injection (GDI) vehicles: A case study with two GDI vehicles. *Environ. Sci. Technol.* **2018**, *52*, 3275–3284. [[CrossRef](#)] [[PubMed](#)]
17. Zheng, X.; Wu, Y.; Zhang, S.J.; Hu, J.N.; Zhang, K.M.; Li, Z.H.; He, L.Q.; Hao, J.M. Characterizing particulate polycyclic aromatic hydrocarbon emissions from diesel vehicles using a portable emissions measurement system. *Sci. Rep.* **2017**, *7*, 10058. [[CrossRef](#)] [[PubMed](#)]

18. Silverman, D.T.; Samanic, C.M.; Lubin, J.H.; Blair, A.E.; Stewart, P.A.; Vermeulen, R.; Coble, J.B.; Rothman, N.; Schleiff, P.L.; Travis, W.D.; et al. The diesel exhaust in miners study: A nested case-control study of lung cancer and diesel exhaust. *J. Natl. Cancer Inst.* **2012**, *104*, 855–868. [[CrossRef](#)] [[PubMed](#)]
19. Libalova, H.; Rossner, P.; Vrbova, K.; Brzicova, T.; Sikorova, J.; Vojtisek-Lom, M.; Beranek, V.; Klema, J.; Ciganek, M.; Neca, J.; et al. Comparative analysis of toxic responses of organic extracts from diesel and selected alternative fuels engine emissions in human lung BEAS-2B cells. *Int. J. Mol. Sci.* **2016**, *17*, 1833. [[CrossRef](#)] [[PubMed](#)]
20. Storey, J.M.; Lewis, S.; Szybist, J.; Thomas, J.; Barone, T.; Eibl, M.; Nafziger, E.; Kaul, B. Novel characterization of GDI engine exhaust for gasoline and mid-level gasoline-alcohol blends. *SAE Int. J. Fuels Lubr.* **2014**, *7*, 571–579. [[CrossRef](#)]
21. Kim, K.H.; Jahan, S.A.; Kabir, E.; Brown, R.J.C. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. *Environ. Int.* **2013**, *60*, 71–80. [[CrossRef](#)] [[PubMed](#)]
22. Kim, K.H.; Kabir, E.; Kabir, S. A review on the human health impact of airborne particulate matter. *Environ. Int.* **2015**, *74*, 136–143. [[CrossRef](#)] [[PubMed](#)]
23. Pedersen, M.; Vinzents, P.; Petersen, J.H.; Kleinjans, J.C.S.; Plas, G.; Kirsch-Volders, M.; Dostal, M.; Rossner, P.; Beskid, O.; Sram, R.J.; et al. Cytogenetic effects in children and mothers exposed to air pollution assessed by the frequency of micronuclei and fluorescence in situ hybridization (FISH): A family pilot study in the czech republic. *Mutat. Res.* **2006**, *608*, 112–120. [[CrossRef](#)] [[PubMed](#)]
24. Meo, S.A.; Memon, A.N.; Sheikh, S.A.; Rouq, F.A.; Usmani, A.M.; Hassan, A.; Arain, S.A. Effect of environmental air pollution on type 2 diabetes mellitus. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19*, 123–128. [[PubMed](#)]
25. Eze, I.C.; Schaffner, E.; Foraster, M.; Imboden, M.; von Eckardstein, A.; Gerbase, M.W.; Rothe, T.; Rochat, T.; Kunzli, N.; Schindler, C.; et al. Long-term exposure to ambient air pollution and metabolic syndrome in adults. *PLoS ONE* **2015**, *10*, e0130337. [[CrossRef](#)] [[PubMed](#)]
26. Alberti, K.; Zimmet, P.Z. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet. Med.* **1998**, *15*, 539–553. [[CrossRef](#)]
27. World Bank. *The Cost of Air Pollution: Strengthening the Economic Case for Action*; World Bank: Washington, DC, USA, 2016.
28. Einarson, T.R.; Acs, A.; Ludwig, C.; Panton, U.H. Economic burden of cardiovascular disease in type 2 diabetes: A systematic review. *Value Health* **2018**, *21*, 881–890. [[CrossRef](#)] [[PubMed](#)]
29. Riediker, M. Cardiovascular effects of fine particulate matter components in highway patrol officers. *Inhal. Toxicol.* **2007**, *19*, 99–105. [[CrossRef](#)] [[PubMed](#)]
30. Alexeeff, S.E.; Roy, A.; Shan, J.; Liu, X.; Messier, K.; Apte, J.S.; Portier, C.; Sidney, S.; Van Den Eeden, S.K. High-resolution mapping of traffic related air pollution with google street view cars and incidence of cardiovascular events within neighborhoods in Oakland, CA. *Environ. Health* **2018**, *17*, 38. [[CrossRef](#)] [[PubMed](#)]
31. Riediker, M.; Franc, Y.; Bochud, M.; Meier, R.; Rousson, V. Exposure to fine particulate matter leads to rapid heart rate variability changes. *Front. Environ. Sci.* **2018**, *6*, 2. [[CrossRef](#)]
32. Mazidi, M.; Speakman, J.R. Impact of obesity and ozone on the association between particulate air pollution and cardiovascular disease and stroke mortality among US adults. *J. Am. Heart Assoc.* **2018**, *7*, e008006. [[CrossRef](#)] [[PubMed](#)]
33. Peretz, A.; Sullivan, J.H.; Leotta, D.F.; Trenga, C.A.; Sands, F.N.; Allen, J.; Carlsten, C.; Wilkinson, C.W.; Gill, E.A.; Kaufman, J.D. Diesel exhaust inhalation elicits acute vasoconstriction in vivo. *Environ. Health Perspect.* **2008**, *116*, 937–942. [[CrossRef](#)] [[PubMed](#)]
34. Wu, S.W.; Deng, F.R.; Niu, J.; Huang, Q.S.; Liu, Y.C.; Guo, X.B. The relationship between traffic-related air pollutants and cardiac autonomic function in a panel of healthy adults: A further analysis with existing data. *Inhal. Toxicol.* **2011**, *23*, 289–303. [[CrossRef](#)] [[PubMed](#)]
35. Gan, W.Q.; Koehoorn, M.; Davies, H.W.; Demers, P.A.; Tamburic, L.; Brauer, M. Long-term exposure to traffic-related air pollution and the risk of coronary heart disease hospitalization and mortality. *Environ. Health Perspect.* **2011**, *119*, 501–507. [[CrossRef](#)] [[PubMed](#)]

36. Hou, L.; Wang, S.; Dou, C.; Zhang, X.; Yu, Y.; Zheng, Y.; Avula, U.; Hoxha, M.; Díaz, A.; McCracken, J.; et al. Air pollution exposure and telomere length in highly exposed subjects in Beijing, China: A repeated-measure study. *Environ. Int.* **2012**, *48*, 71–77. [[CrossRef](#)] [[PubMed](#)]
37. Steenhof, M.; Janssen, N.A.H.; Strak, M.; Hoek, G.; Gosens, I.; Mudway, I.S.; Kelly, F.J.; Harrison, R.M.; Pieters, R.H.H.; Cassee, F.R.; et al. Air pollution exposure affects circulating white blood cell counts in healthy subjects: The role of particle composition, oxidative potential and gaseous pollutants—The raptex project. *Inhal. Toxicol.* **2014**, *26*, 141–165. [[CrossRef](#)] [[PubMed](#)]
38. Wagner, J.G.; Allen, K.; Yang, H.Y.; Nan, B.; Morishita, M.; Mukherjee, B.; Dvonch, J.T.; Spino, C.; Fink, G.D.; Rajagopalan, S.; et al. Cardiovascular depression in rats exposed to inhaled particulate matter and ozone: Effects of diet-induced metabolic syndrome. *Environ. Health Perspect.* **2014**, *122*, 27–33. [[CrossRef](#)] [[PubMed](#)]
39. Chen, H.; Burnett, R.T.; Kwong, J.C.; Villeneuve, P.J.; Goldberg, M.S.; Brook, R.D.; van Donkelaar, A.; Jerrett, M.; Martin, R.V.; Brook, J.R.; et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. *Environ. Health Perspect.* **2013**, *121*, 804–810. [[CrossRef](#)] [[PubMed](#)]
40. Dijkema, M.B.A.; Mallant, S.F.; Gehring, U.; van den Hurk, K.; Alsema, M.; van Strien, R.T.; Fischer, P.H.; Nijpels, G.; Stehouwer, C.D.A.; Hoek, G. Long-term exposure to traffic-related air pollution and type 2 diabetes prevalence in a cross-sectional screening-study in the Netherlands. *Environ. Health* **2011**, *10*, 76. [[CrossRef](#)] [[PubMed](#)]
41. Ruckerl, R.; Hampel, R.; Breitner, S.; Cyrys, J.; Kraus, U.; Carter, J.; Dailey, L.; Devlin, R.B.; Diaz-Sanchez, D.; Koenig, W.; et al. Associations between ambient air pollution and blood markers of inflammation and coagulation/fibrinolysis in susceptible populations. *Environ. Int.* **2014**, *70*, 32–49. [[CrossRef](#)] [[PubMed](#)]
42. Hou, J.; Sun, H.; Xiao, L.; Zhou, Y.; Yin, W.; Xu, T.; Cheng, J.; Chen, W.; Yuan, J. Combined effect of urinary monohydroxylated polycyclic aromatic hydrocarbons and impaired lung function on diabetes. *Environ. Res.* **2016**, *148*, 467–474. [[CrossRef](#)] [[PubMed](#)]
43. Ponticciello, B.G.; Capozzella, A.; Di Giorgio, V.; Casale, T.; Giubilati, R.; Tomei, G.; Tomei, F.; Rosati, M.V.; Sancini, A. Overweight and urban pollution: Preliminary results. *Sci. Total Environ.* **2015**, *518–519*, 61–64. [[CrossRef](#)] [[PubMed](#)]
44. Hu, H.; Kan, H.D.; Kearney, G.D.; Xu, X.H. Associations between exposure to polycyclic aromatic hydrocarbons and glucose homeostasis as well as metabolic syndrome in nondiabetic adults. *Sci. Total Environ.* **2015**, *505*, 56–64. [[CrossRef](#)] [[PubMed](#)]
45. Yang, B.Y.; Qian, Z.M.; Vaughn, M.G.; Nelson, E.J.; Dharmage, S.C.; Heinrich, J.; Lin, S.; Lawrence, W.R.; Ma, H.; Chen, D.H.; et al. Is prehypertension more strongly associated with long-term ambient air pollution exposure than hypertension? Findings from the 33 communities Chinese health study. *Environ. Pollut.* **2017**, *229*, 696–704. [[CrossRef](#)] [[PubMed](#)]
46. Chung, M.; Wang, D.D.; Rizzo, A.M.; Gachette, D.; Delnord, M.; Parambi, R.; Kang, C.M.; Brugge, D. Association of PNC, BC, and PM_{2.5} measured at a central monitoring site with blood pressure in a predominantly near highway population. *Int. J. Environ. Res. Public Health* **2015**, *12*, 2765–2780. [[CrossRef](#)] [[PubMed](#)]
47. Thiering, E.; Cyrys, J.; Kratzsch, J.; Meisinger, C.; Hoffmann, B.; Berdel, D.; Von Berg, A.; Koletzko, S.; Bauer, C.P.; Heinrich, J. Long-term exposure to traffic-related air pollution and insulin resistance in children: Results from the giniplus and lisaplu birth cohorts. *Diabetologia* **2013**, *56*, 1696–1704. [[CrossRef](#)] [[PubMed](#)]
48. Cosselman, K.E.; Krishnan, R.M.; Oron, A.P.; Jansen, K.; Peretz, A.; Sullivan, J.H.; Larson, T.V.; Kaufman, J.D. Blood pressure response to controlled diesel exhaust exposure in human subjects. *Hypertension* **2012**, *59*, 943–948. [[CrossRef](#)] [[PubMed](#)]
49. Matsuda, M.; Krempel, P.G.; André, P.A.; Freitas, J.R. Traffic-related air pollution effect on fast glycemia of aged obese type 2 diabetic mice. *J. Clin. Exp. Cardiol.* **2013**, *4*, 255.
50. Brocato, J.; Sun, H.; Shamy, M.; Kluz, T.; Alghamdi, M.A.; Khoder, M.I.; Chen, L.C.; Costa, M. Particulate matter from Saudi Arabia induces genes involved in inflammation, metabolic syndrome and atherosclerosis. *J. Toxicol. Environ. Health A* **2014**, *77*, 751–766. [[CrossRef](#)] [[PubMed](#)]
51. Xu, M.X.; Zhu, Y.F.; Chang, H.F.; Liang, Y. Nanoceria restrains PM_{2.5}-induced metabolic disorder and hypothalamus inflammation by inhibition of astrocytes activation related NF- κ B pathway in Nrf2 deficient mice. *Free Radic. Biol. Med.* **2016**, *99*, 259–272. [[CrossRef](#)] [[PubMed](#)]

52. Wang, X.K.; Chen, M.J.; Zhong, M.H.; Hu, Z.Y.; Qiu, L.L.; Rajagopalan, S.; Fossett, N.G.; Chen, L.C.; Ying, Z.K. Exposure to concentrated ambient PM_{2.5} shortens lifespan and induces inflammation-associated signaling and oxidative stress in drosophila. *Toxicol. Sci.* **2017**, *156*, 199–207. [[PubMed](#)]
53. Araujo, J.A.; Nel, A.E. Particulate matter and atherosclerosis: Role of particle size, composition and oxidative stress. *Part. Fibre Toxicol.* **2009**, *6*, 24. [[CrossRef](#)] [[PubMed](#)]
54. Franck, U.; Odeh, S.; Wiedensohler, A.; Wehner, B.; Herbarth, O. The effect of particle size on cardiovascular disorders—The smaller the worse. *Sci. Total Environ.* **2011**, *409*, 4217–4221. [[CrossRef](#)] [[PubMed](#)]
55. Karottki, D.G.; Bekö, G.; Clausen, G.; Madsen, A.M.; Andersen, Z.J.; Massling, A.; Ketzel, M.; Ellermann, T.; Lund, R.; Sigsgaard, T.; et al. Cardiovascular and lung function in relation to outdoor and indoor exposure to fine and ultrafine particulate matter in middle-aged subjects. *Environ. Int.* **2014**, *73*, 372–381. [[CrossRef](#)] [[PubMed](#)]
56. Zhao, S.; Yu, Y.; Yin, D.; Qin, D.; He, J.; Dong, L. Spatial patterns and temporal variations of six criteria air pollutants during 2015 to 2017 in the city clusters of Sichuan basin, China. *Sci. Total Environ.* **2018**, *624*, 540–557. [[CrossRef](#)] [[PubMed](#)]
57. Mukherjee, A.; Agrawal, M. Air pollutant levels are 12 times higher than guidelines in Varanasi, India. Sources and transfer. *Environ. Chem. Lett.* **2018**, *16*, 1009–1016. [[CrossRef](#)]
58. Khaefi, M.; Geravandi, S.; Hassani, G.; Yari, A.R.; Soltani, F.; Dobaradaran, S.; Moogahi, S.; Mohammadi, M.J.; Mahboubi, M.; Alavi, N.; et al. Association of particulate matter impact on prevalence of chronic obstructive pulmonary disease in Ahvaz, southwest Iran during 2009–2013. *Aerosol Air Qual. Res.* **2017**, *17*, 230–237. [[CrossRef](#)]
59. Oakes, M.; Baxter, L.; Long, T.C. Evaluating the application of multipollutant exposure metrics in air pollution health studies. *Environ. Int.* **2014**, *69*, 90–99. [[CrossRef](#)] [[PubMed](#)]
60. Gan, W.Q.; Allen, R.W.; Brauer, M.; Davies, H.W.; Mancini, G.B.J.; Lear, S. Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: A prospective cohort study. *BMJ Open* **2014**, *4*, e004743. [[CrossRef](#)] [[PubMed](#)]
61. Malik, M.; Bigger, J.T.; Camm, A.J.; Kleiger, R.E.; Malliani, A.; Moss, A.J.; Schwartz, P.J. Heart rate variability standards of measurement, physiological interpretation, and clinical use. *Eur. Heart J.* **1996**, *17*, 354–381. [[CrossRef](#)]
62. Park, S.K.; Auchincloss, A.H.; O'Neill, M.S.; Prineas, R.; Correa, J.C.; Keeler, J.; Barr, R.G.; Kaufman, J.D.; Diez Roux, A.V. Particulate air pollution, metabolic syndrome, and heart rate variability: The multi-ethnic study of atherosclerosis (MESA). *Environ. Health Perspect.* **2010**, *118*, 1406–1411. [[CrossRef](#)] [[PubMed](#)]
63. Connes, P.; Martin, C.; Barthelemy, J.-C.; Monchanin, G.; Atchou, G.; Forsuh, A.; Massarelli, R.; Wouassi, D.; Thiriet, P.; Pichot, V. Nocturnal autonomic nervous system activity impairment in sickle cell trait carriers. *Clin. Physiol. Funct. Imaging* **2006**, *26*, 87–91. [[CrossRef](#)] [[PubMed](#)]
64. Jennings, B.J.; Ozanne, S.E.; Hales, C.N. Nutrition, oxidative damage, telomere shortening, and cellular senescence: Individual or connected agents of aging? *Mol. Genet. Metab.* **2000**, *71*, 32–42. [[CrossRef](#)] [[PubMed](#)]
65. IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. *Diabetes Res. Clin. Pract.* **2015**, *109*, 461–465. [[CrossRef](#)] [[PubMed](#)]
66. Chen, L.; Magliano, D.J.; Zimmet, P.Z. The worldwide epidemiology of type 2 diabetes mellitus—Present and future perspectives. *Nat. Rev. Endocrinol.* **2011**, *8*, 228–236. [[CrossRef](#)] [[PubMed](#)]
67. Eze, I.C.; Hemkens, L.G.; Bucher, H.C.; Hoffmann, B.; Schindler, C.; Künzli, N.; Schikowski, T.; Probst-Hensch, N.M. Association between ambient air pollution and diabetes mellitus in Europe and North America: Systematic review and meta-analysis. *Environ. Health Perspect.* **2015**, *123*, 381–389. [[CrossRef](#)] [[PubMed](#)]
68. Bai, Y.; Sun, Q. Fine particulate matter air pollution and atherosclerosis: Mechanistic insights. *BBA Gen. Subj.* **2016**, *1860*, 2863–2868. [[CrossRef](#)] [[PubMed](#)]
69. Nichols, J.L.; Owens, E.O.; Dutton, S.J.; Luben, T.J. Systematic review of the effects of black carbon on cardiovascular disease among individuals with pre-existing disease. *Int. J. Public Health* **2013**, *58*, 707–724. [[CrossRef](#)] [[PubMed](#)]
70. Li, W.; Wilker, E.H.; Dorans, K.S.; Rice, M.B.; Schwartz, J.; Coull, B.A.; Koutrakis, P.; Gold, D.R.; Keaney, J.F.; Lin, H.; et al. Short-term exposure to air pollution and biomarkers of oxidative stress: The framingham heart study. *J. Am. Heart Assoc.* **2016**, *5*, e002742. [[CrossRef](#)] [[PubMed](#)]

71. Park, S.K.; O'Neill, M.S.; Vokonas, P.S.; Sparrow, D.; Spiro, A., III; Tucker, K.L.; Suh, H.; Hu, H.; Schwartz, J. Traffic-related particles are associated with elevated homocysteine. *Am. J. Resp. Crit. Care* **2008**, *178*, 283–289. [[CrossRef](#)] [[PubMed](#)]
72. Vivanco-Hidalgo, R.M.; Wellenius, G.A.; Basagaña, X.; Cirach, M.; González, A.G.; Ceballos, P.; Zabalza, A.; Jiménez-Conde, J.; Soriano-Tarraga, C.; Giralte-Steinhauer, E.; et al. Short-term exposure to traffic-related air pollution and ischemic stroke onset in Barcelona, Spain. *Environ. Res.* **2018**, *162*, 160–165. [[CrossRef](#)] [[PubMed](#)]
73. Wichmann, H.E. Diesel exhaust particles. *Inhal. Toxicol.* **2007**, *19*, 241–244. [[CrossRef](#)] [[PubMed](#)]
74. Meier, R.; Cascio, W.E.; Ghio, A.J.; Wild, P.; Danuser, B.; Riediker, M. Associations of short-term particle and noise exposures with markers of cardiovascular and respiratory health among highway maintenance workers. *Environ. Health Perspect.* **2014**, *122*, 726–732. [[CrossRef](#)] [[PubMed](#)]
75. Van Eeden, S.F.; Tan, W.C.; Suwa, T.; Mukae, H.; Terashima, T.; Fujii, T.; Qui, D.; Vincent, R.; Hogg, J.C. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM₁₀). *Am. J. Resp. Crit. Care* **2001**, *164*, 826–830. [[CrossRef](#)] [[PubMed](#)]
76. Fossati, S.; Baccarelli, A.; Zanobetti, A.; Hoxha, M.; Vokonas, P.S.; Wright, R.O.; Schwartz, J. Ambient particulate air pollution and microRNAs in elderly men. *Epidemiology* **2014**, *25*, 68–78. [[CrossRef](#)] [[PubMed](#)]
77. Cherng, T.W.; Campen, M.J.; Knuckles, T.L.; Bosc, L.G.; Kanagy, N.L. Impairment of coronary endothelial cell ETB receptor function after short-term inhalation exposure to whole diesel emissions. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2009**, *297*, R640–R647. [[CrossRef](#)] [[PubMed](#)]
78. Rückerl, R.; Greven, S.; Ljungman, P.; Aalto, P.; Antoniadou, C.; Bellander, T.; Berglund, N.; Chrysoshoou, C.; Forastiere, F.; Jacquemin, B.; et al. Air pollution and inflammation (interleukin-6, c-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ. Health Perspect.* **2007**, *115*, 1072–1080. [[CrossRef](#)] [[PubMed](#)]
79. Hansen, A.B.; Ravnskjaer, L.; Loft, S.; Andersen, K.K.; Brauner, E.V.; Baastrup, R.; Yao, C.; Ketzel, M.; Becker, T.; Brandt, J.; et al. Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort. *Environ. Int.* **2016**, *91*, 243–250. [[CrossRef](#)] [[PubMed](#)]
80. Rao, X.; Jessica, M.L.; Puett, R.; Rajagopalan, S.; Brook, R.D. Ambient air pollution: An emerging risk factor for diabetes mellitus. *Curr. Diabetes Rep.* **2015**, *15*, 33. [[CrossRef](#)] [[PubMed](#)]
81. Rajagopalan, S.; Brook, R.D. Air pollution and type 2 diabetes mechanistic insights. *Diabetes* **2012**, *61*, 3037–3045. [[CrossRef](#)] [[PubMed](#)]
82. Delfino, R.J.; Gillen, D.L.; Tjoa, T.; Staimer, N.; Polidori, A.; Arhami, M.; Sioutas, C.; Longhurst, J. Electrocardiographic ST-segment depression and exposure to traffic-related aerosols in elderly subjects with coronary artery disease. *Environ. Health Perspect.* **2011**, *119*, 196–202. [[CrossRef](#)] [[PubMed](#)]
83. Mauderly, J.L.; Chow, J.C. Health effects of organic aerosols. *Inhal. Toxicol.* **2008**, *20*, 257–288. [[CrossRef](#)] [[PubMed](#)]
84. Evans, J.L.; Goldfine, I.D.; Maddux, B.A.; Grodsky, G.M. Oxidative stress and stress-activated signaling pathways: A unifying hypothesis of type 2 diabetes. *Endocr. Rev.* **2002**, *23*, 599–622. [[CrossRef](#)] [[PubMed](#)]
85. Kim, J.H.; Yamaguchi, K.; Lee, S.H.; Tithof, P.K.; Sayler, G.S.; Yoon, J.H.; Baek, S.J. Evaluation of polycyclic aromatic hydrocarbons in the activation of early growth response-1 and Peroxisome Proliferator Activated Receptors. *Toxicol. Sci.* **2005**, *85*, 585–593. [[CrossRef](#)] [[PubMed](#)]
86. Ferré, P. The biology of peroxisome proliferator-activated receptors: Relationship with lipid metabolism and insulin sensitivity. *Diabetes* **2004**, *53*, S43–S50. [[CrossRef](#)] [[PubMed](#)]
87. Lamb, R.E.; Goldstein, B.J. Modulating an oxidative-inflammatory cascade: Potential new treatment strategy for improving glucose metabolism, insulin resistance, and vascular function. *Int. J. Clin. Pract.* **2008**, *62*, 1087–1095. [[CrossRef](#)] [[PubMed](#)]
88. Everett, C.J.; King, D.E.; Player, M.S.; Matheson, E.M.; Post, R.E.; Mainous, A.G., III. Association of urinary polycyclic aromatic hydrocarbons and serum c-reactive protein. *Environ. Res.* **2010**, *110*, 79–82. [[CrossRef](#)] [[PubMed](#)]
89. Li, Z.; Sandau, C.D.; Romanoff, L.C.; Caudill, S.P.; Sjödin, A.; Needham, L.L.; Patterson, D.G., Jr. Concentration and profile of 22 urinary polycyclic aromatic hydrocarbon metabolites in the US population. *Environ. Res.* **2008**, *107*, 320–331. [[CrossRef](#)] [[PubMed](#)]

90. Zhou, J.; Zotter, P.; Bruns, E.A.; Stefenelli, G.; Bhattu, D.; Brown, S.; Bertrand, A.; Marchand, N.; Lamkaddam, H.; Slowik, J.G.; et al. Particle-bound reactive oxygen species (Pb-ROS) emissions and formation pathways in residential wood smoke under different combustion and aging conditions. *Atmos. Chem. Phys.* **2018**, *18*, 6985–7000. [[CrossRef](#)]
91. Venkatachari, P.; Hopke, P.K.; Grover, B.D.; Eatough, D.J. Measurement of particle-bound reactive oxygen species in rubidoux aerosols. *J. Atmos. Chem.* **2005**, *50*, 49–58. [[CrossRef](#)]
92. Venkatachari, P.; Hopke, P.K. Development and laboratory testing of an automated monitor for the measurement of atmospheric particle-bound reactive oxygen species (ROS). *Aerosol Sci. Technol.* **2008**, *42*, 629–635. [[CrossRef](#)]
93. Brook, R.D.; Urch, B.; Dvonch, J.T.; Bard, R.L.; Speck, M.; Keeler, G.; Morishita, M.; Marsik, F.J.; Kamal, A.S.; Kaciroti, N.; et al. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. *Hypertension* **2009**, *54*, 659. [[CrossRef](#)] [[PubMed](#)]
94. Langrish, J.P.; Mills, N.L.; Chan, J.K.K.; Leseman, D.L.A.C.; Aitken, R.J.; Fokkens, P.H.B.; Cassee, F.R.; Li, J.; Donaldson, K.; Newby, D.E.; et al. Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Part. Fibre Toxicol.* **2009**, *6*, 8. [[CrossRef](#)] [[PubMed](#)]
95. De Rosa, S.; Arcidiacono, B.; Chiefari, E.; Brunetti, A.; Indolfi, C.; Foti, D.P. Type 2 diabetes mellitus and cardiovascular disease: Genetic and epigenetic links. *Front. Endocrinol.* **2018**, *9*, 2. [[CrossRef](#)] [[PubMed](#)]
96. Leshinsky-Silver, E.; Cheng, S.; Grow, M.A.; Schwartz, S.; Scharf, L.; Lev, D.; Boaz, M.; Brunner, D.; Zimlichman, R. Candidate gene polymorphism in cardiovascular disease: The BIP cohort. *Isr. Med. Assoc. J.* **2006**, *2*, 103–105.
97. Altshuler, D.; Hirschhorn, J.N.; Klannemark, M.; Lindgren, C.M.; Vohl, M.; Nemesh, J.; Lane, C.R.; Schaffner, S.F.; Bolk, S.; Brewer, C. The common PPAR γ Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat. Genet.* **2000**, *26*, 76–80. [[CrossRef](#)] [[PubMed](#)]
98. Rong, Y.; Bao, W.; Rong, S.; Fang, M.; Wang, D.; Yao, P.; Hu, F.B.; Liu, L. Hemochromatosis gene (HFE) polymorphisms and risk of type 2 diabetes mellitus: A meta-analysis. *Am. J. Epidemiol.* **2012**, *176*, 461–472. [[CrossRef](#)] [[PubMed](#)]
99. De Majo, F.; Calore, M. Chromatin remodelling and epigenetic state regulation by non-coding RNAs in the diseased heart. *Non-Coding RNA Res.* **2018**, *3*, 20–28. [[CrossRef](#)]
100. Pandey, A.K.; Agarwal, P.; Kaur, K.; Datta, M. Micrnas in diabetes: Tiny players in big disease. *Cell. Physiol. Biochem.* **2009**, *23*, 221–232. [[CrossRef](#)] [[PubMed](#)]



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