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Review

Methylomic, Proteomic, and Metabolomic Correlates of Traffic-Related Air Pollution in the Context of Cardiorespiratory Health: A Systematic Review, Pathway Analysis, and Network Analysis

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Abstract: A growing body of literature has attempted to characterize how traffic-related air pollution (TRAP) affects molecular and subclinical biological processes in ways that could lead to cardiorespiratory disease. To provide a streamlined synthesis of what is known about the multiple mechanisms through which TRAP could lead to cardiorespiratory pathology, we conducted a systematic review of the epidemiological literature relating TRAP exposure to methylomic, proteomic, and metabolomic biomarkers in adult populations. Using the 139 papers that met our inclusion criteria, we identified the omic biomarkers significantly associated with short- or long-term TRAP and used these biomarkers to conduct pathway and network analyses. We considered the evidence for TRAP-related associations with biological pathways involving lipid metabolism, cellular energy production, amino acid metabolism, inflammation and immunity, coagulation, endothelial function, and oxidative stress. Our analysis suggests that an integrated multi-omics approach may provide critical new insights into the ways TRAP could lead to adverse clinical outcomes. We advocate for efforts to build a more unified approach for characterizing the dynamic and complex biological processes linking TRAP exposure and subclinical and clinical disease and highlight contemporary challenges and opportunities associated with such efforts.

Keywords: traffic-related air pollution; DNA methylation; methylomics; proteomics; metabolomics; multi-omics; cardiovascular disease; respiratory disease

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1. Introduction

It is well established that exposure to traffic-related air pollution (TRAP) is associated with adverse respiratory and cardiovascular outcomes [1–3]. Research suggests that the pathways underlying associations between TRAP exposure and cardiorespiratory outcomes likely involve oxidative stress, endothelial dysfunction, and inflammatory responses [1,4–9]. A growing number of epidemiological studies are investigating how changes in DNA methylation patterns (methylomics), proteomic profiles, and metabolomic profiles underlie the physiological pathways linking TRAP exposure to respiratory and cardiovascular health (e.g., [10–15]). Nevertheless, no large-scale longitudinal study to date has identified common biological pathways involving TRAP-related methylomic, proteomic, and metabolomic patterns. Such evidence could help establish a unified multi-omics framework to gain a better understanding of the adverse health consequences of air pollutants. Furthermore, this knowledge could be used to help design relevant interventions.

Previous work has outlined many of the challenges of establishing a unified multi-omics approach to air pollution epidemiology. Common challenges include the need for repeated samples, the identification of an appropriate exposure metric, and the availability of appropriate statistical techniques to handle the large number of omics analytes [16–20]. Furthermore, challenges related to heterogeneity in study designs, populations, air pollutants of interest, exposure windows, omics measurement methods, and analytic techniques arise when synthesizing the literature [10,11,20–23]. Despite these challenges, multi-omics integration (i.e., integrating across multiple levels of biology such as methylation patterns, proteomic profiles, and metabolomic profiles) aimed at understanding mechanisms linking environmental risk factors to chronic disease can advance clinical and public health knowledge and inform the design and implementation of relevant interventions [24–26]. To advance the goal of developing an integrated multi-omics approach, we conducted the first systematic review focused on the associations between three types of omic markers and ambient TRAP exposure. Using these signals from across omics types, we aimed to pinpoint common biological pathways known to be involved in respiratory and cardiovascular disease (CVD), assess the challenges and benefits of a multi-omics approach, and identify research needs. The number of studies directly linking TRAP exposure to clinical outcomes through changes in omics signals is relatively small. Despite this, we believe that identifying omics signals and pathways known to be associated with both TRAP exposure and cardiorespiratory disease is a prudent step toward advancing clinical and public health decision-making.

2. Materials and Methods

2.1. Search Strategy and Study Selection

We searched Embase and PubMed for English-language epidemiologic articles published between January 2010 and February 2023 that reported on the association between TRAP exposure and one or more of three omics types (DNA methylation [methylomics], proteomics, and metabolomics). We included both studies that examined at least one targeted biomarker in association with TRAP (some of which were not truly 'omics' approaches given the small number of biomarkers assayed), as well as studies that assessed a large number of omic markers through an untargeted approach. Given the rapid expansion of the omics field, 2010 was chosen as a date that could capture the important recent developments in technology and understanding. Indeed, metabolomics was considered an "emerging field" up until 2010, top-down proteomics was not widely used until 2011 [27], and methylation research had just benefited from landmark technological developments in the form of upgraded methylation arrays. For example, the Illumina Infinium Methylation 450 K array was released in 2011 and represented a leap forward compared to the previous model (450,000 versus 27,000 CpG sites) [28]. Additionally, foundational databases that annotate genes, proteins, and metabolites, such as KEGG and UniProt, underwent major changes post-2010 and continue to update their knowledge banks routinely [29]. Furthermore, although pathway analysis tools such as Reactome and NIH-DAVID were released in 2003, the addition of the open-source platform MetaboAnalyst in 2009 allowed researchers to gain more insight from their omics data without significant training [30]. Search terms included DNA methylation, proteomics, metabolomics, TRAP, and particulate matter (PM). The search strategy and screening process are described in detail in Supplementary File S1. We screened the extracted articles by title and abstract. We excluded reviews and reports, as well as in vitro, in silico, ex vivo, and animal studies. We excluded articles not containing one or more TRAP exposures. Relevant pollutants included particulate matter < 2.5 microns ($PM_{2.5}$), particulate matter < 10 microns (PM_{10}), PM constituents, ultrafine particulate matter (UFP), black carbon (BC), elemental carbon (EC), organic carbon (OC), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), carbon monoxide (CO), sulfur dioxide (SO_2), sulfate (SO_4^{2-}), ozone (O_3), diesel exhaust (DE), and polycyclic aromatic hydrocarbons (PAHs). Some studies that examined high versus low traffic scenarios did not specify individual pollutants but rather called the pollution mixture

"TRAP". Such pollutant mixtures have been called "TRAP" throughout this review. Studies containing TRAP without further specification were either (1) traffic-specific and focused on pollutants originating directly from traffic or commuter exposures, or (2) levels of ambient pollutants typically associated with traffic. We excluded studies that identified the source of air pollution as anything other than traffic-related (e.g., we excluded occupational exposures); however, we did not require source apportionment, nor did we comment on whether ambient pollution is necessarily due to TRAP. Studies focused on people who were pregnant or under 18 years of age were also excluded. The focus of this review was to capture the available literature regarding adult exposure to TRAP, given the importance of examining these sub populations separately and the likelihood of different physiological responses to TRAP in terms of disease risks [31]. In addition to the 115 articles that remained after screening, we identified 24 papers through expert knowledge, for a total of 139 unique studies. There were 54 methylomic, 57 proteomic, 37 metabolomic, and 9 overlapping studies—four of which included both proteomics and metabolomics and five that included both proteomics and methylation (Figure 1).

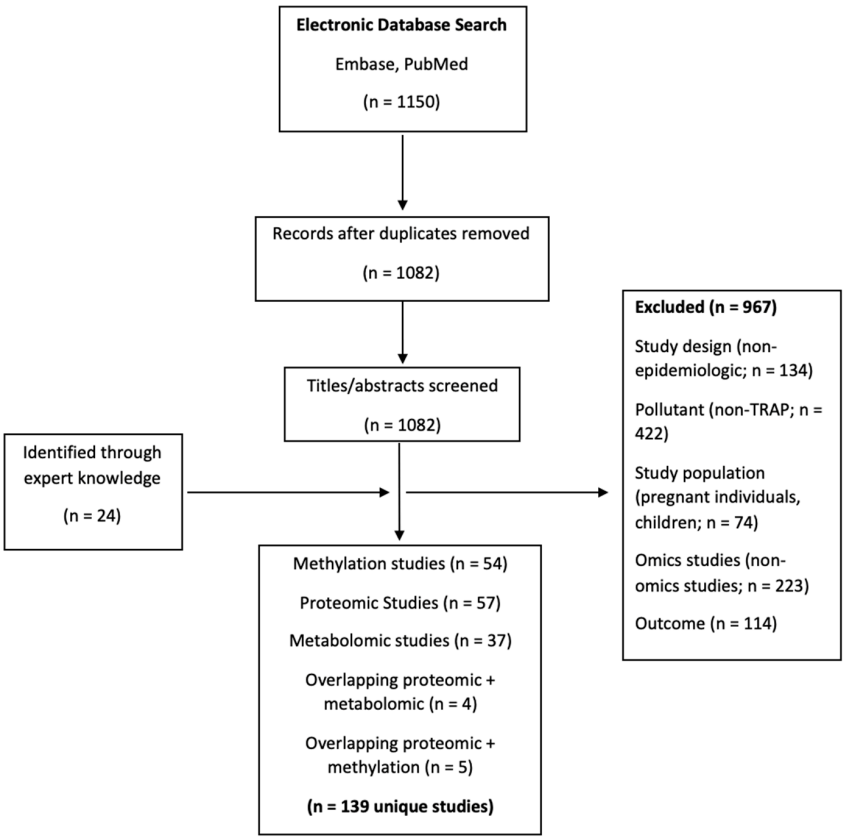

Figure 1. Flow diagram of the article selection process with exclusion criteria.

2.2. Data Extraction and Organization

We extracted the following from each article: study design and sample size, air pollution exposure methods, exposure metrics, omics assay methods, participant demographics, statistical methods, and results (Table 1 and Supplementary File S2 Tables S1–S3). Statistically significant associations between different TRAP exposures and each omics article type (methylomic, proteomic, and metabolomic) were identified (Supplementary File S2, Tables S4–S6). We used statistical significance thresholds determined by the original authors, which included both adjusted and non-adjusted *p*-values. The specific statistical thresholds used in each study to determine the significance of association among TRAP and various omics signals are given in Supplementary File S2, Tables S1–S3. Air pollution exposures were split by pollutant type and averaging period (short-term: $\leq$30 days; long-term: >30 days).

Using the significant associations shown in Supplementary File S2 Tables S4–S6, we identified common biological processes and types of biomarkers represented across the omics types (an abbreviated version of results shown in Table S7 and full results shown in Supplementary File S2 Table S8). Gene Ontology (GO) molecular functions (molecular-level activities performed by gene products, e.g., glucose transmembrane transport) were extracted for each gene and protein [32]. Where available, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (pathways of common molecular interaction, e.g., tumor necrosis factor signaling) were indicated for all genes, proteins, and metabolites [29,33,34]. For genes and proteins without KEGG data, GO biological processes (functions of gene products) were used instead. The neXtProt knowledgebase [35] was used to extract GO molecular functions, GO biological processes, and KEGG pathways for all genes and proteins. The GenomeNet KEGG COMPOUND Database [36] was used to extract KEGG functions for all available metabolite markers. To integrate omics signals in terms of their biological function (regardless of the omics approaches that were used or not in the original literature), we categorized each biomarker and their assigned biological functions (both KEGG and GO) to create a list of all biological functions that could be involved in respiratory and CVD processes. Within these lists, we identified methylomic, proteomic, and metabolomic signals involved in particular pathways. Based on this analysis, the analyses described in Section 2.3 below, and the relevant literature, we theorized about possible interactions among these markers that may affect disease states. Based on Supplementary File S2 Tables S4–S8, we created a simplified conceptual diagram of the putative relationships among TRAP, omics signals, subclinical processes, and clinical outcomes (Figure 2).

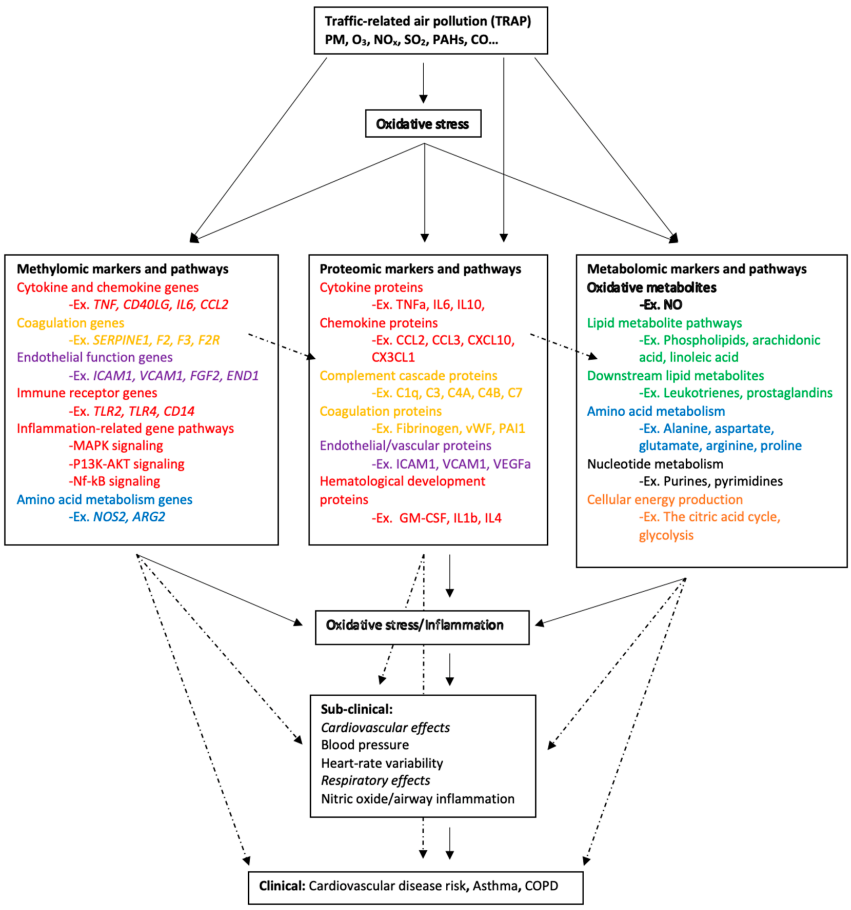

Figure 2. Overview of the relationships among traffic-related air pollution, omics markers, and subclinical and clinical cardiovascular and respiratory disease outcomes. Solid arrows indicate a

well-established, known relationship, as evidenced by the biomedical literature. Dashed arrows indicate a probable association or an association with possible mediators that needs to be further investigated. The color coding of text within methylomic, proteomic, and metabolomic text boxes corresponds to a category of biological pathways. Green—lipid metabolism; orange—cellular energy production; blue—amino acid metabolism; red—inflammation and immunity; yellow—coagulation; purple—endothelial function; white—oxidative stress; black—analytes that do not fit into the above categories (vitamins, purines, xanthines, etc.). Abbreviations: ARG2—Arginase 2; C1q—Complement component 1q; C3—Complement component 3; C4A—Complement component 4A; CCL2—CC motif chemokine ligand 2/monocyte chemoattractant protein 1; CCL3—CC motif chemokine ligand 3/macrophage inflammatory protein 1 alpha; CD14—Cluster of differentiation 14; CD40LG—Cluster of differentiation 40 ligand; CX3CL1—Fractalkine; CXCL10; CXC motif chemokine ligand 10/interferon gamma inducible protein 10; F2—Coagulation factor 2; F2R- Coagulation factor 2 receptor; F3—Coagulation factor 3; FGF2—Fibroblast growth factor 2; GM-CSF—Granulocyte macrophage colony stimulating factor; ICAM1—Intercellular adhesion molecule 1; IL1b—Interleukin 1 beta; IL4—Interleukin 4; IL6—Interleukin 6; IL10—Interleukin 10; MAPK—Mitogen activated protein kinase; NOS2—Nitric oxide synthase 2; Nf-KB—Nuclear factor kappa light chain enhancer of activated B cells; P13K-AKT—Phosphatidylinositol 3 kinase and AKT/protein kinase B; SERPINE1—Serpin family E member 1/Plasminogen activator inhibitor 1; TLR2—Toll like receptor 2; TLR4—Toll like receptor 4; TNF—Tumor necrosis factor alpha; TNFa—Tumor necrosis factor alpha; VCAM1—Vascular cell adhesion molecule 1; VEGFa—Vascular endothelial growth factor alpha; vWF—Von Willebrand factor.

2.3. Pathway and Network Analyses

We conducted bioinformatics analyses synthesizing the results across the omics studies using the lists of relevant biomarkers shown in Supplementary File S2 Table S9 (representing all significant associations shown in Supplementary File S2 Tables S4–S6). We included all biomarkers identified as significantly associated, even if individual studies chose different statistical significance thresholds (reflecting in part differences in omic assay approaches, the number of biomarkers assessed, and study-specific analytic approaches). This reflects the individual study authors' decisions about which biomarkers were most salient given the methodological characteristics of the study and allows us to be most comprehensive in including a large set of possible biomarkers. We used the open-source tools Reactome (Version 85) [37] and MetaboAnalyst 5.0 [38] to conduct pathway analyses. Specifically, we used Reactome to perform overrepresentation pathway analyses on the gene methylation sites and proteins that were significantly associated with TRAP exposure (separately for each omic type and associations with short- and long-term TRAP exposures). We chose Reactome because it allows for pathway analysis with methylation markers and proteins, its strength in providing visualization of salient pathways, and its clear cross-linkages to other databases. For our Reactome analysis, relevant parameters selected to perform these analyses included "project to human" and "include interactors," limiting the results to human genes and proteins, and drawing from the IntAct database to increase the analysis background, respectively. MetaboAnalyst was used to conduct a KEGG pathway analysis of all metabolites that were significantly associated with TRAP (separately for short- and long-term exposures) since this software is commonly used with metabolites and provides additional analytic features. Relevant parameters selected included a hypergeometric test for enrichment analysis and relative betweenness centrality topology analysis. These programs generate lists of pathways indicated by the extracted analytes. Some pathways discussed in this review were not on the indicated lists of these pathway analyses, and therefore statistical significance values were not given. Given that we extracted the KEGG functions and/or GO data for each analyte, we were able to group omics signals effectively, despite pathway analysis-related statistical thresholds that may be limiting in representing all biological pathways involved in TRAP exposure.

MetaboAnalyst was also used to conduct four KEGG network analyses representing the functional relationships among biomarkers. We created two networks incorporating methylation markers and metabolites that were significantly associated with short- and long-term TRAP exposure (Figures 3 and 4) and two networks incorporating proteins and metabolites that were significantly associated with short- and long-term TRAP exposure (Figures 5 and 6). In each case, we used separate networks for short- and long-term exposures. In network analyses, networks are parameterized by degree (i.e., the number of incoming/outgoing edges on each node) and betweenness (i.e., the number of shortest paths between each pair of nodes). Higher values for degree and betweenness restrict the network to only the most highly connected and relevant nodes [39,40]. For our two short-term network analyses, degree and betweenness filters were constrained to a degree of at least three. In the long-term exposure analyses, networks did not contain enough nodes to apply these filters. This is due to the relative sparsity of literature examining associations between long-term exposures and omics signals.

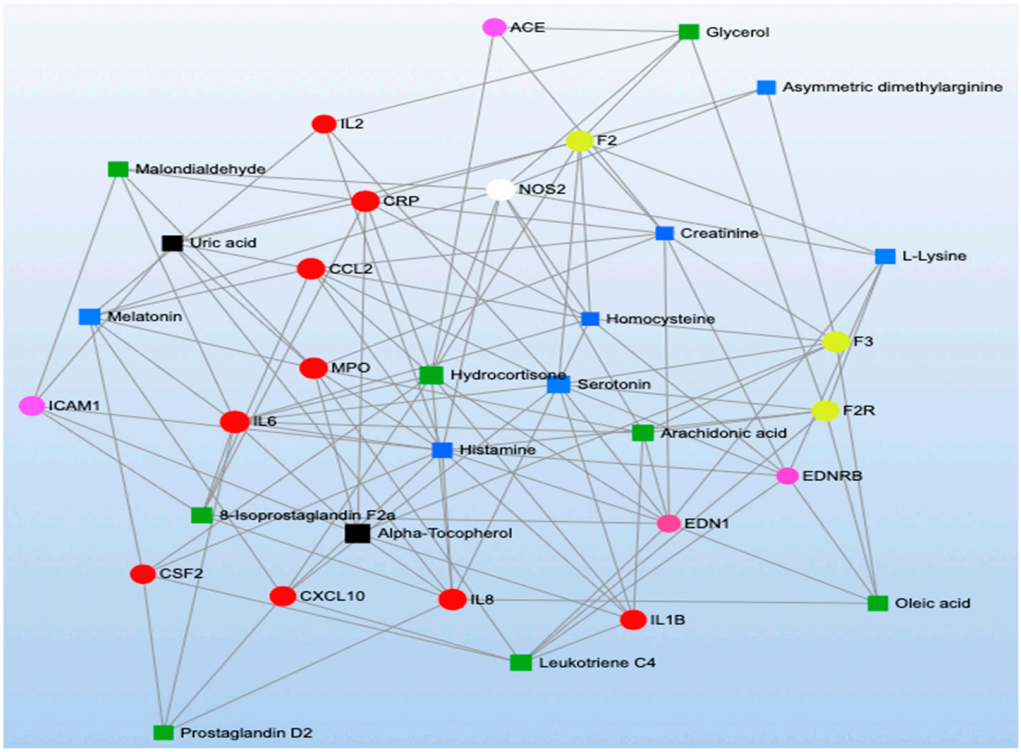

Figure 3. Short-term air pollution and gene–metabolite network analysis. Circular nodes represent genes, whereas square nodes represent metabolites. The color of each node corresponds to the category of the biological pathway to which that analyte belongs. Green—lipid metabolism; orange—cellular energy production; blue—amino acid metabolism; red—inflammation and immunity; yellow—coagulation; pink—endothelial function; white—oxidative stress; black—analytes that do not fit into the above categories (vitamins, purines, xanthines, etc.). Abbreviations: ACE—Angiotensin converting enzyme; CCL2—Monocyte chemoattractant protein 1; CRP—C-reactive protein; CSF2—Colony stimulating factor 2; CXCL10—Interferon gamma-induced protein 10; EDN1—Endothelin 1; EDNRB—Endothelin receptor type B; F2—Coagulation factor 2; F2R—Coagulation factor 2 receptor; F3—Coagulation factor 3; IL1B—Interleukin 1 beta; IL2—Interleukin 2; IL6—Interleukin 6; IL-8—Interleukin 8; ICAM1—Intercellular adhesion molecule 1; MPO—Myeloperoxidase; NOS2—Nitric oxide synthase 2.

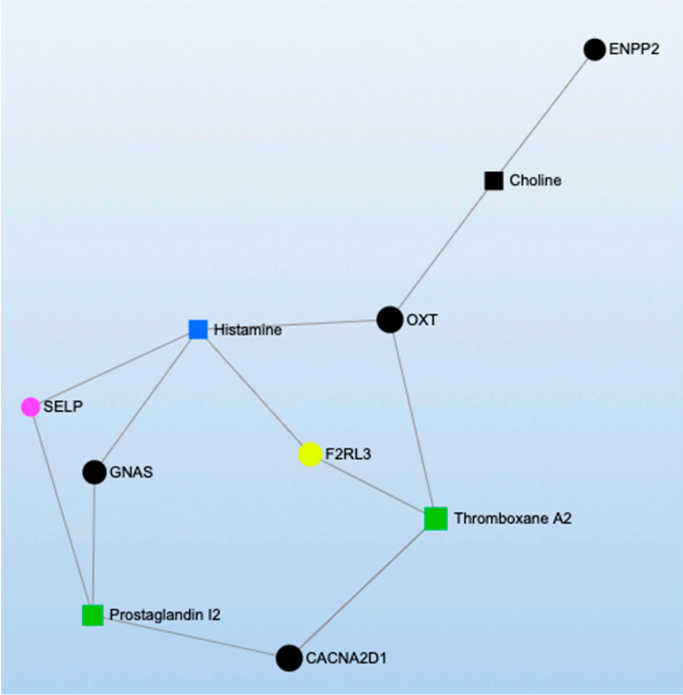

Figure 4. Long-term air pollution and gene–metabolite network analysis. Circular nodes represent genes, whereas square nodes represent metabolites. The color of each node corresponds to the category of the biological pathway to which that analyte belongs. Green—lipid metabolism; orange—cellular energy production; blue—amino acid metabolism; red—inflammation and immunity; yellow—coagulation; pink—endothelial function; white—oxidative stress; black—analytes that do not fit into the above categories (vitamins, purines, xanthines, etc.). Abbreviations: CACNA2D1—Calcium voltage-gated channel auxiliary subunit alpha2delta 1; ENPP2—Ectonucleotide pyrophosphatase 2; F2RL3—Coagulation factor 2 receptor-like thrombin or trypsin receptor 3; GNAS—GNAS complex locus; OXT—Oxytocin prepropeptide; SELP—P selectin.

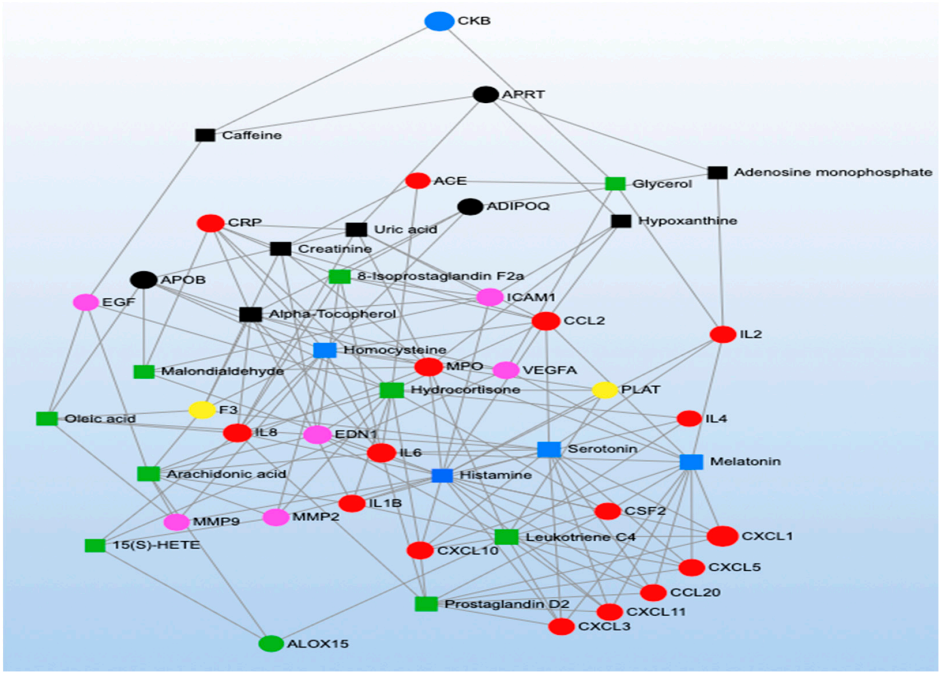

Figure 5. Short-term air pollution and protein–metabolite network analysis. Circular nodes represent proteins, whereas square nodes represent metabolites. The color of each node corresponds to the

category of the biological pathway to which that analyte belongs. Green—lipid metabolism; orange—cellular energy production; blue—amino acid metabolism; red—inflammation and immunity; yellow—coagulation; pink—endothelial function; white—oxidative stress; black—analytes that do not fit into the above categories (vitamins, purines, xanthines, etc.). Abbreviations: 15(3)-HETE—15 Hydroxyeicosatetraenoic acid; ACE—Angiotensin converting enzyme; ALOX15—Arachidonate 15 lipoxygenase; APRT—Adenine phosphoribosyltransferase; APOB—Apolipoprotein B; CCL2—monocyte chemoattractant protein 1; CCL20—CC motif chemokine ligand 20; CKB—Creatine kinase B; CRP—C reactive protein; CSF2—Colony stimulating factor 2; CXCL1—CXC motif chemokine ligand 1; CXCL3—CXC motif chemokine ligand 3; CXCL5—CXC motif chemokine ligand 5; CXCL10—Interferon gamma induced protein 10; CXCL11—CXC motif chemokine ligand 11; EGF— Epidermal growth factor; EDN1—Endothelin 1; F3—Coagulation factor 3; IL1B—Interleukin 1 beta; IL2—Interleukin 2; IL4—Interleukin 4; IL6—Interleukin 6; IL8—Interleukin 8, ICAM1—Intercellular adhesion molecule 1; MMP2—Matrix metalloproteinase 2; MMP9—Matrix metalloproteinase 9; MPO—Myeloperoxidase; PLAT—Plasminogen activator, tissue type; VEGFA—Vascular endothelial growth factor A.

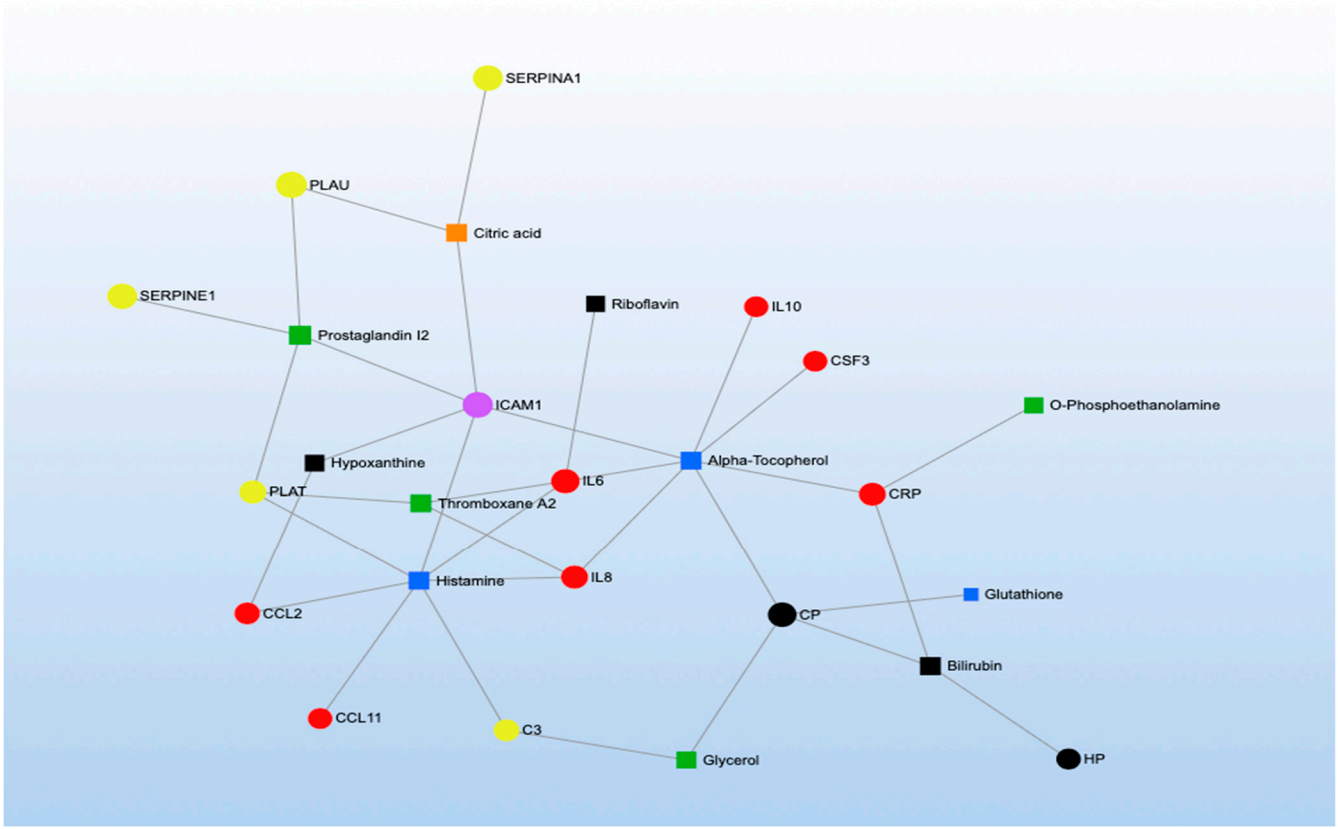

Figure 6. Long-term air pollution and protein–metabolite network analysis. Circular nodes represent proteins, whereas square nodes represent metabolites. The color of each node corresponds to the category of the biological pathway to which that analyte belongs. Green—lipid metabolism; orange—cellular energy production; blue—amino acid metabolism; red—inflammation and immunity; yellow—coagulation; pink—endothelial function; white—oxidative stress; black—analytes that do not fit into the above categories (vitamins, purines, xanthines, etc.). Abbreviations: C3—Complement component 3; CCL2—Monocyte chemoattractant protein 1; CCL11—CC motif chemokine ligand 11; CP—Ceruloplasmin; CRP—C reactive protein; CSF3—Colony stimulating factor 3; HP—Haptoglobin; ICAM1—Intercellular adhesion molecule 1; IL6—Interleukin 6; IL8—Interleukin 8; IL10—Interleukin 10; PLAT—Plasminogen activator, tissue type; PLAU—Plasminogen activator, urokinase; SERPINA1—Alpha 1 proteinase inhibitor; SERPINE1—Plasminogen activator inhibitor 1.

Table 1. Overview of the literature.

Omics Type	Study Design	Exposure Assessment	Exposure Window	Study Populations [a]	Country	Sample Size	Sex Distribution	Omics Approach
Methylomics *n* = 54 studies	Cross-sectional: 29 Panel: 9 Cohort: 5 Cross-over: 9 Quasi-experimental: 2	Fixed site measurement: 16 Spatiotemporal model: 21 Personal measurement: 12 Controlled exposure: 5	Short-term: 29 Long-term: 25	NAS: 10 [41–50] KORA: 3 [45,49,51] WHI: 3 [52–54] ARIC: 3 [52–54] EPIC-Italy: 2 [55,56] MESA: 2 [57,58] Sister Study: 2 [59,60] BAPE: 2 [61,62] Taiwan Biobank: 2 [63,64] REGICOR: 1 [55] EPIC-Netherlands: 1 [56] Lifelines: 1 [51] EXPOsOMICS: 1 [65] SAPALDIA: 1 [66] Lothian Birth Cohort: 1 [67] SPHERE: 1 [68]	USA: 17 China: 15 Italy: 8 Canada: 4 Netherlands: 3 Taiwan: 3 Germany: 2 Switzerland: 2 UK: 2 Belgium: 2 Spain: 1 South Korea: 1 Czech Republic: 1	<50: 20 50–99: 3 100–1000: 20 >1000: 11	100% female: 4 100% male: 11 Other: 39	Candidate gene: 26 Epigenome-wide association study: 24 Global methylation: 4
Proteomics *n* = 57 studies	Cross-sectional: 28 Panel: 8 Cohort: 3 Cross-over: 10 Quasi-experimental: Case-control: 3	Fixed site measurement: 24 Spatiotemporal mode: 19 Personal measurement: 9 Biomarker: 2 Controlled exposure: 4	Short-term: 36 Long-term: 21	NAS: 3 [69–71] SWAN: 3 [72–74] KORA: 3 [75–77] Heinz–Nixdorf Recall: 3 [75,78,79] Framingham Offspring: 2 [80,81] AIRCHD: 2 [82,83] EPIC-Italy: 1 [84] BPRHS: 1 [85] Malmo Diet and Cancer: 1 [86] AHAB-II: 1 [87] SAGE: 1 [88] Nurse's Health Study: 1 [89] ELISABET: 1 [90] ESCAPE: 1 [91] SAPALDIA: 1 [75] FINRISK: 1 [75] TwinGene: 1 [75] MESA: 1 [92] CAFEH: 1 [93] CoLaus: 1 [94]	USA: 17 China: 17 Canada: 6 Germany: 4 India: 3 Taiwan: 3 Italy: 2 Sweden: 1 UK: 1 France: 1 Brazil: 1 Sweden: 1 Finland: 1 Switzerland: 1	<50: 15 50–99: 10 100–1000: 13 >1000: 19	100% female: 3 100% male: 6 Other: 48	Targeted: 54 Untargeted: 3

Table 1. *Cont.*

Omics Type	Study Design	Exposure Assessment	Exposure Window	Study Populations [a]	Country	Sample Size	Sex Distribution	Omics Approach
Metabolomics *n* = 37 studies	Cross-sectional: 15 Panel: 7 Cohort: 2 Cross-over: 7 Natural Experiment: 1	Fixed site measurement: 8 Spatiotemporal model: 10 Personal measurement: 14 Biomarker: 1 Controlled exposure: 4	Short-term: 26 Long-term: 11	DRIVE: 3 [95–97] NAS: 2 [98,99] Children's Health Study: 2 [100,101] KORA: 2 [102,103] SAPALDIA: 1 [104] EPIC-Italy: 1 [104] ACE: 1 [105] ACE-2: 1 [106] Oxford St. 2: 1 [13] TAPAS II: 1 [13] CAFEH: 1 [107] EARTH: 1 [108] AIRCHD: 1 [83] SCOPE: 1 [109] TwinsUK: 1 [110]	USA: 17 China: 12 Germany: 2 UK: 2 Sweden: 1 Switzerland: 1 Italy: 1 India: 1 Spain: 1 Netherlands: 1 Brazil: 1	<50: 15 50–99: 6 100–1000: 7 >1000: 4	100% female: 1 100% male: 5 Other: 31	Targeted: 8 Untargeted: 29

[a] Numbers represent the number of papers reviewed that contain the given characteristic. Where the original study included multiple study populations, all study populations and countries were counted. Abbreviations: ACE—Atlanta Commuters Exposure; AHAB-II—Adult Health and Behavior; AIRCHD—Air Pollution and Cardiovascular Dysfunctions in Healthy Adults Living in Beijing: ARIC—Atherosclerosis Risk in Communities; BPRHS—Boston Puerto Rican Health Study; CAFEH—Community Assessment of Freeway Exposure and Health; DRIVE—Dorm Room Inhalation to Vehicle Emissions; EARTH—Environmental and Reproductive Health; ELISABET—Enquête Littoral Souffle Air Biologie Environnement; EPIC—European Prospective Investigation into Cancer and Nutrition; ESCAPE—European Study of Cohorts for Air Pollution Effects; KORA—Cooperative Health Research in the Region of Augsburg; MESA—Multiethnic Study of Atherosclerosis; NAS—Normative Aging Study: REGICOR—REgistre GIroní del COR; SAGE—Study on Global Aging and Adult Health; SAPALDIA—Swiss Study on Air Pollution and Lung Disease in Adults; SCOPE—A Prospective Study Comparing the Cardiometabolic and Respiratory Effects of Air Pollution Exposure on Healthy and Prediabetic Individuals; SPHERE—Susceptibility to Particle Health Effects, miRNA and Exosomes; SWAN—Study of Women's Health Across the Nation; TAPAS—Transportation, Air Pollution, and Physical Activities; WHI—Women's Health Initiative.

3. Results and Discussion

3.1. Overview of the Literature

Table 1 provides an overview of the study designs, exposure assessment approaches, study populations, sample sizes, sex distributions, and omics approaches used in the studies included in this review.

We did not conduct a formal analysis of study quality for two primary reasons. First, for our hypothesis-generating study, our goal was to be as comprehensive as possible in identifying biomarkers and biological processes putatively important to the relationship between air pollution and respiratory disease and/or CVD. Second, given that the omics field is relatively new and is rapidly evolving, the common study quality assessment criteria 'checklists' would not be appropriate for the types of studies we included in our review. Some elements—such as study design, sample size, adjustment for confounders, exposure assessment methods, etc.—were elements we considered and discussed below. However, we suggest that, moving forward as a field, the assessment of multi-omics studies requires study quality evaluation criteria. Some work has already been published to this effect (e.g., [111]), but a more general guideline is warranted. Relevant considerations could include whether the study was targeted or untargeted, assay technology and process (e.g., assay size, laboratory quality checks), relevance of the biological matrix used, and appropriateness of the bioinformatics approaches.

3.1.1. TRAP Exposure Assessment

Exposure assessment approaches differed by omics type: spatiotemporal modeling was most common for methylomic papers, fixed site monitoring was most common for proteomics papers, and personal monitoring was most common for metabolomics papers (Table 1). Short-term exposures were more commonly assessed than long-term exposures for each omic type. For long-term exposures, the most common exposure window was an annual average (44, 28, and 22% of methylomic, proteomic, and metabolomic studies, respectively). As in air pollution epidemiology generally, each exposure assessment approach and exposure window have strengths and weaknesses in the context of different study designs; a potential benefit of a multi-omics approach is the enhanced reliability of knowledge obtained from triangulating findings from studies that employ the diverse combinations of exposure assessment techniques and windows.

The most common pollutant studied across all three omics (regardless of exposure window) was $PM_{2.5}$. Forty-six methylation papers, 41 proteomics papers, and 32 metabolomics papers measured $PM_{2.5}$ exposure. PM_{10}, UFP, BC, NO_2, NO_x, and O_3 were all considered in each omic type; however, they were less commonly studied in papers focused on long-term exposures. Papers that did not investigate $PM_{2.5}$ generally focused on O_3 or diesel exhaust. Given the study designs and exposure assessment methods, time-varying exposures and TRAP mixtures were generally not accounted for in the analyses; future studies should consider time-varying exposures and mixtures.

3.1.2. Study Populations

Research in this field predominantly draws from populations in North America, China, and Western Europe (Table 1); future studies should include more geographic diversity, requiring an investment in TRAP exposure and omics assessment in other geographic regions. Additionally, although most study populations included people regardless of sex, single-sex cohorts were common (especially for methylomic papers, where 28% were single-sex). Three methylomic, two proteomic, and four metabolomic papers considered effect modification by sex [45,57,67,86,101,102,112–114] (Supplementary File S2, Tables S1–S3). Fourteen methylomic, 16 proteomic, and 21 metabolomic studies contained populations with a mean age or entire age range of 35 years old or younger. Twenty-three methylomic, nine proteomic, and four metabolomic studies contained populations with a mean age or entire age range of 60 years or older. In general, the methylomic literature had slightly older participants, and the metabolomics literature had slightly younger participants. However,

there was adequate representation of all ages throughout all three omics types. Most studies included healthy participants or did not specify health conditions as criteria for eligibility.

3.1.3. Biological Matrices

Methylomic, proteomic, and metabolomic markers were assessed using a variety of biological matrices (Supplementary File S2 Tables S1–S3). Leukocytes and whole blood were the most common biological matrices for methylomic papers (27 and 17 papers, respectively). All studies adjusted for cell composition except those exclusively using $CD4^+$ helper cells or buccal cells as the matrix of interest or those using paired samples with a short lag time [115–120]. Methylation data can readily be obtained from blood samples. It is shown that blood methylation levels correlate with methylation levels in other tissues and relate to external exposures [121]. Given that leukocytes are derived from whole blood, these biological matrices are equivalent. Peripheral blood mononuclear cells (PBMCs), however, are a specific subset of leukocytes. The choice to utilize PBMCs or leukocytes in methylomic research depends on research goals and the cell type of interest; however, both are sufficient [122,123]. For proteomic papers, serum and plasma were the most common biological matrices (34 and 21 papers, respectively). Nine proteomics papers used both serum and plasma, with the inclusion of plasma serving primarily to measure fibrinogen levels [71,72,75,81,92,124–127]. Three proteomics papers used bronchoalveolar lavage fluid to understand the associations between TRAP and the bronchoalveolar proteome, serving as a more direct measure of TRAP's influence [128–130]. Both serum and plasma matrices in proteomics research are well-accepted; however, some studies suggest that plasma has superior predictive power for physiological outcomes [131], while others suggest that serum is preferred for clinical chemistry [132]. Plasma is used over serum for the exploration of coagulation proteins; however, the presence of added anticoagulants in plasma can influence research outcomes [132]. Similar to proteomics, serum and plasma were the most common biological matrices for metabolomics papers (17 and 14 papers, respectively). Serum is currently considered the gold standard in metabolomics research, providing more sensitive results in biomarker detection; however, plasma also provides accurate results and has high reproducibility [133,134]. Five metabolomics papers utilized urine [101,135–138] and two used bronchoalveolar lavage fluid [139,140].

In general, decisions about the biological matrix were largely determined based on the availability of samples within a cohort rather than on the biological relevance of a given matrix for TRAP-cardiorespiratory relationships. Although other matrices (e.g., myocytes, bronchiolar cells, endothelial cells, etc.) may serve as a more direct source of omics signals, they are often inaccessible and/or invasive to procure [141,142]. Additionally, none of the studies explicitly considered biomarker interactions (e.g., protein–protein or protein–metabolite) or the possibility of biomarker degradation or metabolism (e.g., considering how TRAP exposure may only affect biomarker levels over a specific temporal window) [141,143–145]. Finally, without the ability to obtain repeated measures of multiple omics types within individuals over relevant periods, it is not possible to directly assess putative relationships between TRAP exposure and cascading biological processes. That is, although we can view the associations among multiple omics layers and pollutants across similar short- and long-term exposure windows, we do not have a direct means to measure the exact temporal changes in methylomic, proteomic, and metabolomic makers occurring at consistent points post-exposure.

3.1.4. Omics Assessment

In the methylomics literature, multiple high-throughput approaches and bioinformatics technologies were used (Supplementary File S2, Table S1). The most common forms of methylation quantification were methylation arrays (37 papers) and bisulfite polymerase chain reaction (PCR) sequencing (13 papers). The PCR sequencing papers focused on candidate gene approaches (primarily for inflammatory and immune-related proteins, as well as genes related to circadian rhythm and epigenetic age) [41,50,118–120,125,146–152].

Analyses using arrays took advantage of the evolving technology to capture the most comprehensive set of biomarkers possible: one paper utilized a 385 K array [46], twenty-four utilized a 450 K array [42–45,47–49,51–60,65–67,153–156], and twelve utilized an 850 K array [61–64,116,117,157–162]. Although we recommend the use of the most comprehensive technology available, the contribution of groundbreaking studies using older arrays to the current body of knowledge should not be understated [163,164]. Similarly, for the bioinformatics analyses of the methylomics results, researchers took advantage of the rapidly evolving tools such as KEGG for pathway analysis [42,46,116,140,160,161], the National Institutes of Health Databases for Annotation, Visualization, and Integrated Discovery (NIH-DAVID) [42,56,65,155,156], Ingenuity Pathway Analysis (IPA) [43,66,130,153,157,165], Mummichog [14,95–97,104–108,166,167], and MetaboAnalyst [98–100,102,136,168–171].

Compared to the methylomics literature, there was homogeneity in approaches used across the proteomics literature (Supplementary File S2, Table S2). Only three of the fifty-seven proteomics papers used untargeted omics approaches (and therefore, the use of bioinformatics approaches for analysis was limited to relatively few studies) [130,138,165]. Instead, many studies assessed the concentration of approximately 20 targeted proteins (e.g., cytokines, chemokines, and other immune/inflammatory-related markers). This led to abundant data on the associations among TRAP and the concentration of key proteins related to inflammation and immunity, and therefore cardiorespiratory disease. The proteins represented often overlapped well with the proteins encoded by candidate genes targeted in methylation studies. While this is useful for multi-omics interpretation, the relative lack of untargeted analyses may limit our understanding of the complete proteomic response to TRAP and potentially bias our analyses by over-representing certain processes already considered important in cardiorespiratory disease. Furthermore, it can make it difficult to integrate methylomic, proteomic, and metabolomic results together.

In contrast to the proteomics literature, most (28/37) of the metabolomics papers used untargeted approaches and twenty-two incorporated bioinformatics approaches for the interpretation of results (e.g., eleven used Mummichog [14,95–97,104–108,166,167] and nine used MetaboAnalyst [98–100,102,136,168–171]; Supplementary File S2, Table S3). Specific to metabolomics is the challenge of metabolite identification. Fourteen of the thirty-seven metabolomics papers had level one confidence (the highest level of confidence confirmed by the reference standard) [83,97,100,103–105,108–110,113,139,166,171,172], whereas an additional six studies contained some level one matches mixed with lower confidence findings [13,96,106,107,167,173]. Thirteen studies had level two confidence, primarily confirmed by library spectrum match [14,99,102,119,135,136,138,140,168–170,174,175]. Only two studies did not contain metabolites with level two or greater confidence [99,101]. The variation in metabolite identification confidence reflects a level of uncertainty in the metabolomics signals observed across different studies [176,177].

3.2. Omics Markers and Associated Biological Pathways

Omics markers representing biological pathways related to lipid metabolism, cellular energy production, amino acid metabolism, inflammation and immunity, coagulation, endothelial function, and oxidative stress were present across the literature. In this section, we outline trends in common biological pathways and molecular functions associated with methylomic, proteomic, and metabolomic markers of TRAP exposure, along with the hypothesized connections to cardiorespiratory disease. Not all omics markers may be related to clinical outcomes, and further research is needed to identify the most critical pathways underlying the relationship between TRAP exposure and disease. Figure 2 shows a simplified diagram of the relationships. The supporting literature is summarized in Supplementary File S2, Tables S4–S8. Throughout this section, 'TRAP' refers to the air pollutant mixture (or studies in which individual pollutants are not specified). We also identified individual pollutants in all cases where the original researchers did. For the pathway and network analyses, we combined all results regardless of the specific pollutant and thus used the more general 'TRAP'.

Table S7 synthesizes the methylomic, proteomic, and metabolomic literature together. The table is organized by KEGG pathway and only includes those pathways most represented and explored in the literature: lipid metabolism, cellular energy production, amino acid metabolism, inflammation and immunity, coagulation, endothelial function, and oxidative stress. Within each KEGG pathway, all methylomic, proteomic, and metabolic markers significantly associated with short- and/or long-term TRAP are noted. Each omics type was separated into associations for short- and long-term exposure. Details are given in the following sections.

3.2.1. Lipid Metabolism

Phospholipids, sphingolipids, and acylcarnitines were represented throughout the metabolomics literature. However, no studies explored the associations between TRAP and methylomic or proteomic markers related to lipid metabolism (Supplementary File S2, Tables S6–S8). In the metabolomics literature, both short- and long-term $PM_{2.5}$ exposures were negatively associated with phospholipid levels [25–29]. In contrast, short-term UFP, NO_2, and O_3 were consistently and positively associated with levels of phospholipids [98,103,140]. Phospholipid metabolism is essential for normal cellular function as it is involved in generating biological membranes and plays an important role in cellular signaling processing in nearly all tissues [178]. Phospholipid imbalances are implicated in neurological disorders and neurodegenerative diseases, while damaged and oxidized phospholipids are associated with atherosclerosis and CVD (Figure 2) [179,180]. It is not understood exactly how TRAP associations with phospholipid metabolites contribute to the aforementioned diseases.

Sphingolipids, such as sphingosines and some sphingomyelins, were negatively associated with short- and long-term $PM_{2.5}$ as well as with short-term UFP [98,101,171] but were positively associated with short-term O_3 and Ni [98,101,140,181]. For example, sphingosine 1-phosphate (a known risk factor for coronary artery disease (CAD)) [182] was negatively associated with short-term UFP and positively associated with short-term Ni [98]. Additionally, ceramide (a reaction product of sphingomyelin and/or sphingosine that is elevated in patients with hypertension, angina pectoris, myocardial infarction, and stroke [183–185]) was negatively associated with short-term $PM_{2.5}$ and UFP exposure [98,171]. However, eight sphingomyelins were positively associated with long-term $PM_{2.5}$ and short-term O_3 [98,140]. Given these findings, it is possible that TRAP (and particularly the PM components) may not predominately work through pathways involving sphingolipids to affect CVD. However, future studies should confirm this hypothesis and also consider whether methylation patterns or proteins related to lipid metabolism are implicated.

In contrast to the trends with sphingolipids, acylcarnitines were positively associated with short-term TRAP and negatively associated with short-term NO_2 [13,98,114,138,168,173,175]. It has been shown that higher levels of medium- and long-chain acylcarnitines are positively associated with both CVD and the risk of cardiovascular death in patients with stable angina pectoris [186–188].

Although most markers of lipid metabolism were considered only in the metabolomics literature, arachidonic acid and linoleic acid metabolism KEGG pathways were considered in both the proteomics (one protein involved in each) and metabolomics (20 and 13 metabolites, respectively) literature (Table S7). Synthesizing the results from these studies, our MetaboAnalyst pathway analyses suggested that the arachidonic acid metabolism KEGG pathway was significantly enriched by metabolites associated with both short- and long-term TRAP exposure ($p = 4.29 \times 10^{-4}$ and $p = 0.01$, respectively). Specifically, exposure to short-term diesel exhaust was associated with higher concentrations of the protein arachidonate 15-lipoxygenase (ALOX15). This enzyme helps generate bioactive lipid molecules, such as eicosanoids, hepoxilins, and lipoxins [189]. Interestingly, short-term diesel exhaust was also associated with lower levels of multiple metabolites related to ALOX15 [130,139]. The metabolomics literature also considered other components of the arachidonic acid and linoleic acid metabolism pathways. For example, short-term $PM_{2.5}$ and diesel exhaust ex-

posure were associated with higher and lower levels of eicosanoids, respectively [109,139]. These signaling lipids regulate homeostatic and inflammatory processes, making them important markers in the progression of CVD [189,190]. Additionally, short-term $PM_{2.5}$ and other TRAP exposures were associated with higher levels of thromboxane, prostaglandin, and leukotriene metabolites [101,139,167,168,172]. These metabolites are associated with modifications of the immune and inflammatory responses and help mediate leukocyte accumulation [191]. Finally, short-term $PM_{2.5}$, NO_2, and other short-term TRAP exposures, as well as long-term $PM_{2.5}$ and NO_2, were associated with higher levels of metabolites involved in linoleic acid metabolism [102,103,139,167,168,170]. Dysregulated linoleic acid metabolism is traditionally considered pro-inflammatory and pathological, but the linoleic acid pathway is still not well understood [190].

The network analyses we conducted consistently identified metabolites related to arachidonic and linoleic metabolism, such as arachidonic acid, leukotrienes, prostaglandins, and thromboxanes (Figures 3–6; green symbols correspond to lipid metabolism). These metabolites associated with short-term air pollution exposures were connected with genes and proteins related to inflammation and the immune system (red symbols), endothelial function (pink symbols), and coagulation (yellow symbols; Figures 3 and 5). Lipid metabolism markers associated with long-term air pollution exposures had similar trends, though fewer nodes were identified for the gene–metabolite network overall (Figures 4 and 6).

3.2.2. Cellular Energy Production

Three cellular energy production KEGG pathways were associated with short- and long-term TRAP exposure: (1) the citric acid cycle, (2) glycolysis/gluconeogenesis, and (3) the pentose phosphate pathway (Table S7, Figure 2). Although no methylomic or proteomic markers related to the citrate cycle were identified as significantly associated with TRAP, our MetaboAnalyst pathway analyses synthesizing results across studies identified the citric acid cycle KEGG pathway as being significantly enriched by the metabolites significantly associated with short- and long-term TRAP exposure ($p = 8.86 \times 10^{-3}$ and $p = 1.65 \times 10^{-3}$, respectively). Specifically, exposure to short-term TRAP was associated with higher levels of some citric acid cycle intermediates (e.g., succinyl-CoA, succinate, cis-aconitic acid, and alpha-ketoglutaric acid) [136–138,168]. But short-term $PM_{2.5}$ exposure was associated with lower levels of pyruvate, while short-term EC was associated with lower levels of citric acid and isocitric acid [97]. In contrast, long-term $PM_{2.5}$ exposure was associated with higher levels of malic acid and succinic acid [98,166]. Notably, citric acid cycle dysregulation has been associated with CVD [192,193]. For example, one case-cohort study found an increased risk of CVD with higher concentrations of fasting plasma malic acid, 2-hydroxyglutarate, and fumarate [193], while a nested case-control study found higher levels of succinic acid, malic acid, citric acid, and 2-hydroxyglutarate to be associated with a higher risk of atrial fibrillation [192]. Higher levels of malic acid and succinic acid associated with long-term $PM_{2.5}$ exposure may underlie part of the known association between TRAP and the risk of CVD. Future studies could explore whether TRAP exposure is also associated with the methylation of genes encoding for key rate limiting and regulatory enzymes in the citric acid cycle, such as citrate synthase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase, as well as the concentrations of these enzymes. Additionally, future studies could explore functional relationships among citric acid, coagulation, and endothelial function, given the relationships we identified in the long-term air pollution and protein–metabolite network analysis (Figure 6).

The central carbohydrate metabolism pathways represented by biomarkers associated with TRAP include the glycolysis/gluconeogenesis and pentose phosphate pathways (Figure 2). The glycolysis/gluconeogenesis KEGG pathway was represented by two proteomic and five metabolomic markers significantly associated with TRAP, but no methylomic markers (Table S7). Similarly, five metabolomic (but no methylomic or proteomic) markers identified as belonging to the pentose phosphate KEGG pathway were significantly

associated with TRAP (Table S7). For the glycolysis/gluconeogenesis KEGG pathway, exposure to short-term diesel exhaust was associated with lower levels of the protein alcohol dehydrogenase class four mu/sigma chain and higher levels of the protein aldehyde dehydrogenase dimeric nicotinamide adenine dinucleotide phosphate-preferring [130]. In metabolomics studies, exposure to short-term $PM_{2.5}$ was associated with lower levels of the metabolites lactate, pyruvate, and glyceric acid 1,3-bisphosphate [96,97,135], and exposure to long-term $PM_{2.5}$ was associated with lower levels of 3-phosphoglycerate and lactate [98]. Short-term exposure to O_3 was associated with higher levels of glucose and lactate [140], whereas exposure to short-term TRAP was associated with lower levels of glucose and 3-phosphoglycerate [98,138]. For the pentose phosphate KEGG pathway, short-term $PM_{2.5}$, PM components, and certain other TRAP exposures were associated with lower levels of the metabolites glyceraldehyde, glycerate, 3-phosphoglycerate, and pyruvate [96–98], and long-term $PM_{2.5}$ was associated with lower levels of glycerate and 3-phosphoglycerate [96–98,110,138,140,166]. However, short-term exposure to O_3 was associated with higher levels of glucose and glycerate [140]. In pathological circumstances such as CVD, glucose metabolism (glycolysis and the pentose phosphate pathway) typically increases relative to fatty acid oxidation [194–196]. Further longitudinal research exploring multi-omic markers of carbohydrate metabolism in response to TRAP exposure would help clarify the salient relationships.

3.2.3. Amino Acid Metabolism

Although no methylomic or proteomic markers related to the alanine, aspartate, and glutamate metabolism KEGG pathway were identified as significantly associated with TRAP, our MetaboAnalyst pathway analysis synthesizing results from across studies identified the alanine, aspartate, and glutamate metabolism KEGG pathway as significantly enriched by metabolites associated with short- and long-term TRAP exposure ($p = 3.39 \times 10^{-4}$ and $p = 6.0 \times 10^{-3}$, respectively). There were 14 metabolites representing the KEGG pathway, but there were no consistent patterns of associations among short- and long-term TRAP exposure and concentrations of these metabolites [83,97,98,100,107,110,135–137,140,166–168,168,170] (Supplementary File S2, Tables S6–S8).

The arginine and proline metabolism KEGG pathway was represented by biomarkers of all three omics types (two genes, one protein, and fourteen metabolites) (Table S7), and our MetaboAnalyst pathway analysis synthesizing the metabolomics literature suggested this pathway was significantly enriched by metabolites significantly associated with short-term TRAP exposure ($p = 6.62 \times 10^{-4}$) but not long-term TRAP exposure. Taken together, there is moderately strong evidence that arginine and proline metabolism may affect the relationship between TRAP and CVD. For example, in the methylomics literature, exposure to short-term $PM_{2.5}$ was associated with hypomethylation of the genes that code for nitric oxide synthase 2 (*NOS2*) and arginase 2 (*ARG2*) [61,118,137]. These are key enzymes for macrophage pathways linking L-arginine metabolism to inflammation and immunity [197]. The protein NOS2 catalyzes the reaction of L-arginine to nitric oxide (NO), which inhibits cell proliferation and kills pathogens [198,199]. The protein ARG2 catalyzes the reaction of L-arginine to L-ornithine, which can metabolize further into polyamines and L-proline. Notably, L-ornithine production promotes cell proliferation and repairs tissue damage [200,201]. ARG2 activity is also associated with the killer-type macrophage response [197,202,203]. Many of the metabolites related to this arginine and proline metabolism pathway were implicated across the metabolomics literature, though some of the results were inconsistent in terms of direction of association (Supplementary File S2 Table S6) [83,96–98,101,107,110,136,138,166,167]. For example, short-term $PM_{2.5}$ was associated with lower levels of L-arginine, L-glutamate, phosphocreatine, and pyruvate and with higher levels of L-ornithine and nitric oxide [83,97,101,113,119]. However, short-term O_3 exposure was associated with higher levels of creatinine, L-arginine, L-glutamate, L-ornithine, and L-proline [113,140]. Furthermore, other short-term PM exposures were associated with lower levels of creatinine and higher levels of

L-arginine, L-glutamate, L-ornithine, L-proline, D-proline, and sarcosine [138,168]. Finally, in the proteomics literature, short-term diesel exhaust was associated with lower levels of the protein creatine kinase B-type [130], and in our network analysis for short-term exposure to TRAP, the protein creatine kinase B-type was also associated with a metabolite related to lipid metabolism (Figure 5). Given the overlap in the biomarkers identified using the three omics types, further research is warranted into how TRAP exposure may plausibly result in clinically meaningful biological cascades involving arginine and proline metabolism. Such an undertaking would require repeated measures of exposures and omics markers to ensure that the relevant temporal relationships are captured for different levels of biology along the pathway (e.g., how methylation changes related to *NOS2* and *ARG2* could affect protein expression and subsequent metabolic processes). Future work should also explore the potential connections among amino acid metabolism (blue symbols), coagulation (yellow symbols), inflammation (red symbols), and endothelial pathways (pink symbols) given the results of our network analyses for both short- and long-term TRAP exposures (Figures 3–6).

3.2.4. Inflammation and Immunity

Many methylomic and proteomic markers (but not metabolomic markers) identified in the literature review as associated with TRAP exposure were involved in pathways involved in inflammation and immunity (Figure 2). The most enriched pathways included cytokine and chemokine signaling, toll-like receptor (TLR) signaling, and mitogen-activated protein kinase (MAPK) signaling. Biomarkers of these pathways (especially of the cytokine and chemokine signaling pathways) were also well-represented in our network analyses (Figures 3–6; red symbols correspond to inflammation and immunity).

Our Reactome pathway analysis identified cytokine signaling in the immune system as significantly enriched by genes related to the methylation sites and proteins associated with short-term TRAP exposure ($p = 1.11 \times 10^{-16}$ and $p = 1.11 \times 10^{-16}$, respectively). This pathway was also significantly enriched by proteins associated with long-term TRAP exposure ($p = 1.11 \times 10^{-16}$), but not genes related to the methylation sites. In particular, there were 13 genes and 40 proteins (with 10 overlapping gene–protein markers) that were part of the cytokine–cytokine receptor interaction KEGG pathway, as well as eight genes and nineteen proteins (with four overlapping gene–protein markers) that were part of the chemokine signaling KEGG pathway (Table S7). Short-term $PM_{2.5}$ exposure was associated with hypermethylation of the genes encoding for cytokines and chemokines, such as Interleukin 6 (*IL6*), Interleukin 10 (*IL10*), granulocyte-macrophage colony-stimulating factor 2 (*CSF2*), fractalkine (*CX3CL1*), interferon-gamma inducible protein 10 (*CXCL10*), and macrophage inflammatory protein 1 alpha (*CCL3*) [61,117]. In contrast, short-term $PM_{2.5}$ was associated with hypomethylation of the genes that encode monocyte chemoattractant protein 1 (*CCL2*) and a cluster of differentiation 40 ligands (*CD40LG*) [61,117,125,147,148]. Additionally, long-term $PM_{2.5}$ exposure was associated with hypomethylation of tumor necrosis factor (*TNF*) and *TNF* receptor superfamily member 13C (*TNFRSF13C*) [48,147]. Consistent with some but not all of the methylation trends, proteomics studies found that both short- and long-term exposure to TRAP was associated with higher levels of most cytokine and chemokine proteins (exceptions included inverse associations with tumor necrosis factor receptor superfamily member 11B, Interleukin 4, Interleukin 8, and eotaxin-1) [76,82,84,89,91,93,94,105,115,117,125,128,138,147,165,204–207]. These observations were consistent across pollutants and exposure windows. Additional research on the associations among pollutants other than $PM_{2.5}$ and the methylation of genes encoding for cytokines and chemokines would further strengthen the already compelling evidence that TRAP may impact cytokine and chemokine signaling in ways that could affect respiratory and cardiovascular outcomes. Cytokines and chemokines regulate the immune response by controlling immune cell trafficking and the cellular arrangement of immune organs [208,209]. High levels of both cytokines and chemokines represent immune activation and inflammation and are predictive of CVD and adverse cardiovascular

events, such as heart failure and myocardial infarction [209–212]. In addition, many of the key cytokines identified here are involved in the pathogenesis of asthma, COPD, and pulmonary fibrosis [213]. Finally, as shown in our network analyses, many of the genes and proteins associated with short-term TRAP exposure (e.g., *IL6*/IL6, *CXCL10*/CXCL10, *CCL2*/CCL2) were interconnected and were also connected to metabolites of amino acid and lipid metabolism (Figures 5 and 6)—strengthening the argument for the involvement of cytokine signaling in the physiological response to TRAP.

Eight methylomic markers and eleven proteomic markers, with four overlapping gene–protein markers and no metabolomic markers, represented the TLR signaling KEGG pathway (Table S7). Short-term exposure to $PM_{2.5}$ and BC was associated with hypomethylation and hypermethylation of *TLR2*, respectively [41,61]. Exposure to short-term PM_{10} and other short-term TRAP was associated with hypomethylation of *TLR4* [150,151]. Exposure to short-term PM_{10} and SO_4 were associated with hypomethylation of *CD14* and *MAP3K7*, respectively [46,151]. The remaining methylomic and proteomic markers belonging to the TLR KEGG pathway overlapped with the cytokine–cytokine receptor interaction KEGG pathway described previously and in Table S7. These trends are important because the TLR signaling pathway detects pathogen-associated molecular patterns, stimulating both the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and MAPK pathways, as well as cytokine production, thereby affecting inflammatory and immune responses associated with CVD and adverse respiratory outcomes [214,215].

In addition to the trends for cytokine and chemokine signaling and the TLR signaling pathways, we identified 12 methylomic markers and nine proteomic markers associated with TRAP as belonging to the MAPK signaling KEGG pathway, with two overlapping gene-protein markers and no metabolomic markers (Table S7). In the methylomics literature, short-term BC exposure was associated with hypermethylation of *MAP3K2* and *MAP3K6*, as well as hypomethylation of *MAP4K3* and *MKNK2* [46]. Short-term SO_4 exposure is associated with hypermethylation of *MAP3K11* and hypomethylation of *RPS6KA3*, *MAP3K7*, and *TGFB1* [46]. Long-term exposure to PM_{10} and NO_2 was associated with hypomethylation and hypermethylation of *PDGFB* and *CACNA2D1*, respectively [48,56]. Lastly, for the methylomics literature, short-term $PM_{2.5}$ exposure was associated with hypermethylation of *FGF2* [117]. In the proteomics literature, short-term $PM_{2.5}$, UFP, BC, NO_2, and CO exposures were associated with higher levels of fibroblast growth factor 2 protein [117,138]. In addition, short-term diesel exhaust exposure was associated with higher levels of MAPK 1 and cell division control protein homolog 42 and lower levels of protein kinase C beta type [130,165]. Finally, short-term UFP, BC, NO_2, and CO were associated with higher levels of tropomyosin receptor kinase B [138]. Synthesizing across the studies, our Reactome pathway analysis identified the MAPK signaling cascade pathway as significantly enriched by proteins associated with short-term TRAP exposure ($p = 4.35 \times 10^{-8}$). Although this pathway was not significantly enriched by methylation markers associated with TRAP exposure, the body of evidence taken together suggests that TRAP exposures may affect MAPK signaling cascades, which is critical since this pathway has implications for oxidative stress, vascular remodeling and dysfunction, cardiac hypertrophy, cardiac remodeling, and atherosclerosis [216–221].

3.2.5. Coagulation

The complement and coagulation cascade KEGG pathway was represented by four methylomic markers and fourteen proteomic markers significantly associated with TRAP, with two overlapping gene–protein markers. There were no metabolomic markers of this pathway identified as significantly associated with TRAP (Table S7). Short-term exposure to $PM_{2.5}$ was associated with hypomethylation of the genes that encode plasminogen activator inhibitor type I (*SERPINE1*), coagulation factor III (*F3*), and coagulation factor II receptor (*F2R*), as well as hypermethylation of coagulation factor II (*F2*) [41,49,125,148,160]. Within the proteomics literature, short-term exposure to PM_{10} and $PM_{2.5–10}$ was associated with lower levels of the protein plasminogen activator inhibitor type 1, whereas long-term expo-

sure to $PM_{2.5}$, NO_2, CO, and O_3 was associated with higher levels of this protein [72,74,76]. Additionally, short-term exposure to $PM_{2.5}$, UFP, BC, NO_2, and CO was associated with higher levels of coagulation factor III protein (F3) [127,138]. The combination of associations with short-term exposures and methylation markers and long-term exposures and proteins (e.g., *SERPINE1*) may provide evidence for time-dependent biological cascades or effects; future research should explore this possibility using a study design that can take advantage of repeated measures for exposures and outcomes. Further research could explore the possibility of similar overlap across omics types by building on the TRAP and proteomics literature suggesting significant and generally positive associations with other key coagulation and complement proteins (e.g., complement component 3, complement component 4B, fibrinogen, Von Willebrand factor, coagulation factor VII, D-dimer, alpha-1 antitrypsin, protein C inhibitor, complement C1q subcomponent subunit A, and tissue-type plasminogen activator; Supplementary File S2, Table S5) [71,73,74,76,78,86,92,124–127,130,138,207]. The importance of complement and coagulation cascades is also underscored by the connections of coagulation factors, coagulation factor responses, plasminogen activators, and plasminogen activator inhibitors in the network analyses (represented by yellow markers) to biomarkers of amino acid metabolism (blue markers), lipid metabolism (green markers), and inflammation and immunity (red markers; Figures 3–6). Taken together, there is strong evidence supporting the putative links between TRAP exposure, coagulation and complement cascades, and CVD (Figure 2). This is supported by other studies that show that higher levels of plasminogen activator inhibitor 1, fibrinogen, Von Willebrand factor, coagulation factor VII, and complement component 3 are each associated with the risk of CVD and atherosclerosis [220–227]. Furthermore, higher levels of plasminogen activator inhibitor 1 and Von Willebrand factor have been associated with increased odds of myocardial infarction [220,227].

3.2.6. Endothelial Function

Methylomic, proteomic, and metabolomic markers associated with TRAP exposure were associated with five KEGG pathways related to endothelial function: cell adhesion molecules, vascular endothelial growth factor (VEGF) signaling, vascular smooth muscle contraction, lipid and atherosclerosis, and leukocyte transendothelial migration (Table S7).

The first KEGG pathway, cell adhesion molecules, was represented by five methylomic markers, five proteomic markers (including three overlapping with the methylomic markers), and no metabolomic markers (Supplementary File S2, Tables S4 and S5). The three overlapping markers were a cluster of differentiation 40 ligands (CD40LG), p-selectin (SELP), and intercellular adhesion molecule 1 (ICAM1). For CD40LG, short-term $PM_{2.5}$ was associated with hypomethylation of the corresponding gene [117,125,148], whereas short-term $PM_{2.5}$, NO_2, SO_2, SO_4, EC, and multiple PM components were associated with higher levels of the protein [76,115,117,125,127,147,148,205,207]. For SELP, long-term $PM_{2.5}$ was associated with hypomethylation of the corresponding gene, and long-term PAHs were associated with lower levels of the protein [48,125,172,207]. For ICAM1, short-term BC and O_3 were associated with hypomethylation of the corresponding gene [41], short-term $PM_{2.5}$ had inconsistent associations with the corresponding gene [41,61,125,147], and both short- and long-term TRAP exposures were generally associated with higher levels of the protein [69–71,92,105,124,147,205,228]. Biomarkers of the cell adhesion molecule pathway (e.g., SELP, ICAM1) were also identified in our network analysis for both short- and long-term TRAP exposures as being highly connected to markers of other biological processes (e.g., lipid metabolism; Figures 3–6). Cell adhesion molecules are essential in the normal development of the heart and blood vessels; however, they play a role in the development of respiratory diseases and CVD, such as pulmonary fibrosis and atherosclerosis [229].

The second KEGG pathway, the VEGF signaling pathway, was represented by no methylomic, three proteomic, and two metabolomic markers associated with TRAP exposure (Supplementary File S2, Tables S5 and S6). For proteomics, short-term exposure to diesel exhaust was associated with higher levels of the cell division control protein

42 homolog and lower levels of protein kinase C beta type [130]. In addition, exposure to short-term NO_2 and long-term NO_x was associated with higher levels of VEGF-alpha (VEGFA) [84,115]. VEGFA was also identified as connected to markers of lipid metabolism and amino acid metabolism in our network analysis for short-term TRAP exposure (Figure 5). For metabolomics, short-term $PM_{2.5}$ was associated with higher levels of nitric oxide, and short-term EC was associated with higher levels of prostaglandin I2 [118,119,167]. Upregulation of VEGF signaling is involved in angiogenesis and can be a response to hypoxia [230]. Higher concentrations of these analytes associated with TRAP exposure could indicate difficulty delivering oxygen from the lungs to the periphery; however, VEGF signaling is not always pathological.

The third KEGG pathway, vascular smooth muscle contraction, was represented by one methylomic, three proteomic, and four metabolomic markers associated with TRAP exposure (Supplementary File S2 Tables S4–S6). For methylomics, long-term $PM_{2.5}$ was associated with hypomethylation of the guanine-nucleotide-binding protein alpha subunit complex locus (*GNAS*) [48]. For proteomics, short-term UFP, BC, NO_2, and CO were associated with higher levels of endoglin [138], and short-term diesel exhaust was positively associated with mitogen-activated protein kinase 1 and negatively associated with protein kinase C beta type [130]. For metabolomics, short-term $PM_{2.5}$ was positively associated with nitric oxide and 20-hydroxyeicosatetraenoic (HETE) acid [109,118,119], and short-term TRAP was positively associated with arachidonate and prostaglandin I2 [167,168,173]. Contraction of the vascular smooth muscle within arteries, arterioles, veins, and lymphatic vessels increases resistance in the cardiovascular system and decreases blood flow [231]. TRAP-associated modulation in these signals could inform part of the relationship between TRAP exposure and blood pressure, and therefore CVD. Further research is needed to clarify the exact physiological mechanisms linking TRAP, omics signals, blood pressure, and CVD.

The fourth KEGG pathway, lipid and atherosclerosis, was represented by no methylomic or proteomic markers but three metabolomic markers associated with TRAP exposure (Supplementary File S2 Table S6). Short-term $PM_{2.5}$ was positively associated with nitric oxide, and short-term TRAP was positively associated with cholesterol and triglyceride [118,119,138]. Cholesterol and triglycerides, both positively associated with TRAP exposure, are risk factors for atherosclerosis. Furthermore, TRAP is already known to be associated with atherosclerosis through the exacerbation of risk factors such as hypertension and insulin resistance [232].

The final KEGG pathway, leukocyte transendothelial migration, was represented by three methylomic markers, six proteomic markers (one overlapping with a methylomic marker), and no metabolomic markers associated with TRAP exposure (Supplementary File S2, Tables S4 and S5). The trends for the overlapping marker (ICAM1), as well as two of the other proteomic markers (i.e., protein kinase C beta type and cell division control protein homolog 42), were described previously. The other methylation markers associated with short-term $PM_{2.5}$ encode protein subunit alpha 13 (positive association) and actinin alpha 3 (negative association) [43,161]. The other proteomic markers positively associated with short-term TRAP exposure included vascular cellular adhesion molecule 1 (VCAM1; with $PM_{2.5}$, NO_2, CO, SO_4, and O_3) [71,92,205], matrix metalloproteinase (MMP2; with BC and PNC), and MMP9 (with SO_2) [82]. In our network analysis for short-term TRAP exposures, MMPs shared network connections with markers of processes such as lipid and amino acid metabolism (Figure 5). Leukocyte trans-endothelial migration is critical in the immune response and responsible for facilitating a systemic reaction upon exposure to a pathogen [233]. The subclinical effects of differential leukocyte count post-TRAP exposure have previously been noted [234] and represent part of the well-documented inflammatory response to TRAP.

3.2.7. Oxidative Stress

Multiple KEGG pathways represented in the methylomic, proteomic, and metabolomic literature are associated with the oxidative stress response (Table S7; Figure 2). For example, the citrate cycle, pentose phosphate metabolism, MAPK signaling, p53 signaling, Janus Kinase/signal transducers and activators of transcription (JAK–STAT) signaling, apoptosis, and regulation of autophagy KEGG pathways are all known to be activated in response to oxidative stress [217,235–241]. The biomarkers related to several of these pathways were described previously. Others are described in this section.

The p53 signaling pathway is activated in response to oxidative stress and TRAP exposure and helps to ensure cell survival [236,237]. For this pathway, one methylomic and seven proteomic markers (including one overlapping gene–protein marker) were identified as significantly associated with TRAP (Supplementary File S2, Tables S4, S6, and S8). Short-term exposure to $PM_{2.5}$ was associated with hypomethylation of *SERPINE1* [148]. Additionally, short-term exposure to PM_{10} and $PM_{2.5–10}$ was associated with lower levels of the corresponding protein, whereas long-term exposure to $PM_{2.5}$, $PM_{2.5–10}$, NO_2, CO, and O_3 were associated with higher levels [72,74,76]. Furthermore, short-term BC and NO_2 were associated with higher levels of insulin-like growth factor binding proteins 1 and 3, while short-term diesel exhaust was associated with lower levels of insulin-like growth factor binding protein 2 and 14-3-3 protein sigma [82,130]. Finally, long-term $PM_{2.5}$ and PM_{10} exposures were associated with higher levels of alpha-1 antitrypsin [86]. Given the role of p53 signaling in anti-angiogenesis, programmed cell death, metabolism regulation, and vasodilation, this pathway can affect cardiovascular outcomes [242,243]. In addition, p53 signaling plays a supportive role in the maintenance of lung homeostasis; therefore, dysregulation and deficiency of p53 signaling can be associated with respiratory diseases [244].

Similarly to the p53 signaling pathway, the JAK–STAT signaling pathway is activated by oxidative stress and reactive oxygen species [240]. This signaling pathway is mainly involved in coordinating immune responses, including cytokine signaling [245]. Four methylomic markers and fourteen proteomic markers (including four overlapping gene-protein markers) of this pathway were identified as significantly associated with TRAP (Supplementary File S2, Tables S4, S6, and S8). Three of the methylomic markers (for the genes *CSF2*, *IL6*, and *IL10*) were described in the section on inflammation and immunity. Briefly, short- and long-term TRAP was associated with hypomethylation of these markers and higher levels of the proteins they encode [61,76,91–94,115,117,127,128,147,165,204,228,246,247]. Hypermethylation of one methylomic marker relevant here (related to a gene that encodes interferon gamma (*IFNG*)) was associated with short-term TRAP exposure (though short-term BC was associated with hypomethylation) [41,120]. Relatedly, short-term $PM_{2.5}$, NO_2, CO, PAHs, and PM constituents were associated with higher levels of the protein IFNG [115,204]. Short-term TRAP was also positively associated with other proteins involved in JAK–STAT signaling, including granulocyte colony-stimulating factor 3, granulocyte-macrophage colony-stimulating factor receptor alpha, Interleukin 2 alpha, Interleukin 5, Interleukin 7, Interleukin 12, and signal transducer and activator of transcription 3 (STAT3) [115,117,128,138,165,206]. In contrast, short-term TRAP was associated with lower levels of Interleukin 4, Interleukin 13, and protein tyrosine phosphatase non-receptor type 6 [115,117,165]. These associations with markers related to JAK-STAT signaling are important for the relationship between TRAP exposure and CVD outcomes because dysregulation of JAK–STAT signaling is associated with CVD [248,249]. Furthermore, cytokine signaling induced through the JAK–STAT pathway is implicated in COPD, asthma, and other respiratory conditions [250,251].

Apoptosis, or programmed cell death, can be caused by oxidative stress [238]. Representing the apoptosis KEGG pathway, TRAP was associated with one methylomic marker, three proteomic markers (including one overlapping with a methylomic marker), and one metabolomic marker (Supplementary File S2, Tables S4–S6). Trends for the overlapping methyl-omic-proteomic marker, tumor necrosis factor-alpha, were described previously. For the other proteomic markers, short-term PM_{10}, UFP, NO_2, CO, and PAHs

were positively associated with Interleukin 1 beta, whereas short-term UFP, BC, NO_2, and CO were inversely associated with tropomyosin receptor kinase B [94,138,204]. For metabolomics, short-term $PM_{2.5}$, UFP, and long-term $PM_{2.5}$ were associated with lower levels of the sole metabolite, sphingosine [98,101,171]. Apoptosis is a vital part of normal cell turnover and immune system functioning, implicating this pathway in cardiorespiratory disease [252–254].

The final oxidative-stress-related KEGG pathway, the regulation of autophagy, is involved in apoptosis and helps maintain cellular homeostasis [238,239,241,255]. This pathway was represented by one methylomic marker and two proteomic markers (including one overlapping marker) associated with TRAP. Trends were previously described for the overlapping marker, interferon-gamma. The other protein, interferon alpha 2, was positively associated with short-term $PM_{2.5}$ [117]. Proper functioning of adaptive autophagy processes is important for cardiovascular health and aging [256–258].

3.2.8. TRAP, Omics, and Respiratory Disease

Short- and long-term TRAP exposure is associated with worse respiratory outcomes, including worse lung function [61,90,110,154,259–263], and with more asthma exacerbation and COPD burden [262,264–267]. In our review, three methylomic markers, seven proteomic markers (including three overlapping methylomic–proteomic markers), and three metabolomic markers were represented in the KEGG pathway for asthma (Table S7). The overlapping markers included three inflammation and immunity markers (TNF, CD40LG, and IL-10); we described trends for these previously [61,72,91,94,115,117,125,128,147,147,204,205,207,228,247,260]. For the other proteomics markers, short-term $PM_{2.5}$, PM_{10}, NO_2, CO, and SO_2 were inversely associated with IL-4; short-term CO was inversely associated with IL-13 [115,117,128]; and short-term NO_2 and diesel exhaust were positively associated with IL-5 [115,128]. Additionally, short-term $PM_{2.5}$, PM_{10}, CO, and SO_2 were inversely associated with monocyte chemoattractant protein 1, whereas long-term $PM_{2.5}$, NO_2, and NO_x were positively associated with this protein [84,115,117]. For metabolomic markers, short-term TRAP was positively associated with leukotriene C4 and inversely associated with prostaglandin D2 [168], and short-term NO_2, CO, and EC were inversely associated with histamine [166]. These trends, along with others described in previous sections, suggest plausible biological processes that affect the TRAP exposure-respiratory disease relationship. For example, it has been observed that linoleate metabolism is associated with asthma [104], and arginine and proline metabolism as well as methionine and cysteine metabolism are associated with asthma and COPD [106]; these are processes associated with TRAP exposures. Additionally, elevated NO is characteristic of airway inflammation [268], and we previously described trends relating TRAP to higher NO [61,118,119]. Similar trends are observed between TRAP exposures and markers of systemic inflammation (e.g., CRP, fibrinogen) that are associated with worse lung function [269–272]. Finally, the associations we described previously relating TRAP exposures to cytokines and chemokines have implications for airway remodeling, asthma, and COPD [213].

3.2.9. TRAP, Omics, and CVD

As described above and elsewhere, many studies have observed associations between TRAP exposure and biomarkers related to CVD (e.g., [273–275]). A subset of studies used meet-in-the-middle approaches (i.e., identifying common associations of exposures and CVD outcomes with biomarkers), mediation analyses, and other approaches to more directly link TRAP exposures to CVD outcomes (e.g., heart rate [120], blood pressure [149,150], and incident CVD [84]). As in our review, these studies considered biomarkers for processes related to inflammation and immunity, endothelial function, and oxidative stress. Most of these studies considered only single omic types, but one that considered both proteomic and metabolomic biomarkers identified 20 biomarkers associated with both short-term TRAP and changes in blood pressure or heart rate variability [138]. As in our review, that study identified biomarkers implicated in lipid metabolism (e.g., trimethylamine N-oxide),

cellular energy production (e.g., succinic acid), inflammation (e.g., C-reactive protein), coagulation (tissue factor pathway inhibitor), endothelial function (e.g., angiotensin-converting enzyme), and oxidative stress (e.g., malondialdehyde). Our review was able to take this type of logic one step further—with the network analyses (Figures 3–6). By integrating information across multi-omic types, we can build on the systems biology approaches now being used to understand the pathophysiology of CVD (e.g., [276,277]). Specifically, our network analyses suggest that interconnections among amino acid metabolism, lipid metabolism, inflammation, coagulation, and endothelial function are important to the relationship between TRAP exposures and CVD.

4. Conclusions

To our knowledge, this is the first systematic review synthesizing the literature focused on TRAP-associated methylomic, proteomic, and metabolomic biomarkers in the context of respiratory and cardiovascular outcomes. Through a comprehensive, integrated lens, we explored TRAP-associated pathways involving lipid metabolism, cellular energy production, amino acid metabolism, inflammation and immunity, coagulation, endothelial function, and oxidative stress. We find that a multi-omics synthesis provides new insights into the biological pathways associated with TRAP and has advantages over single-omics approaches. Synthesizing results from the (predominately single-omic) literature, we showed that similar or analogous biomarker signals were observed across multiple omic types (e.g., TRAP exposure associated with methylation of genes encoding for proteins that are also associated with TRAP). Specifically, we identified consistent patterns between methylation status and protein levels within cytokine–cytokine signaling, TLR signaling, MAPK signaling, complement and coagulation cascades, cell adhesion molecules, and asthma KEGG pathways. Additionally, we observed analogous proteomic and metabolomic associations with TRAP exposure within certain lipid and amino acid metabolism KEGG pathways. Finally, within the arginine and proline metabolism KEGG pathway, we were able to integrate methylomic, proteomic, and metabolomic findings to provide evidence suggesting possible mechanistic linkages between TRAP exposure, subclinical indicators, and clinical disease. Corroborating evidence across multiple levels of biology—including with a focus on functional interrelationships and network analyses—is only possible with multi-omics. Furthermore, multi-omics has the potential to aid in the discovery and assessment of quantitative biomarkers at different levels of biology (related methylation patterns, proteins, and metabolites) that could predict subclinical and perhaps clinical respiratory and cardiovascular responses to TRAP exposure, thereby improving clinical and public health decision-making. This could perhaps be clinically translated using advances to epigenetic clocks and other risk prediction tools that address residual risk remaining after the use of current risk prediction tools [211,278–281]. The continued development of omics technologies represents immense potential for the advancement of personalized medicine. Researchers and clinicians should continue to collaborate on the identification of omics signals associated with air pollution exposure, preclinical disease, and clinical disease to develop helpful risk prediction tools.

4.1. Strengths and Limitations

A major strength of our systematic review is that we provided a synthesis of findings from across three types of omics markers. This multi-omics process offers superior insight into the biological underpinnings of respiratory diseases and CVD than single-omics methods alone. We compiled methylomic, proteomic, and metabolomic evidence from methodologically diverse studies in a novel way to understand how short- and long-term TRAP exposure-associated multi-omics signals relate to one another, allowing us to identify the most relevant biological pathways that may be involved in the pathogenesis of cardiorespiratory disease and help inform clinical risk prediction. Nevertheless, our review had several limitations. First, to synthesize results across studies that used heterogeneous exposure metrics and methods, we made the simplifying assumption of categorizing

short- and long-term exposures as ≤30 days and >30 days, respectively. This decision was supported by convention within the literature but does not necessarily reflect a critical biological change occurring at 30 days. Additionally, due to the availability of published studies, there were fewer long-term exposures represented in our analysis. This limitation of our review is a limitation of the field in general. Given the relative sparsity of long-term exposure periods as well as a tendency to select targeted rather than untargeted omics approaches, the omics signals and pathways associated with long-term TRAP exposure may be incomplete or less comprehensive relative to short-term TRAP exposure. Second, to synthesize the biological implications of the individual biomarkers identified as associated with TRAP, we made simplifying assumptions that we could include all individually identified biomarkers together in our pathway and network analyses, and although we considered short- and long-term exposures separately, we did not separate results by pollutant type. Different TRAP components likely have different biological impacts. This could even be true of the same TRAP component; for example, $PM_{2.5}$ toxicity could vary by source and composition, and we did not account for these differences. More generally, it is possible that direct comparisons or synthesis were not warranted in each case due to certain differences in the study population, exposure metric, or other methodological choices within the individual studies that would result in meaningful differences in the true underlying biology. Third, our synthesis of the results and identification of relevant pathways were necessarily limited by the choices of the individual studies (including those related to the ways 'statistical significance' was defined). If the studies did not include certain biomarkers that may be important to the physiological response to TRAP, we could not capture them—particularly for proteomics, this may have limited our findings since there were somewhat fewer studies with large numbers of proteins assayed, and the literature may have overrepresented certain biological pathways due to precedent rather than biology. Targeted omics approaches (as employed with many of the proteomics studies) allow for focused, relatively resource-efficient confirmatory investigations following earlier studies identifying potentially important biomarkers; however, future studies leveraging evolving technology may consider a more comprehensive set of proteins. Conversely, untargeted approaches (as employed with many of the metabolomics studies) are exploratory. They analyze the broadest set of possible biomarkers. While this has the advantage of helping identify the most expansive set of possible biologically relevant biomarkers and pathways, they need to be followed up with confirmatory studies to test the hypotheses they generate. Relatedly, if metabolite identification with a high level of confidence was not provided by the individual untargeted studies, we may have missed critical biological pathways. Next, we limited the scope of our review to exclude people who were pregnant and/or under 18 years old. Future research should consider these important populations. Fourth, reflecting the literature, this review contains a relatively large number of studies representing only single-sex cohorts. Their inclusion is critical to this review as it represents a large proportion of our current knowledge; however, single-sex research limits our understanding of the potentially variable response to TRAP exposure between sexes. Future work should consider sex and gender more fully, including the possibility for effect modification by sex and/or gender. Similarly, our results may not be transportable to children who were not in our study population. Finally, and perhaps most critically, we could not assess whether TRAP exposures resulted in meaningful biological cascades following the gene-to-protein-to-metabolite paradigm, as no study we reviewed included all three omics types and none included the repeated measures of the omics markers that would be needed to assess dynamic biological processes. This is apparent in the occasional inconsistent associations with short- versus long-term exposure windows of the same pollutant (in terms of strength and/or direction of association). It is possible that these differences arise from true differences among study populations and their responses to pollution, or alternatively, from an inability to accurately capture the biological cascades occurring at various time points.

4.2. Future Directions

Building on the strengths of the studies presented in this review and the conclusions that could be drawn by comparing the results using heterogeneous research methodologies, several critical areas for further research are warranted. The primary challenges our field currently faces are related to the true integration of multi-omics signals within studies that can appropriately characterize the dynamic and complex biological processes linking TRAP exposure to subclinical and clinical diseases. To address this critical challenge, we need large, longitudinal studies representing diverse study populations. Ideal features include time-varying, high-resolution exposure assessment coupled with repeated quantification of multi-omics signals in multiple tissue types with comprehensive assay coverage. If multiple cohorts are included in a study, standardization of methods across cohorts would facilitate interpretation and comparability of results. A major goal of such a study would be to consider how air pollution exposures might lead to physiological signals suggestive of the biological cascades leading from exposure to sub-clinical disease to clinical disease (necessitating several repeated measures of the biological matrix over different time courses). A consideration of both the short- and long-term physiological effects of TRAP would be warranted, including a consideration of individual TRAP components and TRAP mixtures. Ideally—and expected based on the historic evolution of technology—omics technology will continue to evolve to analyze larger numbers of biomarkers more quickly and cheaply. It would also be worth examining sex and gender differences, along with other differences that could lead to disparities in health consequences attributed to air pollution exposure. The use of emerging and novel data management and analysis approaches that can handle large and complex data structures inherent in multi-omics studies will be important (e.g., multiblock methods and tensor decomposition methods) [23,276,282–287]. Open-source bioinformatics platforms are an important resource and should be invested in to ensure they are kept up-to-date and able to handle multi-omics analyses. Relatedly, it would be critical to consider the optimal multi-omics integration approach (e.g., whether each omics type is analyzed first and then types are synthesized, or whether processing integrates across omics types earlier) [288–290]. If such a comprehensive study could be conducted, it would provide mechanistic insight into the pathophysiology and progression of the disease and would inform the identification of multi-omic signatures of air pollution exposure that could be predictive of key health outcomes. Insights gained from such studies could inform screening priorities, clinical decision-making, and public policy.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/toxics11121014/s1, Supplementary File S1: Search strategy for systematic review article selection process; Supplementary File S2: Multi-omics synthesis tables and data extraction spreadsheets used in the systematic review process, Table S1: Methylomics data extraction table. Information regarding study author, design, participant demographics, and basic methodology were extracted. Each row corresponds to a unique study. (ACE—Atlanta Commuters Exposure; ARIC—Atherosclerosis Risk in Communities; BPRHS—Boston Puerto Rican Health Study; EPIC—European Prospective Investigation into Cancer and Nutrition; KORA—Cooperative health Research in the Region of Augsburg; MESA—Multi Ethnic Study of Atherosclerosis; NAS—Normative Aging Study: REGICOR—REgistre GIroní del COR; SAPALDIA—Swiss Study on Air Pollution and Lung Disease in Adults; SPHERE—Susceptibility to Particle Health Effects, miRNA and exo-somes; WHI—Women's Health Initiative); Table S2: Proteomics data extraction table. Information regarding study author, design, participant demographics, and basic methodology were extracted. Each row corresponds to a unique study. (ACE—Atlanta Commuters Exposure; AHAB-II—Adult Health and Behavior; AIRCHD—Air Pollution and Cardiovascular Dys-functions in Healthy Adults Living in Beijing; BPRHS—Boston Puerto Rican Health Study; CAFEH—Community Assessment of Freeway Exposure and Health; ELISABET—Enquête Littoral Souffle Air Biologie Environnement; EPIC—European Prospective Investigation into Cancer and Nutrition; ESCAPE—European Study of Cohorts for Air Pollution Effects; KORA—Cooperative Health Research in the Region of Augsburg; MESA—Multi Ethnic Study of Atherosclerosis; NAS—Normative Aging Study; SAGE—Study on Global Aging and Adult Health; SAPALDIA—Swiss Study on Air Pollution and Lung Disease in

Adults; SWAN—Study of Women's Health Across the Nation); Table S3: Metabolomics data extraction table. Information regarding study author, design, participant demographics, and basic methodology were extracted. Each row corresponds to a unique study. (ACE—Atlanta Commuters Exposure; AIRCHD—Air pollution and Cardiovascular Dys-functions in Healthy Adults Living in Beijing; CAFEH—Community Assessment of Freeway Exposure and Health; DRIVE—Dorm Room Inhalation to Vehicle Emissions; EARTH—Environmental and Reproductive Health; EPIC—European Prospective Investigation into Cancer and Nutrition; KORA—Cooperative Health Research in the Region of Augsburg; NAS—Normative Aging Study; SAPALDIA—Swiss Study on Air Pollution and Lung Disease in Adults; SCOPE—A Prospective Study Comparing the Cardiometabolic and Respiratory Effects of Air Pollution Exposure on Healthy and Prediabetic Individuals; TAPAS—Transportation, Air Pollution and Physical Activites); Table S4: Methylomics synthesis table. All statistically significant associations between TRAP and methylomics markers from the methylomics literature were compiled into this table. For each gene, KEGG pathways and Gene Ontology (GO) molecular functions were indicated. If available, sepcific CpG sites corresponding to the genes were given. Each pollutant was broken down into short-term (<30 days) and long-term (>30 days) exposure. ($PM_{2.5}$—Particulate Matter 2.5 Microns or Less; PM_{10}—Particulate Matter 10 Microns or Less; BC—Black Carbon; NO_2—Nitrogen Dioxide; NO_x—Nitrogen Oxides; SO_4—Sulfate; O_3—Ozone; TRAP—Traffic-Related Air Pollution); Table S5: Proteomics synthesis table. All statistically significant associatons between TRAP and proteomics markers within the proteomics literature were compiled into this table. For each protein, KEGG pathways and Gene Ontology (GO) molecular functions were indicated. Each pollutant was broken down into short-term (<30 days) and long-term ($\geq$30 days) exposure. ($PM_{2.5}$—Particulate Matter 2.5 Microns or Less; PM_{10}—Particulate Matter 10 Microns or Less; PM_1—Particulate Matter 1 Micron or Less; UFP—Ultrafine Particulate Matter; BC—Black Carbon; NO_2—Nitrogen Dioxide; NO_x—Nitrogen Oxides; CO—Carbon Monoxide; SO_4—Sulfate; O_3—Ozone); Table S6: Metabolomics synthesis table. All statisically significant associations between TRAP and metabolomics markers within the metabolomics literature were compiled into this table. For each metabolite, KEGG pathways were indicated. Each pollutant was broken down into short-term (<30 days) and long-term ($\geq$30 days) exposure. ($PM_{2.5}$—Particulate Matter 2.5 Microns or Less; PM_{10}—Particulate Matter 10 Microns or Less; PM_1—Particulate Matter 1 micron or Less; UFP—Ultrafine Particulate Matter; BC—Black Carbon; EC—Elemental Carbon; NO_2—Nitrogen Dioxide; NO_x—Nitrogen Oxides; CO—Carbon Monoxide; SO_2—Sulfur Dioxide; O_3—Ozone; Ni—Nickel; V—Vanadium; Al—Aluminium; Si—Silicon; K—Potassium; Cu—Copper; Zn—Zinc; Fe—Iron; Pb—Lead; Se—Selenium; TRAP—Traffic-Related Air pollution); Table S7: Combined synthesis of significant associations; Table S8: Complete synthesis table. This table synthesizes the methylomic, proteomic, and metabolomic literature. The table is organized by KEGG pathway. Within each KEGG pathway, all methylomic, proteomic, and metabolic markers significantly associated with short and/or long-term TRAP are noted. Each pollutant was broken down into short-term (<30 days) and long-term ($\geq$30 days) exposure. ($PM_{2.5}$—Particulate Matter 2.5 Microns or Less; PM_{10}—Particulate Matter 10 Microns or Less; UFP—Ultrafine Particulate Matter; BC—Black Carbon; EC—Elemental Carbon; NO_2—Nitrogen Dioxide; NO_x—Nitrogen Oxides; CO—Carbon Monoxide; SO_2—Sulfur Dioxide; S04—Sulfate; O_3—Ozone; Ni—Nickel; V—Vanadium; Al—Aluminium; Si—Silicon; K—Potassium; Cu—Copper; Zn—Zinc; Fe—Iron; Pb—Lead; Se—Selenium; TRAP—Traffic-Related Air Pollution); Table S9: The list of all methylomic, proteomic, and metabolomic markers used for pathway and network analyses in both MetaboAnalyst and KEGG.

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