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Early-life oxidative stress due to air pollution. A scoping review focusing on identifying potential '-OMICS' biomarkers from body fluids

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Abstract

Exposure to air pollution (AP) is inevitable in daily life and an increasing number of epidemiological studies have reported that exposure to ambient particulate matter (PM) is associated with adverse health outcomes. Intrauterine, childhood, and adolescence are vulnerable periods, during which PM exposure can cause molecular changes, potentially leading to changes in metabolism and development. PM-induced oxidative stress is the underlying mechanism. Biomarkers can be used as illustrative measures of PM exposure to facilitate the assessment of potential health effects and provide a better understanding of the underlying mechanisms. The purpose of this scoping review is to report -OMICS biomarkers found in body fluids that are primarily related to oxidative stress and are already used to evaluate ambient AP exposure, as well as to identify knowledge gaps. Web of Science, PubMed, and Scopus databases were independently searched for all studies published between January 2013 and December 2022 that reported on -OMICS signature changes during pregnancy, childhood, and adolescence. Of the initial 757 articles, 36 met our inclusion criteria and reported on genomic, epigenomic, transcriptomic, proteomic, lipidomic, and metabolomic biomarkers. The findings of this scoping review indicate that exposure to various ambient pollutants in early life can cause oxidative stress. Integrating biomarkers from top-down -OMICS studies in an epidemiological context may provide a clear picture of the biomarker selection process to establish a causal relationship between PM exposure and disease pathogenesis. This knowledge could lead to the conceptualization and subsequent development of novel preventative strategies.

1. Introduction

The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 reported that ambient particulate matter (PM) pollution was among the risk factors with the largest increase in risk exposure, accounting for more than 1% of disability-adjusted life-years [1]. Intrauterine, childhood, and adolescence are particularly sensitive periods, as biological systems and organs are in various stages of development. Therefore, the absorption, distribution, metabolism, and elimination of environmental contaminants present in the air are less efficient. The developmental origins of health and disease, also known as the Baker hypothesis, proposes that chronic noncommunicable diseases in adulthood may originate from exposure to various environmental factors during critical developmental periods [2].

Air pollution (AP) constitutes a heterogeneous, complex mixture of particles that differ based on their size, source (e.g. natural or anthropogenic), time, atmospheric conditions, and location, e.g. urban compared to suburban areas [3]. Factors affecting the toxicity of airborne particulates include their size,

shape, structure, surface reactivity, solubility, bio-persistence, and leachability. Because physicochemical features are not easy attributes, the classification of particles is usually performed by size, with smaller particles having greater health impacts. Three main categories are defined: particles with a diameter <10 μM (PM_{10}), <2.5 μM ($PM_{2.5}$) and <0.1 μM ($PM_{0.1}$ or ultrafine particles (UFPs)) [4]. PM_{10} is normally derived from natural sources, such as dust storms, bushfire smoke, construction, and agricultural activities. $PM_{2.5}$ and $PM_{0.1}$ tend to be derived from anthropogenic sources. In urban environment, up to 90% of anthropogenic particles are attributed to road vehicles, while the rest are derived from the combustion of by-products from industries. As a result, the composition of $PM_{2.5}$ and $PM_{0.1}$ varies greatly (i.e. metal ions, organic carbon (OC) (e.g. polycyclic aromatic hydrocarbons (PAHs), pesticides, phthalates (PAEs), flame retardants, and carboxylic acids), and elemental carbon (EC)). Examination of OC composition revealed that atmospheric PAHs mainly originate from human activities derived from fossil fuel combustion sources, specifically gasoline- and diesel-powered vehicle exhaust [5]. $PM_{0.1}$ poses a greater threat than $PM_{2.5}$, as they can infiltrate bodies to an even greater extent [4].

As reviewed by de Paula Santos *et al* [6], there is growing evidence from epidemiological studies that short- and long-term PM exposures are linked to higher rates of disease prevalence in susceptible populations such as pregnant women, children, and the elderly. The proposed mechanism involves PM-induced oxidative stress [7]. Evidence indicates that fetal PM exposure resulting in oxidative stress may affect fetal development, birth outcomes (low birth weight, preterm birth, and small for gestational age births), lifelong changes in metabolism and the immune system, and diseases that arise later in life, including pulmonary, cardiovascular, and neurological disorders [8]. Due to its small size, $PM_{0.1}$ has a higher pulmonary deposition fraction, penetrates deeper into the lungs, and reaches the circulatory system, causing PM-induced oxidative stress. Additionally, smaller particles with larger surface-to-mass ratios can carry higher concentrations of pro-oxidant chemical components (transition metal ions) and PAHs, both of which have been shown to induce oxidative stress responses [9, 10]. However, linking AP-mediated effects to reactive oxygen species (ROS) pathogenesis remains difficult, because PM causes oxidative damage and systemic effects only if the antioxidant response is overwhelmed. Hence, biomarkers of exposure, susceptibility, and effects may be useful for measuring the impact of oxidative stress after AP exposure [11].

Sequencing and mapping of the human genome, development of mass spectrometry techniques for protein expression analysis, and advances in bioinformatics in relation to large datasets have provided avenues for understanding which biochemical pathways are implicated in the origin of chronic diseases. Despite this, many exposure-disease associations remain unknown, as accurate assessment of many environmental exposures remains difficult. As a result, there is a need for an 'exposome' that matches the genome, transcriptome, proteome, lipidome, and metabolome from the prenatal period onwards [12]. Since exposure assessment can reflect altered levels of DNA, mRNA, proteins, lipids, or metabolites, '-OMICS' biomarkers have the potential to provide at least a partial understanding of the influence of AP on the etiological role of chronic noncommunicable diseases.

Previous reviews have described the links between prenatal and childhood ambient AP exposure, associated biomarkers, and/or health outcomes [13–16], but none have reported the key '-OMICS' biomarkers isolated from body fluids that are used to assess oxidative stress during these critical periods. Therefore, the goal of this scoping review is to summarize and identify -OMICS exposure, susceptibility, and health effect biomarkers that can be used as biomarkers of early life disease development due to PM-related oxidative stress.

2. Methods

This scoping review aimed to provide an answer to the following question:

> *'Within epidemiological research, which "-OMICs" biomarkers have been analysed in body fluids to assess the level of oxidative stress due to air pollution during the prenatal, childhood, and adolescent periods?'*

To answer this question, we used the following Population, Exposure, Comparator, Outcomes elements:

'Population': body fluids (blood, cord blood and urine, amniotic fluid, exhaled breath) from humans withdrawn during the prenatal, childhood (0–13 years old), and adolescent periods (up to 19 years-old).

'Exposure': ambient AP, including $PM_{2.5}$, PM_{10}, UFPs, and PAHs. Ambient AP is defined as the mixture of indoor and outdoor pollutants (traffic and industrial pollutants).

'Comparator': we included studies where comparisons are made between groups in higher and lower concentrations of AP, as well as studies with a continuous exposure scale.

'Outcomes': body fluid -OMICS oxidative stress biomarkers and, if discussed, adverse birth outcomes and disease development.

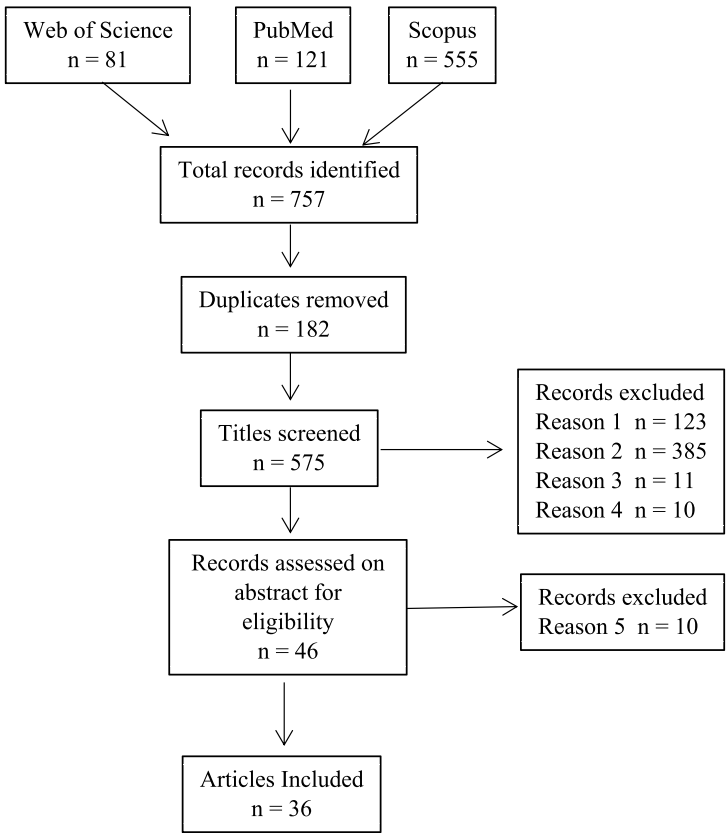

Figure 1. PRISMA flow diagram.

According to the Preferred Reporting Items for Scoping Reviews (PRISMA) guidelines, we performed the last online database search (Web of Science, PubMed, and Scopus) on 25 January 2023, restricting the search to the last 10 years (end date, 31 December 2022), humans, and articles in English. The following search terms were used:

AP: 'air pollution' OR 'ultrafine particle*' OR 'particulate matter*' OR 'PM2.5' OR 'PM 2.5' OR 'PM10' OR 'PM 10' OR 'UFPs' OR 'PAH' OR 'polycyclic aromatic hydrocarbon*'.

For oxidative stress: 'oxidative stress'.

For population: 'women,' 'woman,,' 'female*', 'mother*', 'newborn*', 'child*', 'toddler*, adolescent*'.

For genomic/epigenomic biomarkers: 'DNA*', 'microRNA*', 'DNA adduct*', 'genom*,' DNA methylation, 'telomere length*', 'histone*', 'epigenom*'.

For Transcriptomic biomarker: 'mRNA*', 'transcriptom*'.

For proteomic biomarker: 'protein*', 'proteom*'.

For lipidomic biomarker: 'lipid*', lipidom*'.

For metabolomic biomarker: 'metabolom*', 'metabolite*'.

We limited our search to title/abstract and English articles published in the last 10 years (2013–2022) and not animal studies. Each of the two authors independently reviewed all the articles and selected them for inclusion in the study. It was agreed that a third party would be used in the event of any disagreement that could not be resolved through discussion. However, this was not required. The strategy was to first remove duplicates and then perform a first-pass screening to remove irrelevant material such as reviews, editorials, notes, and conference abstracts (figure 1, reason 1). This was followed by article titles screened to remove obvious irrelevant studies reporting on adults (from age 19), non-pregnant women, and studies reporting on animals, cell lines, and subjects with comorbidities, such as asthma (figure 1, reason 2). For inclusion, articles had to indicate the influence of outdoor AP, specifically from traffic- and industry-related activities. Any article reporting on the influence of occupational and household practices, or tobacco use was removed (figure 1, reason 3). From the retrieved studies, only those that analyzed body fluids such as blood, cord blood, and urine were included and those reporting on placenta and tissues were excluded (table 1, figure 1, reason 5).

Table 1. OMICS categories and body fluid biomarkers analysed to confirm an association between exposure to air pollution and oxidative stress in pregnant women, mother–newborns, children and adolescents. Abbreviations: mtDNAc, mitochondrial DNA content; RT-qPCR: real-time quantitative PCR; FACS, fluorescence activated cell sorting; TL, telomere length; ELISA, enzyme-linked immunosorbent assay kits; LC–MS, liquid chromatography-mass spectrometry; TBARS, thiobarbituric acid reactive substances assay; T-AOC, antioxidant reaction, FRAP, ferric reducing -antioxidant power; SCFAs, short-chain fatty acids; BP, blood pressure.

	Biomarkers and *methods of detection*							
	Genomics	Epigenomics	Transcriptomics	Proteomics	Lipidomics	Metabolomics	Outcomes	Ref.
Pregnant women	mtDNAc and TL (*RT-qPCR*).						Fetal and birth growth outcomes.	[17]
	Mitochondrial viability and depolarization (*PCR, FACS and JC-1 Mitoscreen*).		Expression levels of 84 oxidative stress genes and UCP2, Nrf2 SOD2, OGG1 (*qPCR*).	Nfr2, UCP2 expression level (*Western blot*).	MDA (*TBARS*).			[18]
	Lymphocyte DNA damage (*Single cell gel electrophoresis*).					T-AOC (*FRAP*).		[19]
	GSTP1 and GSTM1 polymorphisms (*PCR*).	8-OHdG (*ELISA*).						[20]
		8-OHdG (*ELISA*).		NY, ClY, diY (*LC–MS*).	8-iso (*ELISA*).	Urinary level of OH-PAH metabolites (*LC–MS*).		[21]
		8-OHdG (*LC–MS*).				Urinary level of PAH metabolites (*LC–MS*).		[22]
					MDA (*TBARS*).	T-AOC (*FRAP*).		[23]
						Metabolomic profiles (*LC–MS*).		[24]
						Metabolomic profiles (*LC–MS*).		[25]

(Continued.)

Table 1. (Continued.)

	Biomarkers and *methods of detection*							
	Genomics	Epigenomics	Transcriptomics	Proteomics	Lipidomics	Metabolomics	Outcomes	Ref.
	mtDNAc (*RT-qPCR*).	8-OHdG (*RT-qPCR*).						[26]
	mtDNAc (*RT-qPCR*).							[27]
	TL (*RT-qPCR*).						Diary for antioxidant intakes.	[28]
	SNPs (*SNP Genotyping Platform*).							[29]
	DNA damage (*Comet assay*).	8-OHdG (*ELISA*).			MDA (*HPLC*).	Urinary level of PAH metabolites (*HPLC*).		[30]
Mother–newborns		8-OHdG (*LC–MS*).				Urinary level of PAH metabolites (*LC–MS*).		[31]
		8-oxodG (*ELISA*).			8-iso (*ELISA*).			[32]
		8-oxodG (*ELISA*).			8-iso (*ELISA*).		Cognitive tests.	[33]
					8-iso (*ELISA*).			[34]
			Whole genome expression level (*Expression BeadChips*).					[35]

(Continued.)

Table 1. (Continued.)

	Biomarkers and *methods of detection*							
	Genomics	Epigenomics	Transcriptomics	Proteomics	Lipidomics	Metabolomics	Outcomes	Ref.
						Metabolomic profiles (*LC–MS*).		[36]
	Oxytocin receptors genes polymorphisms (*PCR*).	8-OHdG, 8-oxodG (*HPLC*).			SCFAs (*GC–MS*).			[37]
		8-OHdG (*ELISA*).				Urinary level of 2-naphthol (*LC–MS*).		[38]
		8-OHdG (*OxyDNA kit combine with flow cytometry*) DNA methylation level (LINE1, OGG1, PARP1, APEX) (*PCR*).				Urinary level of 1-PYR and benzene (*HPLC*).		[39]
Children/adolescents		8-OHdG (*LC–MS*).				Urinary level of PAH metabolites (*LC–MS*).		[40]
		8-OHdG (*LC–MS*).				Urinary level of PAH and PAE metabolites (*LC–MS*).		[41]
		8-oxodG (*HPLC*).			MDA (*LC*).			[42]
				CC16 (*ELISA*).	8-iso (*ELISA*).			[43]
					MDA (*ELISA*).		Lung function tests.	[44]
					MDA, 8-iso, 4-HNE (*ELISA*).		Lung function tests.	[45]
		8-OHdG, 8-NO_2Gua (*LC–MS*).			8-iso, HNE-MA (*LC–MS*).	Urinary level of 1-PYR and heavy metals (*HPLC*). Metabolomic profiles (*GC–MS*).		[46]

(Continued.)

Table 1. (Continued.)

Biomarkers and *methods of detection*							
Genomics	Epigenomics	Transcriptomics	Proteomics	Lipidomics	Metabolomics	Outcomes	Ref.
	8-OHdG, 8-NO_2Gua (*LC–MS*).			8-iso and HNE-MA (*LC–MS*).	Urinary level of 1-PYR and heavy metals (*HPLC*). Metabolomic profiles (*LC–MS*).		[47]
	8-OHdG, 8-NO_2Gua (*LC–MS*).			8-iso, HNE-MA and lipidomic profile analysis (*LC–MS*).	Urinary level of 1-PYR and heavy metals (*HPLC*).		[48]
DNA damage (*Comet assay and micronucleus assay*).	8-oxodG (*ELISA*).						[49]
	8-oxodG (*ELISA*).				Urinary level of PAH metabolites (*LC–MS*).		[50]
			Serum GGT (*Chemistry analyser*).			Renal function tests.	[51]
			Markers of oxidative stress (*Magnetic bead assay and CyTOF*).			BP	[52]

3. Results

3.1. Study characteristics

As described by the PRISMA flow diagram (figure 1), our initial search identified 121 articles in PubMed, 81 in the Web of Science, and 555 in Scopus. Most studies have been observational and carried out in an epidemiological context, using blood, cord blood, and urine as body fluids to study the molecular effects of AP exposure. However, we found one study that used exhaled breath and another that tested saliva. We identified 36 articles that met the inclusion criteria. Studies have been conducted worldwide, with a predominance in China ($n = 9$), the USA ($n = 8$), Taiwan ($n = 4$), the Czech Republic ($n = 4$), Belgium ($n = 4$), Mexico ($n = 2$), and South Africa ($n = 2$), and one each from Saudi Arabia, Italy, and Poland. Table 1 shows the biomarkers studied across the different studies as well as the methods used to quantify them. For all '-OMICS' categories, the majority of research articles used a bottom-up approach, focusing on specific, preselected biomarkers and their already known association with oxidative stress. Sixteen studies compared two groups of participants based on the level of AP or intervention, and twenty related their findings to the level of pollutants in the air. Approximately three-quarters of the studies used data from either monitoring stations or air samplers to correlate their molecular data with AP, while the last quarter relied on urinary PAH metabolite concentrations. The details of each study are summarized in supplemental data.

3.2. Genomic associated studies

As summarized in (table 2), the main genomic oxidative stress biomarkers studied were DNA, mitochondrial DNA (mtDNA) and telomere length (TL). In pregnant women, Kalemba-Drozdz [19] found a positive correlation between DNA damage in lymphocytes and the admissible level of AP and proposed the hormesis theory. Three studies reported on the changes in maternal and cord blood mtDNA in relation to oxidative stress [17, 18, 27]. Iodice *et al* [17] reported a PM_{10} exposure-related increase in mtDNA content in maternal blood during the first trimester (T1) of pregnancy, which could reflect a compensatory mechanism to ensure cell survival. In contrast, Nagiah *et al* [18] observed that in the immune blood mononuclear cells of pregnant women in their third trimester (T3), only half of the mtDNA was viable in the exposed versus control groups. They also found significant upregulation of genes (AOX1, NOX5, and DUOX2) involved in $O_2^{\bullet-}$ production and elevated adenosine triphosphate (ATP) levels. In cord blood, a significant association between increased $PM_{2.5}$ exposure (specifically between 35 and 40 weeks of gestation) and a reduction in mtDNA content has been reported, especially among boys [27].

Two studies investigated the association between oxidative stress due to AP exposure and TL, and reported a significant decrease in maternal [17] and cord blood [28]. The second trimester (T2) of pregnancy appears to be the most vulnerable, and antioxidant intake during pregnancy appears to be a protective factor (relative leukocyte TL, exposed (2.6 ± 0.9) versus unexposed (2.1 ± 0.9)) [28].

Additionally, one study reported the interaction of 11 single nucleotide polymorphisms (SNPs) in oxidative stress-related genes with plasma homocysteine levels in cord blood and exposure to $PM_{2.5}$ [29].

3.3. Epigenomic associated studies

Nineteen articles commented on epigenetic modifications associated with oxidative stress due to AP, including DNA oxidation [20–22, 26, 30, 31–33, 38–40, 42, 46–50, 53] and DNA methylation [39] (table 3).

The most common epigenetic process studied is DNA damage through the analysis of two common products of DNA oxidation: 8-hydroxy-2'-deoxyguanosine (8-OHdG) and 8-oxo7,8-dihydro-2'-deoxyguanosine (8-oxodG). Three studies reported a positive association between 8-OHdG levels in pregnant women [20] and PAH exposure [22], specifically 2-hydroxynapthalene (2-NAP), 2- and 3-hydroxyphenanthrene quantified together (2- and 3-PHE), 9-hydroxyphenanthrene (9-PHE), 1-hydroxyphenanthrene (1-PHE), and 1-hydroxypyrene (1-PYR) [21]. Regarding nitric oxide (NO_x) exposure, a significant positive correlation could potentially be explained by mothers having the genotype variant AG + GG for GSTP1 or GSTM1 null genotype [20]. Moreover, a comparison of 8-OHdG concentration levels between working pregnant women and housewives revealed higher oxidative damage in working women, indicating a possible role of work-related stress [22]. In maternal and cord blood samples obtained from mother–newborn dyads, Grevendonk *et al* [26] reported a positive correlation between PM_{10} and $PM_{2.5}$ exposure and mitochondrial 8-OHdG levels during the entire pregnancy, while Al-Saleh *et al* [30] confirmed a positive association between urine 8-OHdG levels and 1-PYR. Two other studies examined the level of 8-oxodG in urine and found a higher content in newborn urine of mothers exposed to $PM_{2.5}$ [32, 33]. A similar trend has been observed in children [38–42, 46, 50, 53], children/adolescents [46], and adolescents [49], that is, an increase in AP is generally associated with an increase in the level of 8-OHdG or 8-oxodG in urine. It is worth mentioning that boys [8, 41, 50] might be more prone than girls [50], that the

Table 2. Studies reporting on the association between air pollution, oxidative stress and changes in genomic biomarkers.

References	Study population	Air pollution	Main findings
[17]	11th week healthy pregnant women ($n = 199$) from Italy.	PM_{10} (10–90 $\mu g\ m^{-3}$) and $PM_{2.5}$ (7–69 $\mu g\ m^{-3}$) measured in Milan by the Air Quality Monitoring Network.	PM_{10} exposure during T1 was associated with an increased maternal mtDNA copy number and a reduced TL. Both fetal heart rate (FHR) and crown-rump length (CRL) were positively associated with $PM_{2.5}$. PM_{10} exposure is positively associated with FHR and a reduced birth weight.
[19]	Pregnant women ($n = 39$) from Poland.	SO_2, NO, NO_2, CO, O_3, PM_{10} measured using automatic air pollution monitoring system.	The positive correlations between the amounts of DNA damage in lymphocytes and the levels of air pollutant exposure support the hormesis theory. No diet and air pollution interactions were found.
[18]	T3 pregnant women participating in the Mother and Child in the Environment (MACE) cohort pilot study in South Africa. Exposure group ($n = 50$), control group ($n = 50$).	Industrial area with higher levels of SO_2, NO_x, CO, PM_{10}, O_3 and lead compared to a less industrialized area.	Pregnant women in high-polluted areas had higher levels of oxidative stress markers and compromised mtDNA integrity and repair.
[29]	Mother–newborn pairs from the ENVIRONAGE (ENVIRonmental influence ON early AGEing) birth cohort ($n = 609$) from Belgium.	$PM_{2.5}$ using a validated high-resolution spatial temporal interpolation method.	$PM_{2.5}$ is linked to higher levels of homocysteine in the plasma of umbilical cord blood. This may depend on genetic differences in MnSOD, GST1, and the sum score of three single nucleotide polymorphisms (SNPs) in the CAT gene.
[28]	Mother–newborn pairs enrolled in the Programming of Intergenerational Stress Mechanisms (PRISM) ($n = 155$) in USA.	$PM_{2.5}$ using a validated spatiotemporally resolved satellite-based model.	Prenatal $PM_{2.5}$ exposure between 12 and 20 weeks of gestation was linked to a shorter infant TL. These effects were mitigated by higher maternal antioxidant intake.
[27]	Mother–newborns ($n = 456$) from Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study in Mexico.	$PM_{2.5}$ estimated by a satellite-based spatio-temporally resolved prediction model.	Increased $PM_{2.5}$ during T3 was associated with decreased mtDNA content in cord blood.

Table 3. Studies reporting on the association between air pollution, oxidative stress and changes in epigenomic biomarkers.

References	Study population	Air pollution	Main findings
[20]	Pregnant women from the Mother and Child in the Environment (MACE) longitudinal cohort study in South Africa. Control group ($n = 152$). Exposure group ($n = 225$).	NO_X by land regression modeling. Exposure (37.04 μg ml^{-1} $\pm$ 7.46). Control (33.26 μg ml^{-1} $\pm$ 8.51, $p < 0.0001$).	NO_x exposure increased 8-OHdG levels in pregnant women, resulting in a shorter gestational age. Individuals with the GSTP1 variant were more vulnerable to the harmful effects of NO_x.
[21]	Pregnant women in T3 ($n = 200$) from USA.	Measured by urinary PAH metabolites.	Positive associations between the concentrations of some PAH metabolites, CRP, and 8-OHdG.
[22]	Pregnant women ($n = 188$) from China. Working women ($n = 138$); housewife ($n = 24$); unknown ($n = 26$).	Measured by urinary PAH metabolites. Total PAH concentration: 0.52–42.9 μg g^{-1} creatinine.	Positive associations between the concentrations of some PAH metabolites and 8-OHdG. When exposed to the same levels of PAHs, working women had higher 8-OHdG concentrations than housewives.
[30]	Mother–newborn pairs ($n = 1578$) from Saudi Arabia.	Benzo(a)anthracene (BaA), chrysene (Ch), benzo(b)fluoranthene (BbF), benzo(a)pyrene (BaP), and dibenzo(a,h)anthracene (DBahA) levels are measured in placentas, maternal and umbilical cord blood.	Positive relationship between 8-OHdG levels and 1-PYR in urine.
[32]	Mother–newborn pairs from Czech Republic: control region, summer (mothers, $n = 99$, newborns, $n = 99$), winter (mothers, $n = 100$, newborns, $n = 100$). Exposure region, summer (mothers, $n = 70$, newborns, $n = 71$), winter (mothers, $n = 73$, newborns, $n = 74$).	In exposure region: $PM_{2.5}$ Summer 2013 (mean $\pm$ SD: 20.41 $\pm$ 6.28 vs. 9.45 $\pm$ 3.62 μg m^{-3}, $P < 0.001$). Winter 2014 (mean $\pm$ SD: 53.67 $\pm$ 19.76 vs. 27.96 $\pm$ 12.34 μg m^{-3}, $P < 0.001$). B[a]P Summer 2013 (mean $\pm$ SD: 1.16 $\pm$ 0.91 vs. 0.16 $\pm$ 0.26 ng m^{-3}, $P < 0.001$) winter 2014 (5.36 $\pm$ 3.64 vs. 1.45 $\pm$ 1.19 ng m^{-3}, $P < 0.001$).	$PM_{2.5}$ levels were found to be a significant predictor of 8-oxodG -excretion.
[33]	Mother–newborn pairs from Czech Republic: control region, summer (mothers, $n = 99$, newborns, $n = 99$), winter (mothers, $n = 100$, newborns, $n = 100$). Exposure region, summer (mothers, $n = 70$, newborns, $n = 71$), winter (mothers, $n = 73$, newborns, $n = 74$).	$PM_{2.5}$ concentrations: exposure (37.7 $\pm$ 14.7 μg m^{-3}) control (17.1 $\pm$ 4.8 μg m^{-3}, $p < 0.001$).	There were no differences in 8-oxodG urine levels in either region in the mothers. In newborns, the 8-oxodG concentration in urine was higher in girls ($p < 0.01$).

(Continued.)

Table 3. (Continued.)

References	Study population	Air pollution	Main findings
[26]	Mother–newborn pairs ($n = 293$) from Belgium.	PM_{10} exposure was 19.2 (16.6–23.8) $\mu g\ m^{-3}$ for T1, 21 (17.4–23.8) $\mu g\ m^{-3}$ for T2, 22.2 (17.3–26.1) $\mu g\ m^{-3}$ for T3, and 21.4 (19.8–22.8) $\mu g\ m^{-3}$ for the entire pregnancy.	PM increased mitochondrial 8-OHdG levels in both mothers and their newborns during pregnancy.
[31]	Mother–newborns pairs ($n = 77$) from China.	PAHs $\sum_7$PAHs ranged from 1.37 to 45.5 ng ml^{-1}. Median concentrations: 1-NAP: 3.00 ng ml^{-1} 2-NAP 2.58 ng ml^{-1} 2-Fluo: 0.31 ng ml^{-1} $\sum$1,2,3-PHE: 0.44 ng ml^{-1} 1-PYR: 0.51 ng ml^{-1}.	8-OHdG concentrations were positively correlated with PAH concentrations in urine and derived from vehicle exhaust and petrochemical emissions.
[39]	Schoolchildren from Mexico ($n = 150$).	PM_{10} (106.9 $\mu g\ m^{-3}$ (CI 95% 103.1–110.7)) contains organic carbon (35.8 $\mu g\ m^{-3}$), elemental carbon (8.3 $\mu g\ m^{-3}$), 9 environmental metals (total = 3.9 $\mu g\ m^{-3}$) (Fe > Zn > Pb > Cu > Mg > V > Ni >Cr > Cd) and 17 PAHs (total: 0.002 pg m^{-3}). PAHs exposure: 1-PYR (18.5 nmol mol^{-1} Cr (6.1–45.7) and benzene, t,t-MA (142.7 ($\mu g\ g^{-1}$ Cr)) (69.3–298.5).	Positive relationship between PM_{10} and 8-OHdG.
[40]	Children, age 3–6 years ($n = 87$) from China.	Urinary PAHs ($\sum$PAHs = 21.12 $\mu g\ g^{-1}$ Crt.), and 10 metabolites, benzene and toluene (BT), ($\sum$BT = 174.42 $\mu g\ g^{-1}$ Crt.) which corresponds to 2–30 times higher than those in children from the other countries. Urinary PAHs (PAHs = 21.12 g g^{-1} Crt.) and ten metabolites, benzene and toluene (BT), (BT = 174.42 g g^{-1} Crt.), at levels 2–30 times higher than in children from other countries.	There is a significant dose–effect relationship between PAH exposure, BT exposure, and urine 8-OHdG concentration.

(Continued.)

Table 3. (Continued.)

References	Study population	Air pollution	Main findings
[42]	Schoolchildren from China ($n = 38$).	Pollutants, including black carbon (−65%), $PM_{2.5}$ (−72%), and sulphur dioxide (−66%) were lower during the Olympic games.	Substantial reductions in air pollution were associated with a decrease in urinary 8-oxodG concentrations.
[38]	Kindergarten children ($n = 453$) from the Childhood Environment and Allergic Diseases Study in Taiwan.	PAH measured through urine 2-*naphthol* levels.	Positive correlation between 2-*naphthol* and 8-OHdG levels. There is no significant correlation between 2-*naphthol* concentrations and IgE levels. 2-*naphthol* levels are associated with the risk of allergic diseases.
[37]	Children from China ($n = 86$), age 5–6 years old. Exposure group ($n = 46$). Control group ($n = 40$).	$PM_{2.5}$, control (91.53 ± 27.19 $\mu g\ m^{-3}$) and exposure (112.07 ± 26.39 $\mu g\ m^{-3}$), ($p = 0.004$).	Preschoolers on campuses with high pollution had much higher levels of 8-OHdG in their urine than preschoolers on campuses with low pollution.
[41]	Schoolchildren from China ($n = 166$), aged 8–11 years.	PAHs include eight metabolites that varied between 0.36 and 36.5 ng ml^{-1}, with a median of 3.86 ng ml^{-1}. Phthalates (PAEs) (from plastic packaging) include 12 compounds; ΣmPAEs varied between 9.48 and 1609 ng ml^{-1}, with a median of 240 ng ml^{-1}.	8-OHdG levels were positively correlated with urinary PAHs and mPAEs. At the same concentrations, PAHs made a greater contribution to oxidative DNA damage than mPAEs.
[46]	Children/adolescents from Taiwan, age (13.76 ± 0.93 years old). High exposure ($n = 40$) Low exposure ($n = 71$).	Ambient concentrations of V, Cr, Ni, Cu, As, Sr, Cd, Hg, Tl, Pb, and five PAHs. Urine concentrations of 1-PYR, V, Ni, Cu, As, Sr, Cd, Hg, and Tl were significantly increased in high exposure groups compared to low exposure groups.	There was no statistically significant difference in 8-OHdG concentrations between high and low exposures.
[47]	Taiwanese children/adolescents High exposure ($n = 37$). Low exposure ($n = 70$).	AP around a largest petrochemical. Exposure urine biomarkers As, Cd, Cr, Ni, 1-PYR, V, and Hg increased in the high compared to the low exposure group, with As, Cd, 1-PYR, V, and Hg reaching statistical significance and stronger for 1-PYR and V.	There was no statistically significant difference in 8-OHdG concentrations between high and low exposures. A'meet-in-the middle' approach identified an association between 8-OHdG, pyroglutamic acid and inosinic acid.

(Continued.)

Table 3. (Continued.)

References	Study population	Air pollution	Main findings
[48]	Children/adolescents from Taiwan ($n = 99$). High exposure ($n = 34$). Low exposure ($n = 65$).	AP around a largest petrochemical. Urine concentration of As, Cd, Cr, Ni, Pb, Hg, V, Mn, Cu, Sr, Tl, and PAH metabolites, 1-PYR.	There was a no statistically significant increase in 8-OHdG concentrations in the high exposure.
[49]	Adolescents ($n = 2283$) from Belgium.	PM_{10}, $PM_{2.5}$, measured on 36 air quality measurement stations all over Flanders. 1-PYR, benzene metabolite tt'-muconic acid (TT-MA), metals (arsenic, cadmium, copper, nickel, thallium, lead, chromium), organochlorines and phthalates assessed in blood and urine.	There is a significant positive association between urinary 8-oxodG, 1-PYR, urinary copper, and the phthalate DEHP. 8-oxodG was positively related to the urinary metal levels of total As, Ni, and Tl, the blood levels of Tl and Pb, the urinary phthalate metabolite MnBP, and the 7 d-averaged PM_{10} and $PM_{2.5}$. % DNA migration in the comet assay was positively associated with blood metals (Cd, total As, Ni, Pb), serum PCB138, serum TN, urinary TT-MA, negatively associated with urinary Cd and TRA, ΣDEHP, and blood Tl, and either positively or negatively associated with urinary 1-PYR and 7 d-averaged PM_{10} and $PM_{2.5}$.
[50]	Adolescents from Belgium ($n = 393$).	Urinary PAHs and six individual metabolites. ΣPAHs in boys ($p = 0.004$, 0.028 (95% CI: 0.025, 0.032)) μmol l^{-1} and in girls, 0.036 (95% CI: 0.032, 0.040) μmol l^{-1}.	A doubling of 1-PYR, 2-, and 3-PHE concentrations was associated with an increase in 8-oxodG levels.

Table 4. Studies reporting on the association between air pollution, oxidative stress and changes in transcriptomic biomarkers.

References	Study population	Air pollution	Main findings
[18]	T3 pregnant women in the Mother and Child in the Environment (MACE) cohort pilot study in South Africa. Exposure group ($n = 50$). Control group ($n = 50$).	Industrial area with higher levels of SO_2, NO_x, CO, PM_{10}, O_3 and lead compared to a less industrialized area.	26 oxidative stress-related genes are differentially regulated. SOD2 and UCP2 mRNA levels rise, while Nfr2 and OGG1 mRNA levels fall.
[35]	Mother–newborn pairs ($n = 202$) from Czech Republic.	$PM_{2.5}$ and B[a]P concentration Season 1 High exposure: $PM_{2.5}$ ($\mu g\ m^{-3}$): (31.40 ± 28.79) B[a]P (ng m^{-3}): (2.87 ± 4.40) Low exposure: $PM_{2.5}$ ($\mu g\ m^{-3}$): (12.48 ± 6.52) B[a]P (ng m^{-3}): (0.47 ±0.56) Season 2 High exposure: $PM_{2.5}$ ($\mu g\ m^{-3}$): (40.34 ± 31.53) B[a]P (ng m^{-3}): (5.24 ± 5.47) Low exposure: $PM_{2.5}$ ($\mu g\ m^{-3}$): (21.14 ± 13.22) B[a]P (ng m^{-3}): (1.57 ± 1.27).	Small changes in gene expression are linked to the effect of the locality. A pathway analysis showed a deregulation of processes related to cell growth, apoptosis, or cellular homoeostasis, immune response-related processes, or the response to oxidative stress.

level of DNA damage could decrease with age in children [40] and that individual PAH metabolite dependence was observed.

DNA methylation is another common epigenetic biomarker analyzed, and one study reported a possible relationship between oxidative DNA damage levels and DNA methylation. Alvarado-Cruz *et al* [39], using multiple regression analysis, revealed that the methylation of the long interspersed nuclear element-1 (LINE1) was 79.2%, while for the DNA repair genes, it was 1.20% (CI 95% 1.1–1.2) for 8-oxoguanine DNA glycosylase (OGG1) (4 CpG dinucleotides), 1.2% (CI 95% 1.1–1.4) for poly (ADP-ribose) polymerase (PARP1) (7 CpG dinucleotides), and 1.07% (CI 95% 1.0–1.1) for apurinic/apyrimidimic endonuclease 1 (APEX) (4 CpG dinucleotides).

3.4. Transcriptomic associated studies

Two articles [18, 35] used mRNA to study gene expression changes and the deregulated biological pathways associated with AP (table 4).

Nagiah *et al* [18] examined the expression levels of 84 oxidative stress-related genes and discovered that three genes (GSS, B2M, and ANGPTL7) were significantly downregulated, whereas 26 genes involved in oxidative stress response and antioxidant defense were significantly upregulated in women exposed to higher AP. Among them were three glutathione peroxidases (GPX7, GPX2, and GSTZ1), six peroxidases (EPX, PXDNL, PXDN, myeloperoxidase (MPO), LPO, and TPO), two antioxidants (ALB and SRXN1), four genes involved in $O_2^{\bullet -}$ metabolism (NOX5, ALOX12, NCF2, and NOS2), two genes involved in ROS metabolism (AOX1 and MPV17), and six genes associated with oxidative stress response (SIRT2, MBL2, OXSR1, OXR1, NUDT1, and DUOX2). Additionally, they reported that these women displayed a higher level of oxidative stress markers and compromised DNA repair mechanisms, as confirmed by a lower level of OGG1 expression in women with higher AP exposure and a higher antioxidant response, as reflected by the increased expression of both SOD2 and UCP2 mRNA and protein levels. A top-down global gene expression study by Honkova *et al* on cord blood leukocytes revealed that seasonal variability in AP affects biological processes more profoundly than continuous exposure to high AP levels [35]. They reported the differential expression of genes involved in cell growth, differentiation, apoptosis, cellular homeostasis, immune-related processes, and the oxidative stress response.

3.5. Proteomic associated studies

Generally, protein-based studies aim to uncover the underlying mechanisms that lead to the adverse health outcomes caused by AP (table 5). This includes the expression analysis of proteins from the endogenous antioxidant system such as Nfr-2, UCP2 [18], GGT [51], as well as biomarkers released as a result of oxidative stress such as growth/differentiation factor 15 (GDF-15), MPO [52] and club cell protein

Table 5. Studies reporting on the association between air pollution, oxidative stress and changes in proteomic biomarkers.

References	Study population	Air pollution	Main findings
[18]	T3 pregnant women in the Mother and Child in the Environment (MACE) cohort pilot study in South Africa. Exposure group ($n = 50$) control group ($n = 50$).	Industrial area with higher levels of SO_2, NO_x, CO, PM_{10}, O_3 and lead compared to a less industrialized area.	Decrease of Nfr2 and an increase of UCP2 in the exposure group.
[43]	Children ($n = 218$) from Children's Health and Air Pollution Study (CHAPS) in USA.	Average recorded at 1 d, 1 week, 1 month, 3 months, 6 months and 1 year of NO_2, NO_x, elemental carbon, PAH456, CO, $PM_{2.5}$.	The 3- to 6 month exposure time frames were associated with the greatest decrease in CC16 level across all pollutants.
[51]	Adolescents ($n = 660$) from National Health and Nutrition Examination Survey (NHANES) in USA.	Urinary PAHs and ten individual metabolites. ΣPAHs: 13 143.2 ng l^{-1} ($\pm$1262.0) with 1-NAP (5439.1 ng l^{-1}) and 2-NAP (5712.0 ng l^{-1}) having the highest concentration.	Positive and statistically significant associations between PAH metabolites and GGT serum levels.
[52]	Adolescents from USA ($n = 100$).	$PM_{2.5}$ (0.96 μg m^{-3} (0.88–1.05)) PM_{10} (39.3 μg m^{-3} (31.4–50.5)) PAHs (2.73 ng m^{-3} (2.16–3.24)) O_3 (64.1 ppb (56.3–68.6)) CO (0.29 ppb (0.25–0.34)) NO (1.36 ppb (1.02–2.36)) NO_2 (7.63 ppb (6.34–9.61)).	Exposure to air pollution was linked to oxidative stress markers (GDF-15 and myeloperoxidase), acute inflammation (C-reactive protein), hemostasis (ADAMTS, D-dimer), inflammasome markers (e.g. IL-18 and IL1-β), and both innate and adaptive immune regulators (e.g. monocytes and T regulatory cells).

(CC16) [43]. Circulating levels of C-reactive protein (CRP), inflammasomes (e.g. IL1-β, IL-18), hemostasis, and innate and adaptive immune regulators have all been documented to reflect the immune response [43, 51]. Overall, the expression of these proteins confirmed an association between AP and higher levels of oxidative stress biomarkers, lower antioxidant response, compromised DNA repair mechanisms, systemic inflammation, endothelial dysfunction, and altered hemostasis, all of which could impair metabolic function and lead to pulmonary, cardiovascular, and kidney impairment [18, 43, 51, 52].

3.6. Lipidomic associated studies

As shown in (table 6), oxidative stress induces lipid peroxidation and the formation of lipid peroxidation products, such as 15-F2t-isoprostane, 8-isoprostaglandin F2α, 8-isoprostane (8-iso), 4-hydroxynonenal (4-HNE), 4-hydroxy-2-nonenal-mercapturic acid (HNE-MA), and malondialdehyde (MDA). In general, an increase in their levels has been associated with higher levels of PM, benzo(a)pyrene (B[a]P) or PAHs [18, 34, 43–45, 48]. In pregnant women, if this is associated with insufficient antioxidant capacity, early pregnancy loss may occur 23.

Additionally, Chen *et al* [48] reported lipidomic profiles of 64 lipid species. Using partial least squares discrimination analysis, they found that the high- and low-exposure groups could be separated by three components (accuracy = 0.85, R2 = 0. 66, Q2 = 0.42). In the high-exposure group, this was characterized by the upregulation of one potential lysophosphatidylcholine (LPC) (18:1), four phosphatidylcholines (PCs), and two sphingomyelins (SMs) and the downregulation of two LPCs, four PCs, and two phosphatidylinositol. Furthermore, they showed altered expression of acylcarnitines, which could reflect the early health effects associated with renal and liver diseases.

3.7. Metabolomic associated studies

Five studies used a metabolomic approach to link environmental exposure to the possible health effects of oxidative stress [24, 25, 36, 46, 47] (table 7). The 2017 study by Chen *et al* [46] examined the link between metabolites as biomarkers of effect and living close to high-pollution facilities that emit heavy metals and PAHs. They identified 163 oxidative stress-related metabolites and alterations in three biological pathways:

Table 6. Studies reporting on the association between air pollution, oxidative stress and changes in lipidomic biomarkers.

References	Study population	Air pollution	Main findings
[18]	T3 pregnant women in the Mother and Child in the Environment (MACE) cohort pilot study in South Africa. Exposure group ($n = 50$), control group ($n = 50$).	Industrial area with higher levels of SO_2, NO_x, CO, PM_{10}, O_3 and lead compared to a less industrialized area.	Higher MDA levels were found in the exposure group compared to the control group.
[23]	Chinese women in T1 ($n = 206$), normal early pregnancy (NEP) ($n = 103$) women with early pregnancy loss (CREPL) ($n = 103$).	$PM_{2.5}$ annual average (52 mg m^{-3}).	$PM_{2.5}$-related early pregnancy loss could be due to susceptibility relating to increased lipid peroxidation and an insufficient antioxidant response.
[34]	Mother–newborns pairs from Czech Republic Exposure: • Summer 2013 Mother ($n = 70$) Newborn ($n = 71$) • Winter 2014 Mother ($n = 73$) Newborn ($n = 74$) Control • Summer 2013 Mother ($n = 99$) Newborn ($n = 99$) • Winter 2014 Mother ($n = 100$) Newborn ($n = 100$).	Exposure vs. control $PM_{2.5}$ Summer (20.41 ± 6.28 vs. 9.45 ± 3.62 $\mu g\ m^{-3}$, $p < 0.001$) Winter (53.67 ± 19.76 vs. 27.96 ± 12.34 $\mu g\ m^{-3}$, $p < 0.001$) B[a]P Summer (1.16 ± 0.91 vs. 0.16 ± 0.26 ng m^{-3}, $p < 0.001$) Winter (5.36 ± 3.64 vs. 1.45 ± 1.19 ng m^{-3},) $p < 0.001$.	Increased concentrations of $PM_{2.5}$ and B[a]P have a significant effect on the plasma level of isoprostanes (8-iso) in newborns.
[44]	Schoolchildren from China ($n = 304$) from two districts, one with good air quality (school A), the other in an industrial zone (school B).	$PM_{2.5}$ and 4–6 ring PAHs during heating and nonheating seasons.	Positive association between ambient $PM_{2.5}$-bound BbF, BaP, and DahA with MDA. MDA concentration was higher in school B than in school A.
[45]	Schoolchildren from China Air purification ($n = 124$) No purification ($n = 116$).	Outdoor PM_{10} (140.3 $\mu g\ m^{-3}$) $PM_{2.5}$ (73.0 $\mu g\ m^{-3}$) PM_1 (55.5 $\mu g\ m^{-3}$) Indoor *With purification* PM_{10} (50.0 $\mu g\ m^{-3}$) $PM_{2.5}$ (37.0 $\mu g\ m^{-3}$) PM_1 (31.5 $\mu g\ m^{-3}$) *No purification* PM_{10} (72.0 $\mu g\ m^{-3}$) $PM_{2.5}$ (63.0 $\mu g\ m^{-3}$) PM_1 (41.5 $\mu g\ m^{-3}$) ($p < 0.05$).	Reduction of $PM_{2.5}$ (10 $\mu g\ m^{-3}$) by air cleaner intervention reduces the levels of FeNO, exhaled breath condensate (EBC) 4-HNE, IL-1β and IL-6. Boys showed higher percentage changes than girls.

(Continued.)

Table 6. (Continued.)

References	Study population	Air pollution	Main findings
[43]	Children ($n = 218$) from Children's Health and Air Pollution Study (CHAPS) in USA.	Average recorded at 1 d, 1 week, 1 month, 3 months, 6 months and 1 year of NO_2, NO_x, elemental carbon, PAH456, CO, $PM_{2.5}$.	Positive association between 8-iso and short-term exposure to all measured traffic-related pollutants.
[46]	Children/adolescents from Taiwan. High exposure ($n = 40$) Low exposure ($n = 71$).	Ambient concentrations of V, Cr, Ni, Cu, As, Sr, Cd, Hg, Tl, Pb, and five PAHs. Urine concentrations of 1-PYR, V, Ni, Cu, As, Sr, Cd, Hg, and Tl were significantly increased in high exposure groups compared to low exposure groups.	Significant increase level of HNE-MA and 8-iso in exposure group.
[47]	Taiwanese children/adolescents High exposure ($n = 37$) Low exposure ($n = 70$).	AP around a largest petrochemical. Exposure urine biomarkers As, Cd, Cr, Ni, 1-PYR, V, and Hg increased in the high compared to the low exposure group, with As, Cd, 1-PYR, V, and Hg reaching statistical significance and stronger for 1-PYR and V.	Increased levels of oxidative stress biomarkers with more statistical differences for lipid peroxidation biomarkers (HNE − MA, 8-iso) than DNA damage biomarkers (8-OHdG, 8-NO_2Gua).
[48]	Children/adolescents from Taiwan ($n = 99$). High exposure ($n = 34$) Low exposure ($n = 65$).	AP around a largest petrochemical. Urine concentration of As, Cd, Cr, Ni, Pb, Hg, V, Mn, Cu, Sr, Tl, and PAH metabolites, 1-PYR.	Identified lipid profile changes associated with higher exposure to industrial pollutants. Industrial pollutants were linked to elevated oxidative stress biomarkers and altered serum acylcarnitines.

Table 7. Studies reporting on the association between air pollution, oxidative stress and changes in metabolomic biomarkers.

References	Study population	Air pollution	Main findings
[24]	Women from the Environment and Reproductive Health (EARTH) study ($n = 200$) undergoing a fresh assisted reproductive technology (ART) in USA.	$PM_{2.5}$, NO_2, O_3, BC. AP in the three months prior to serum sample was: NO_2 (24.2 (14.1, 33.4) ppb), O_3 (34.0 (26.1, 42.2) ppb) $PM_{2.5}$ 8.6 (7.6, 10.0) $\mu g\,m^{-3}$ BC 0.5 (0.4, 0.6) $\mu g\,m^{-3}$.	Eight features were confirmed as metabolites implicated in amino acid and nutrient metabolism with downstream effects on oxidative stress and inflammation. Tryptophan and vitamin B3 metabolism were found to be common pathways linking air pollution exposure to a lower likelihood of live birth.
[25]	Women from USA in mid-pregnancy High exposure ($n = 98$) Low exposure ($n = 62$).	$PM_{2.5}$, CO, NO_x retrieves from California Line Source Dispersion Model, version 4 (CALINE4).	Identified metabolomic features and pathways associating air pollution exposure with oxidative stress and inflammation pathways, including the fatty acid metabolism, phospholipid metabolism, linoleate metabolism, and eicosanoids (leukotriene and prostaglandin) metabolism.
[36]	Children form USA ($n = 241$).	Estimated $PM_{2.5}$ retrievals from the California Line Source Dispersion Model, version 4 (CALINE4).	$PM_{2.5}$ exposure was linked to nine enriched pathways, including lipid-related metabolic pathways (fatty acid activation, de novo fatty acid biosynthesis, fatty acid metabolism, the carnitine shuttle, and glycerophospholipid metabolism), prostaglandin formation (arachidonate and arachidonate metabolism), and amino acid metabolism pathways (methionine and cysteine metabolism).
[46]	Taiwanese children/adolescents High exposure ($n = 40$) Low exposure ($n = 70$).	Ambient concentrations of V, Cr, Ni, Cu, As, Sr, Cd, Hg, Tl, Pb, and five PAHs Urine concentrations of 1-PYR, V, Ni, Cu, As, Sr, Cd, Hg, and Tl were significantly increased in high exposure groups compared to the low exposure group.	Urine metabolite profiles clearly separated high and low exposure groups, and this was associated with oxidative stress biomarkers. 45 exposure-related potential urinary metabolites identified three main biological pathways potentially affected: alanine, aspartate, and glutamate metabolism; phenylalanine metabolism; and tryptophan metabolism.
[47]	Taiwanese children/adolescents High exposure ($n = 37$) Low exposure ($n = 70$).	AP around a largest petrochemical. Exposure urine biomarkers As, Cd, Cr, Ni, 1-PYR, V, and Hg increased in the high compared to the low exposure group, with As, Cd, 1-PYR, V, and Hg reaching statistical significance and stronger for 1-PYR and V.	Identified ten potential metabolites that may link increased exposure to As, Cd, Cr, Ni, V, Hg, and PAHs to elevated oxidative stress and deregulated serum acylcarnitines, including inosine monophosphate and adenosine monophosphate (purine metabolism), malic acid and oxoglutaric acid (citrate cycle), carnitine (fatty acid metabolism), and pyroglutamic acid (glutathione metabolism).

alanine, aspartate, and glutamate metabolism; phenylalanine metabolism; and tryptophan metabolism. As a result of exposure to multiple carcinogens, they identified perturbations in purine metabolism, which can increase oxidative stress and alter serum acylcarnitine levels [47]. Furthermore, Gaskins *et al* [24] investigated the influence of periconceptional AP exposure on the association between metabolites, amino acids, and nutrient metabolism pathways with downstream effects on oxidative stress and inflammation. Ritz *et al* [36] in their study of the newborn serum metabolome, found that increasing $PM_{2.5}$ concentrations during T3 increased oxidative stress and changes in lipid-related metabolic pathways, including the carnitine shuttle. In T2 women who have been exposed to higher levels of traffic-related pollution, metabolomic analysis identified pathways associated with oxidative stress as well as nine-lipid-related pathways and disruption of eicosanoid metabolism, including leukotrienes and prostaglandins, both of which are major proinflammatory mediators.

3.8. Triple relationship, AP leading to oxidative stress, biomarkers and birth outcome or disease development

Seven articles attempted to correlate AP, oxidative stress, and associated possible health outcomes [17, 24, 33, 44, 45, 51, 52]. Gaskins *et al* [24] reported a correlation between alterations in tryptophan and vitamin B3 metabolism and decreased probability of live births. Iodice *et al* [17] discovered a relationship between fetal heart rate, crown-rump length, and $PM_{2.5}$, as well as between fetal heart rate, reduced birth weight, and PM_{10} levels. However, they did not show an association between the oxidative stress marker mtDNA and any of the fetal outcomes and speculated on the existence of other pathways linked to PM exposure.

Three studies examined health outcomes in children. The longitudinal study of Blazkova *et al* [33] examined the impact of prenatal exposure to $PM_{2.5}$ on cognitive development in five-year-old children. They found a correlation between maternal plasma levels of the lipid peroxidation biomarker 8-iso, resulting from higher exposure to $PM_{2.5}$ levels, and child neurodevelopment. The relationship between prenatal AP exposure and neurodevelopmental outcomes, including autism spectrum disorder, attention deficit hyperactivity disorder, intelligence, general cognition, and mood, has recently been reviewed [54]. Kang *et al* [44] found that $PM_{2.5}$-bound 4–6-ring PHA levels increased the incidence of pulmonary ventilation and small airway dysfunction (SAD) in children during the heating season, with ambient $PM_{2.5}$-bound benzo(b)fluoranthene (BbF) and (dibenzo(a,h)anthracene) DBahA having the highest impact on the incidence of SAD. The use of air cleaners in classrooms could potentially improve this outcome, as Yang *et al* [45] reported that a reduction in PM_1 levels in classrooms leads to a decrease in exhaled nitric oxide (FeNO), IL-1β, and IL-6. In adolescents, all air pollutants ($p \leqslant 0.0030$) except O_3 ($p = 0.03$) were associated with a significant increase in diastolic BP [52], and some PAH metabolites were associated with high serum uric acid levels and eGFR [51], indicating possible early renal dysfunction and onset of other health outcomes, such as hypertension [55].

4. Discussion

The early detection of pathophysiological processes related to hazardous substances can be valuable in indicating the need for preventive actions to protect children's health. Biomarkers, such as chemicals, their metabolites, or their reaction products in a person's blood, urine, saliva, sputum, or exhaled breath condensate can be useful biological observations that can serve as an index of detrimental pathophysiological processes. The first goal of this scoping review was to determine which '-OMICS' biomarkers are used to assess AP-related oxidative stress during the prenatal, childhood, and adolescent development periods. Having established this, the second aspect of the scoping review was to provide a structural overview of the exposure and early effect, susceptibility, and health effect biomarkers used to evaluate the molecular '-OMICS' oxidative stress signatures (figure 2). Our search identified '-OMICS' biomarkers in each of these categories.

4.1. Biomarkers of exposure and early effect

Biomarkers are useful tools for detecting current or past exposures to toxic substances in biological samples. Measuring the actual concentration of a specific agent that has been absorbed or its resulting biologically effective outcome, such as molecules resulting from the oxidation of lipids, proteins, or DNA, can provide useful information regarding the effective internal dose absorbed and distributed throughout the body [56].

4.1.1. Internal PAH metabolites level

Exposure to environmental toxicants can endanger pregnancy, the fetus, and the health of children and adolescents. Several studies have found associations between prenatal environmental toxicant exposure and maternal and fetal health outcomes [13, 57–60]. Maternal urine is a noninvasive sample that best reflects the

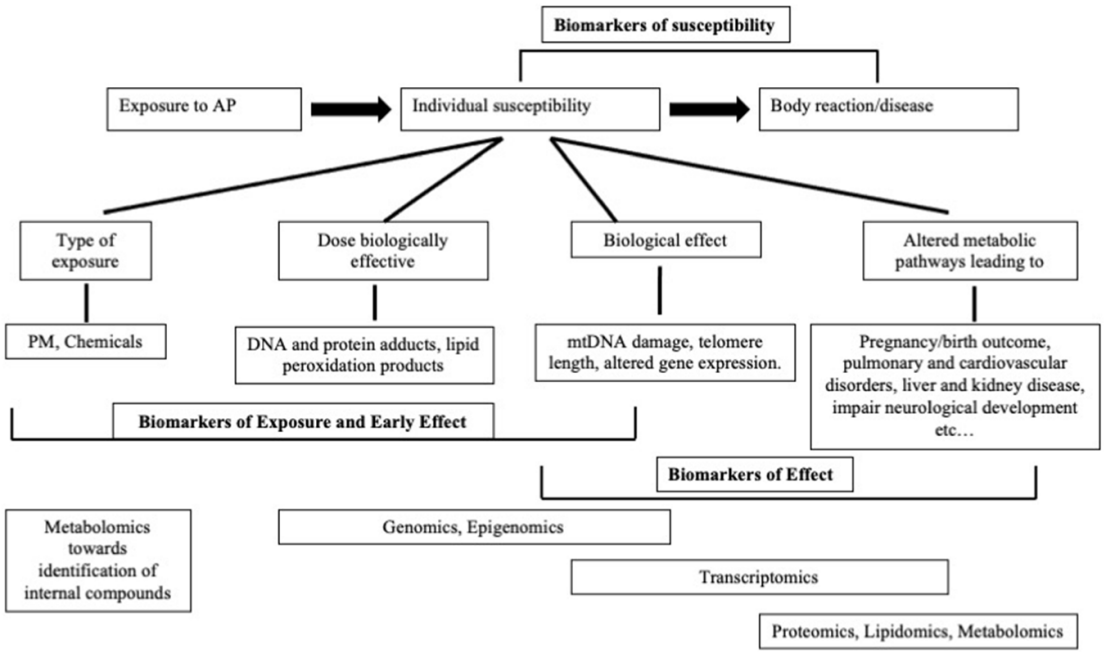

Figure 2. Scheme of biomarkers of exposure, effect, and susceptibility in ambient particulate matter exposure. The different categories of biomarkers are presented temporally, from exposure to disease development/progression.

intrauterine environment, whereas cord blood can be used to identify toxicants that can affect fetal development and growth [61]. Our scoping review reported the direct identification of PAHs and PAEs metabolites or heavy metals in the urine of pregnant mothers [21, 22], cord blood [30], and urine and blood of children and adolescents [39–41, 46–48, 50].

The potential health effects of an increase in internal PAH metabolites have been reviewed [16, 62]. Similar to our study, a meta-analysis [63] determined that, in addition to the total exposure level of PAH metabolites, the levels of 1-PYR, 2-NAP, 2-Fluo, 3-PHE, and 4-PHE were most commonly studied, and that the 1-PYR level is suitable for evaluating AP exposure in children and adolescents.

4.1.2. Early effect biomarkers

In the event of a disequilibrium between antioxidants and ROS leading to an increase in the level of ROS and therefore oxidative stress, damage to lipids, proteins, and DNA occurs, all of which could lead to cell death and tissue damage [64]. For instance, excess ROS can cause lipid peroxidation, resulting in damage to the cell membranes and lipoproteins. Proteins can undergo conformational modifications that lead to impairment or loss of enzymatic activity, which in turn causes oxidative DNA damage [65]. As a result, oxidative stress brought on by AP can be measured using biomarkers of early effects, such as damaged lipids, proteins, and DNA products that are excreted in urine.

MDA, HNE, HNE-MA, and 8-iso are the by-products of ROS-mediated lipid peroxidation. They are highly reactive compounds that cause toxic stress in cells by interacting with proteins and DNA. Thirteen of the identified studies confirmed that increased exposure to AP results in a higher level of oxidative stress in the population studied [18, 21, 23, 30, 32–34, 42–44, 46–48].

The formation of carcinogen-protein adducts has not been studied extensively. Only one study [21] used the oxidation tyrosine products of proteins, 3-chlorotyrosine (ClY), 3-nitrotyrosine (NY), and (o,o′-dityrosine) diY, to assess AP exposure, and found elevated levels of CIY and diY with increasing concentrations of 1-NAP and 4-PHE metabolites.

Endogenous oxidative DNA damage may play an important role in aging, chronic degenerative diseases, and cancer [66]. The other most common way to assess oxidative stress is to quantify 8-OHdG or 8-oxodG in the urine. These DNA adducts appear when guanine derivatives in the nuclear and mtDNA are oxidized. Fourteen studies reported a positive association between AP and markers of oxidative DNA damage, including 8-OHdG [20–22, 26, 30, 31, 38–41, 46–48, 53] and 8-oxodG [32, 33, 42, 49, 50, 53].

4.1.3. Correlation between internal PAH metabolites level and early effect biomarkers

Our scoping review confirmed a positive association between the levels of some urinary PAHs and early effect oxidative stress biomarkers (8-OHdG, 8-oxodG, 8-NO_2Gua, HNE-MA and 8-iso) [21, 22, 31, 39–41, 46–48,

50]. Four studies reported an increase in 8-OHdG, 8-NO_2Gua, HNE-MA, and 8-iso with a similar 1-PYR concentration to the one determined by Huang *et al* [63] (i.e. 18.5 $\pm$ 0.52 μmol mol^{-1} of creatinine for the age groups (12–20 years)), but, none of these studies could confirm a significant association [39, 46–48]. Three additional studies used a panel of PAH metabolites and reported a significant association [40, 41, 50]. Li *et al* [40], suggested, based on the observed urinary PAH profile, that exposure occurs mostly through inhalation and therefore depends on ambient AP, as the atmospheric PAH profile of low molecular weight OH-PAHs is very similar, whereas larger urinary PAH concentrations reflect additional sources such as diet.

4.1.4. Early effect biomarkers leading to possible biological effect

Since DNA methylation is a critical process in the regulation of gene transcription initiation, changes in DNA methylation can affect the global gene expression profile and lead to a number of disorders. DNA methylation is catalyzed by a family of DNA methyltransferases (Dnmts) that transfer a methyl group from S-adenosyl methionine to the fifth carbon of a cytosine residue to form 5-methylcytosine (5mC) [67]. Differential blood DNA methylation in response to AP exposure has been reported in different settings and has recently been reviewed [37]. We identified one study that estimated the global DNA methylation content in children after chronic PM_{10} exposure. Using LINE1 methylation as a surrogate marker for global methylation and methylation (5mC) of the promoter regions of three repair genes (APEX1, OGG1, and PARP1), they found an association between DNA oxidation but no significant relationship between LINE1 methylation and overall PM_{10} levels. When they assessed individual PM_{10} components, they found a positive relationship with BbF concentration [39]. Other studies that attempted to link PM exposure to DNA methylation, did not support these findings [68, 69]. The complexity of the PM composition and exposure duration is most likely responsible for this inconsistency. Thus, PM-induced modification of the global methylation content remains to be explored.

AP exposure that leads to oxidative stress can also cause DNA damage [70]. The main function of the mitochondria is to satisfy the metabolic and energy demands of tissues and cells. Therefore, multiple copies of small circular mtDNA ($\sim$16.5 kb) are the main intracellular source of ROS and an oxidative stress target [71]. Owing to their highly lipophilic nature and deficient robust capacity to repair their DNA compared to nuclear DNA, mitochondria are 40- to 500-fold more susceptible to air pollutants, such as PAHs, resulting in an increase in mtDNA copy number and altered mitochondrial gene expression [72]. Three studies attempted to correlate PM exposure with mtDNA modifications [17, 18, 27] and reported a positive association.

Telomeres are ribonucleoprotein complexes that cap the ends of chromosomes and protect them from degradation, thereby preventing loss of genetic information. Their vulnerability to ROS makes them plausible biomarkers of overall oxidative stress and systemic inflammation. Furthermore, they have been linked to age-related diseases such as cardiovascular diseases and cancer [73]. Recent systematic reviews have identified a link between AP and the TL. In adults, Miri *et al*'s meta-analysis study [74], which encompasses short- and long-term exposure to a wide range of air pollutants including PM_{10}, $PM_{2.5}$, UFPs, NO_2, NO, NO_x, PAHs, PCBs, benzene, toluene, persistent organic pollutants, BC, and EC, reported a negative association between long-term $PM_{2.5}$ exposure and TL, and a direct association between exposure to PCBs and short-term $PM_{2.5}$ exposure. A systematic review by Isaevska *et al* [75] reported that, in general, there is an inverse association between gestational exposure to AP and TL in newborn blood and the placenta. A multicenter European birth cohort study [76] reported that prenatal and one-year-old childhood, NO_2 and $PM_{2.5}$ exposures were inversely associated with shorter TL. Two studies on pregnant mothers identified a link between oxidative stress caused by AP and shorter TL [17, 28]. Interestingly, Lee *et al* [28] also reported a linear relationship between maternal antioxidant intake and newborn relative leukocyte TL (Pearson's $r = 0.25$, $p = 0.0002$). This suggests that a high antioxidant intake could be an effective preventative strategy for reducing telomere oxidative damage. Further research is needed to confirm this hypothesis.

4.2. Biomarkers of susceptibility

Susceptibility biomarkers are related to the absorption, distribution, metabolism, and excretion of exogenous chemicals and their subcellular biological effects [56]. We identified two studies reporting the antioxidant capacity response [18, 23] and two additional studies that provided valuable information on the genetic polymorphism of oxidative stress-related genes [29] and phase II detoxification enzymes, GSTM1 and GSTP1, from the glutathione S-transferase superfamily [20]. A recent review [77] summarized the recent literature on these two antioxidant genes and their association with respiratory and cardiovascular health, and reported strong evidence for respiratory outcomes in adults and children. Our study enhanced our understanding of GSTP1 and GSTM1 variant carriers by demonstrating that GTSP1 variant and GSTM1 wt mothers were more susceptible to gestational age reduction due to NO_x exposure due to increased oxidative stress [20] and confirmed that variant alleles of rs1695 in GSTP1 have significantly higher cord blood homocysteine levels, an established cardiovascular disease risk factor, than homozygous wildtypes [29].

Another type of susceptibility biomarker that could be studied is DNA repair capacity. The base excision repair pathway is a major player in this process, and research on the OGG1, PARP1, and APEX1 enzymes involved in the early stages has been valuable [78]. Nagiah *et al* [18] observed a 2.78-fold decrease in OGG1 expression, explaining the increased DNA fragmentation levels in AP-exposed mothers, which could result in early tumorigenesis [79]. This could be because of the increased methylation of PM_{10} components observed by Alvarado-Cruz *et al* [39] at specific CpG nucleotides in OGG1, APEX, and PARP1. Altered DNA methylation following AP exposure was confirmed by the ENVIR*ONA*GE birth cohort study of 463 mother–newborn pairs that reported placental methylation of APEX, OGG1, and PARP1 [80].

4.3. Biomarkers of effect

In addition to the DNA, protein, and lipid adducts that increase cancer risk [56], among the effect biomarkers are molecules that indicate early, reversible, or irreversible structural damage, as well as biological or molecular changes caused by AP toxicant interactions.

4.3.1. Transcriptomic biomarkers

Targeted transcriptomic analysis of 84 genes involved in oxidative stress revealed that 26 genes were differentially regulated in the peripheral lymphocytes of pregnant women. These include genes involved in oxidative stress responses and antioxidant defense [18]. A gene expression profiling analysis of cord blood by Honkova *et al* [35] reported similar findings as well as a decrease in processes associated with cell proliferation, apoptosis, and homeostasis.

4.3.2. Proteomic biomarkers

At the protein level, analysis of cardiovascular and immune cell biomarkers in adolescents has confirmed that AP levels are associated with oxidative stress, acute inflammation, altered homeostasis, and endothelial dysfunction [52].

Other biomarkers in this category include proinflammatory and structural damage biomarkers. Proinflammatory biomarkers include CRP, interleukin, tumor necrosis factor, biomarkers of metabolic dysfunction, and biomarkers of structural damage. Studies [21, 45, 51] reporting on the proinflammatory biomarkers confirmed that oxidative stress induces an inflammatory response as they observed an increase in CRP levels [21, 51]. In relation to interleukins, an unexpected lower inverse association or null association was observed with urinary PAH metabolites in the plasma of pregnant mothers, possibly reflecting an immunosuppressive effect [21]. The use of air purification systems reduces the levels of IL-β (10.83%) and IL-6 (4.33%) in exhaled breath condensate, indicating that these molecules might be sensitive indicators for evaluating the effects of PM on respiratory health in acute exposure settings [45].

CC16 is an anti-inflammatory protein predominantly secreted by non-ciliated bronchiolar club cells in the respiratory epithelium of the bronchioles. Because of its predominant expression in the airway and ability to diffuse into the plasma, CC16 has been studied as a putative biomarker of lung blood–air barrier leakage in acute and chronic lung diseases [81]. A recent review confirmed that CC16 can be used as an AP biomarker of effect [82]. Zhang *et al* [43] reported a decrease in urine CC16 levels over time (from 1 d to 1 year) due to traffic-related pollutants in children. Interestingly, when urinary CC16 levels were studied in relation to recent AP exposure, a significant positive association was observed between $PM_{2.5}$ and PM_{10} [83]. These findings suggest that AP may have a short-term acute effect on epithelial integrity, whereas the long-term decrease observed by Zhang *et al* [43] may reflect the impact of AP on ongoing lung development in children.

4.3.3. Lipidomic and metabolomic biomarkers

A recent review summarized the effects of PAH-related pathologies. During pregnancy, AP exposure can lead to preeclampsia, intrauterine growth retardation, and adverse birth outcomes such as impaired fetal growth, congenital abnormalities, and stillbirths [84]. PAH exposure during childhood can increase the likelihood of developing asthma, obesity, and aberrant behavior. In addition to PAHs, exposure to PAEs has been linked to various morphological, endocrine, and molecular outcomes [85, 86] while metal exposure has been associated with several negative health outcomes [87]. Our search yielded a few studies that employed a high-resolution metabolomic top-down approach followed by pathway enrichment analysis to identify underlying causal interactions between AP and oxidative stress [24, 25, 36, 46, 47].

In maternal serum, AP has been linked to modifications in lipid-related metabolic pathways, including fatty acid, phospholipid, lineolate, and eicosanoid metabolism, indicating its association with oxidative stress and inflammatory reactions [25]. A similar finding was reported by Ritz *et al* [36] in their pathway enrichment metabolite analysis of the neonatal blood. They found that nine lipid-related metabolic pathways were enriched. Some of these are related to oxidative stress (fatty acid activation, de novo fatty acid biosynthesis, fatty acid metabolism, carnitine shuttle, and glycerophospholipid metabolism), methionine,

and cysteine metabolism, which may indicate the need for a methyl-group donor and precursor necessary for the antioxidant glutathione, and finally, pathways suggesting an inflammatory response (prostaglandin biosynthesis pathways). Metabolomic analysis of women's serum seeking fresh assisted reproductive technology revealed that higher periconceptional AP exposure induces alterations in tryptophan and vitamin B3 metabolic pathways and decreases the probability of live birth [24].

Three studies by Chen *et al* [46–48] reported on PAH levels in children/adolescents living in an industrial area and their association with metabolomic and lipidomic changes. Their first study [46] identified 163 stress-related potential metabolites that could be associated ($p < 0.05$) with at least one of the four oxidative stress biomarkers (8-OHdGH, HNE-MA, 8-iso, and 8-NO_2Gua). Additionally, they reported that the tryptophan and phenylalanine metabolisms are mainly affected, both of which are known to be affected by oxidative stress and disrupted in numerous chronic diseases [88, 89]. Their second study [47] revealed changes associated with purine metabolism, which is an essential response to increased oxidative stress [90] and serum acylcarnitines, possibly resulting from alterations in fatty acid oxidation and energy production. Their lipidomic analysis confirmed these findings by identifying lipid features associated with oxidative stress and altered serum acylcarnitines, both of which have been linked to renal and liver diseases [48].

4.4. OMICS technologies

This scoping review highlights the fact that most studies have adopted bottom-up methods and used PCR, ELISA, and target LC–MS (table 1) to study known specific molecules associated with oxidative stress. Although this has provided confirmation that AP triggers oxidative stress, the information on the range of molecular changes associated with exposure to harmful AP is limited. On the other hand, top-down approaches like expression bead assays [35, 52], high-resolution metabolomic [25, 36, 46, 47], and lipidomic [48] profiling by untargeted chromatography combined with mass spectrometry methodologies and pathway enrichment analysis have helped us to understand the range of molecular changes caused by exposure to harmful AP as well as the biological complexity of the response. Therefore, the use of top-down approaches, if associated with advanced biostatistics and bioinformatics tools, has the potential to improve our understanding of the disturbances that occur after AP exposure. As such, 'integrative -OMICS' from single to multiple '-OMICS' data and their exploitation have emerged in other fields as an approach that provides a more comprehensive view of biological processes that lead to human diseases [91].

5. Conclusion

AP exposure in daily life is practically unavoidable. But there are critical time windows for exposure during human life's developmental stages, such as fetal development, childhood, and adolescence. This scoping review showed that oxidative stress biomarkers can be found in blood, urine, saliva, and exhaled breath and reflect differences in AP exposure and susceptibility to toxic insults. If associated with epidemiological research, these biomarkers may help establish an association between AP exposure, oxidative stress, detrimental birth, and child health outcomes. However, because of the molecular heterogeneity of AP, selecting sensitive and specific biomarkers for prevention and intervention remains challenging. To this end, longitudinal studies that use top-down approaches would help to understand the origins of adult disease development caused by AP exposure. This will require vigorous efforts towards careful study design, enhancement of analytical measurement techniques, and integrative long-term projects, such as the EXPOsOMICS project [92] which focuses on identifying the relationships between external exposure and global molecular profiles in individuals.

Data availability statement

No new data were created or analysed in this study.

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Conflict of interest

No funding or conflicts of interest to disclose.

Authors's notes

J V F Coumans selected literature, extracted data, and drafted the paper. Al Jaaidi selected the literature, confirmed the extracted data, and revised the manuscript accordingly. J V F Coumans wrote the final manuscript.

Ethical statement

Ethical approval was not required for this work.

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