Environmental Research 244 (2024) 117990

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

Prenatal air pollution exposure in relation to the telomere-mitochondrial axis of aging at birth: A systematic review

Shradha Mishra [a], Charlotte Van Der Stukken [a], Stacy Drury [b], Tim S. Nawrot [a,c], Dries S. Martens [a,*]

[a] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium
[b] Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
[c] Department of Public Health & Primary Care, Occupational & Environmental Medicine, Leuven University, Leuven, Belgium

ARTICLE INFO

Keywords:
Air pollution
Mitochondrial DNA
Prenatal exposure
Telomere length
Early life
Newborns

ABSTRACT

Background: Telomere length (TL) and mitochondrial DNA (mtDNA) are central markers of vital biological mechanisms, including cellular aging. Prenatal air pollution exposure may impact molecular markers of aging leading to adverse health effects.
Objective: To perform a systematic review on human population-based studies investigating the association between prenatal air pollution exposure and TL or mtDNA content at birth.
Methodology: Searches were undertaken on PubMed and Web of Science until July 2023. The framework of the review was based on the PRISMA-P guidelines.
Results: Nineteen studies studied prenatal air pollution and TL or mtDNA content at birth. Studies investigating TL or mtDNA content measured at any other time or did not evaluate prenatal air pollution were excluded. Twelve studies (including 4381 participants with study sample range: 97 to 743 participants) investigated newborn TL and eight studies (including 3081 participants with study sample range: 120 to 743 participants) investigated mtDNA content at birth. Seven studies focused on particulate matter ($PM_{2.5}$) exposure and newborn TL of which all, except two, showed an inverse association in at least one of the gestational trimesters. Of the eight studies on mtDNA content, four focused on $PM_{2.5}$ air pollution with two of them reporting an inverse association. For $PM_{2.5}$ exposure, observations on trimester-specific effects were inconsistent. Current literature showing associations with other prenatal air pollutants (including nitrogen oxides, sulfur dioxide, carbon monoxide and ozone) is inconsistent.
Conclusion: This review provides initial evidence that prenatal $PM_{2.5}$ exposure impacts the telomere-mitochondrial axis of aging at birth. The current evidence did not reveal harmonious observations for trimester-specific associations nor showed consistent effects of other air pollutants. Future studies should elucidate the specific contribution of prenatal exposure to pollutants other than PM in relation to TL and mtDNA content at birth, and the potential later life health consequences.

Funding sources

This study has received funding from the European Union's Horizon 2020 research and innovation programme 'SURREAL' under grant agreement No 956780. TSN holds funding by Methusalem. SD holds funding by National Institutes of Health (NIH U24AG066528). DSM holds a postdoctoral grant by the Research Foundation-Flanders (FWO12X9623N).

1. Introduction

Exposure to ambient air pollution impacts healthy life and is ranked fourth for the global attributable burden of deaths; while the largest increase in risk exposure was reported for ambient particulate matter (PM) pollution (Global burden of 87 risk, 2020). Air pollution can induce cellular inflammation and oxidative stress that accelerates cellular aging, which may be an underlying explanation for air pollution-associated adverse health effects (Martens and Nawrot, 2016).

* Corresponding author. Centre for Environmental Sciences, Hasselt University, Agoralaan gebouw, D BE-3590 Diepenbeek, Belgium.
E-mail address: dries.martens@uhasselt.be (D.S. Martens).

https://doi.org/10.1016/j.envres.2023.117990
Received 12 July 2023; Received in revised form 6 December 2023; Accepted 18 December 2023
Available online 22 December 2023

Telomere attrition and mitochondrial functioning have been highlighted as important hallmarks of aging and these are potentially vulnerable cellular targets for air pollution-induced oxidative stress (López-Otín et al., 2023). A clear connection between telomeres and mitochondrial functioning has been shown (Sahin and Depinho, 2010). One of the multiple effector pathways by which air pollution exposure could induce cellular aging via the telomere-mitochondrial-driven molecular cascade is as follows: First, any damage to telomeres by air pollution-caused reactive oxygen species (ROS), may lead to an alteration in tumor suppressor p53 and sirtuin 1 (SIRT1) production (Martens and Nawrot, 2016). Elevated levels of p53 and reduced levels of SIRT1 suppress peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α: the master regulator of mitochondrial biogenesis), resulting in mitochondrial dysfunction accompanied by impaired ATP generation and increased mitochondrial ROS production (Sahin and Depinho, 2010). The latter may subsequently cause further DNA and telomere damage. Additionally, air pollution-induced oxidative stress might also directly impact mitochondrial functioning, inducing further damage to telomeres as a consequence of the mitochondrial-related increases in cellular ROS (Martens and Nawrot, 2016). Since mitochondrial DNA (mtDNA) does not contain protective histones, nor a chromatin structure and has a less efficient DNA repair mechanism, it is especially considered a sensitive target for ROS-induced damage (Ide et al., 2001). Such damage may further play a pivotal role in causing cell cycle arrest, senescence, and apoptosis (Sahin and DePinho, 2012).

Population-based studies have investigated the association between air pollution, telomeres and mitochondria in several age segments in the general population (Ling et al., 2016; Ward-Caviness et al., 2016; Wong et al., 2014; Byun et al., 2016). To date, few studies have explored the impact of prenatal environmental exposures on these molecular outcomes at birth, despite the potential hypothesis that prenatal exposure to air pollution may also negatively affect cellular aging in the fetus which is reflected by shorter telomere length (TL) and reduced mtDNA content at birth. These molecular changes at birth may underlie prenatal air pollution-related later-life health effects as suggested in the fetal programming of health and disease hypothesis (Kwon and Kim, 2017). Initial findings on the potential link between prenatal air pollution, TL and mtDNA content at birth were made in the ENVIR*ON*AGE (ENVIronmental influence *ON* early AGEing) birth cohort where it was found that prenatal PM air pollution was associated with shorter telomeres in both cord blood and placenta (Martens et al., 2017) and decreased placental mtDNA content (Janssen et al., 2012).

The objective of this review was to systematically identify and summarize all current findings from studies that investigated the association between prenatal exposure to air pollution and TL as well as mtDNA content at birth. We aimed to 1) confirm the initial hypothesis that air pollution may be negatively associated with TL and mtDNA content at birth and 2) gain insights into sensitive windows of exposures during gestation based on trimester-specific observations.

2. Methods

The present review was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42022378098 (2022)). The methodology adopted for this review was based on the 'Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) and Cochran Collaboration guidelines (Higgins et al., 2022). This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol 2015 (PRISMA-P) (Shamseer et al., 2015). The review aimed to answer the following research questions: 'Is prenatal exposure to air pollution associated with TL and mtDNA content in newborns?' and 'Are there any differences observed across the three gestational trimesters for the aforementioned associations?' which included the following PECO components:

Population: The population of interest comprised newborn human males and females born to mothers for whom data on exposure to air pollution during gestation was available.

Exposure: The exposure was defined as 'prenatal air pollution' and air pollution-related proxies, including traffic-related combustions, gaseous pollutants, and solid particulate air pollutants.

Comparator: Studies that reported exposures on a continuous scale as well as those using defined exposure categories were included. There was no restriction of studies based on the air pollution assessment methods (e.g.; studies using modeled exposures, personally monitored exposures and biomarkers/proxies of exposures) nor on the spatial location of the air pollution assessment (maternal residential address, outdoor exposures, indoor exposures or occupational exposures).

Outcome: The TL and mtDNA content determined in newborn-related biological matrices (including cord blood, placenta, saliva, buccal cells or blood cells) at the time of delivery were investigated as the primary outcomes in this review.

2.1. Literature search and selection of studies

This review included epidemiological studies with an observational design, including cohort, case-control, longitudinal or cross-sectional studies. No minimum number of study participants was defined for the inclusion of studies in the review. Studies were excluded if the participants were part of any clinical interventional trial to minimize the risk of alteration to outcomes due to additional confounders. In case multiple studies were found that reported data from the same population cohort, the study with the largest number of participants were included in the review.

Two authors (SM and DSM) undertook searches for Medline via PubMed and Web of Science databases from the date of database inception up to July 3, 2023. The search strategy was developed based on the objective of the review and consisted of English key terms only. This included (newborn OR "at birth" OR prenatal) AND ("air pollution") AND (telomere OR "mitochondrial DNA"). There were no restrictions on the date, status or language of publication of studies. The results were documented in a PRISMA flowchart (Fig. 1), following the PRISMA statement (Shamseer et al., 2015). The titles and abstracts of the search results were screened using the EndNote reference manager. Full texts were obtained and assessed for studies that met the eligibility criteria for inclusion in the review. The reference lists of the included studies were manually searched for any additional studies which might not have been identified using the aforementioned search terms. Reasons for excluding studies at the stage of full-text screening were documented.

2.2. Data extraction and management

Two authors (SM and DSM) independently extracted data from the selected studies using a standardized data extraction form developed on Microsoft Excel. Any differences in the sets of extracted data were resolved through discussions. The form included information on study location, descriptive characteristics of participants, TL and mtDNA content measurements and method, data on maternal exposure to air pollution during gestation and fully adjusted values for the described associations between prenatal exposure to air pollution and newborn TL and mtDNA content. The Quality In Prognostic Studies (QUIPS) tool was used to assess the risk of bias in the studies found eligible for inclusion (Grooten et al., 2019).

3. Results

3.1. Results of searches

The searches of electronic databases yielded sixty-seven (combined from Medline and Web of Science) potentially relevant studies. After the removal of duplicate studies and scanning the titles and abstracts of the remaining search results, the full texts of twenty-four studies were obtained. Finally, nineteen studies were included based on the eligibility

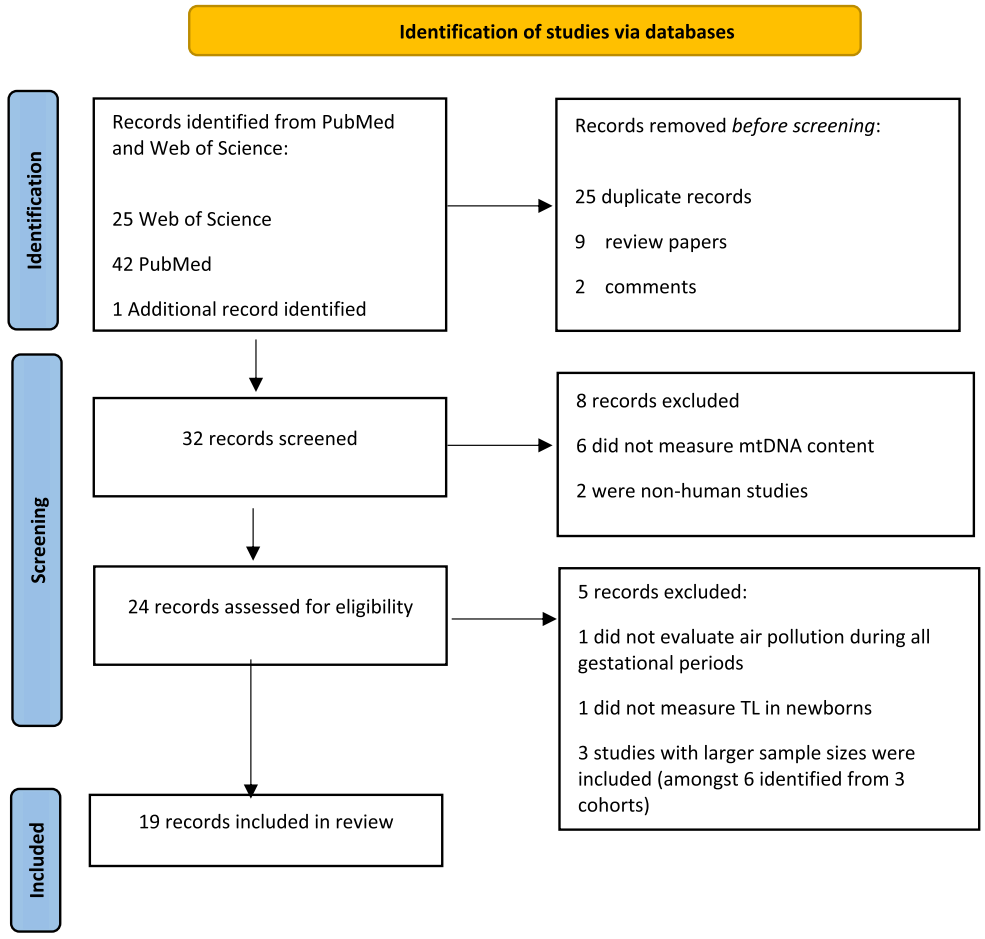

Fig. 1. PRISM 2020 flow diagram (Shamseer et al., 2015) showing the study selection process for the present review.

criteria defined for the review. The process of screening and inclusion of studies is depicted in the PRISMA flow diagram (Fig. 1.). All the studies included were found to have an overall low risk of bias as assessed using the QUIPS tool (Table 1).

3.2. *Prenatal exposures at study*

A total of ten different air pollutants and two proxies of air pollution with a wide range of exposure concentrations were evaluated in the

Table 1
Assessment of risk of bias of included studies using the Quality In Prognostic Studies (QUIPS) tool.

OUTCOME	STUDY	Quality in Prognostic Studies (QUIPS)					
		Study Participation	Study Attrition	Prognostic factor measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Newborn TL	Bijnens et al., 2015	Low	Low	Low	Low	Low	Low
	Martens et al., 2017	Low	Low	Low	Low	Low	Low
	Perera et al., 2018	Low	Low	Low	Low	Low	Low
	Rosa et al., 2019	Low	Low	Low	Low	Low	Moderate
	Song et al., 2019	Low	Low	Low	Low	Low	Low
	Lee et al., 2020	Low	Moderate	Low	Low	Low	Low
	Harnung Scholten et al., 2021	Low	Low	Low	Low	Low	Low
	Kaali et al., 2021	Low	Low	Low	Low	Low	Low
	Mandakh et al., 2021	Low	Low	Low	Low	Low	Low
	Durham et al., 2022	Low	Low	Low	Low	Low	Moderate
	Isaevska et al., 2022	Low	Low	Low	Low	Low	Low
	Song et al., 2022	Low	Low	Low	Low	Low	Low
Newborn mtDNA	Janssen et al., 2012	Low	Low	Low	Low	Low	Low
	Janssen et al., 2015	Low	Low	Low	Low	Low	Low
	Rosa et al., 2016	Low	Low	Low	Low	Low	Moderate
	Clemente et al., 2016	Low	Low	Low	Low	Low	Low
	Brunst et al., 2018	Moderate	Moderate	Low	Low	Moderate	Moderate
	Kaali et al., 2019	Low	Low	Low	Low	Low	Low
	Hu et al., 2020	Low	Low	Low	Low	Low	Low
	Mandakh et al., 2021	Low	Low	Low	Low	Low	Low

The QUIPS tool, as adapted from Grooten WJA et al., 2019 (Grooten et al., 2019).

included studies. An overview of these different exposures and assessment methods are presented in Supplementary Tables 1, 2 and 3. These pollutants comprised PM with an aerodynamic diameter ≤2.5 μm and ≤10 μm ($PM_{2.5}$ and PM_{10}), components of PM such as black carbon (BC) and polycyclic aromatic hydrocarbons (PAH) as well as gaseous air pollutants, including sulfur dioxide (SO_2), carbon monoxide (CO) and nitrogen dioxide (NO_2). Most of the air pollutants were primary air pollutants, emitted largely from combustion sources such as industrial and agricultural processes, transport sectors and the burning of fossil fuels (Xue et al., 2016). These air pollutants contribute to ambient as well as indoor air pollution, the most common ones being PM, CO and NO_2 (Vardoulakis et al., 2020). Furthermore, chemical reactions caused by the emissions of some of the gaseous air pollutants, including nitrogen oxides (NO_x: NO_2 combined with nitrogen monoxide (NO)) and CO also lead to the formation of secondary air pollutants in the atmosphere such as ozone (O_3) (Orru et al., 2017). Although a direct comparison of the identified exposure concentrations of these evaluated air pollutants cannot be made with the World Health Organization's Air Quality Guidelines (WHO AQG) (Organization, 2021), it was observed that most of the air pollutant exposures tend to be above the maximum recommended annual exposure limits (Supplementary Table 1). However, $PM_{2.5}$ exposures during the entire gestational period in only two studies (Lee et al. (2020) and Brunst et al. (2018), both conducted in U.S.A.) were below the annual 2005 WHO AQG limits (10 μg/m^3) in their studies, albeit exceeding the current updated 2021 guidelines (5 μg/m^3). Similarly, NO_2 exposures during the entire gestation in only one study (Clemente et al. (2016), including participants from Spain and Belgium) were within the maximum recommended 2005 annual limit (40 μg/m^3) but exceeded the updated 2021 limit (10 μg/m^3). Exposures to CO and SO_2 could not be put into context with the current guidelines, since their recommended maximum limits are available for 24-h (short-term) exposures only and this data was not presented in the included studies. Recommended limits for any other air pollutants (including PAH, BC, organic carbon (OC) and ammonium (NH_4^+) were also not provided in the WHO AQG.

3.3. Prenatal exposure to air pollution and newborn TL

Twelve studies, with a total of 4381 participants investigated the association between prenatal exposure to air pollution and TL at birth (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Kaali et al., 2021; Harnung Scholten et al., 2021; Song et al., 2019, 2022; Perera et al., 2018; Durham et al., 2022; Isaevska et al., 2022; Mandakh et al., 2021; Bijnens et al., 2015). The study with the smallest sample size had ninety-seven participants (Kaali et al., 2021) and the study with the largest sample size had 743 participants (Song et al., 2019). Eight studies investigated cord blood TL (Lee et al., 2020; Rosa et al., 2019; Kaali et al., 2021; Song et al., 2019, 2022; Perera et al., 2018; Durham et al., 2022; Isaevska et al., 2022), two studies investigated placental TL (Mandakh et al., 2021; Bijnens et al., 2015), while two studies investigated both cord blood as well as placental TL (Martens et al., 2017; Harnung Scholten et al., 2021). Telomere length was assessed in seven studies (Martens et al., 2017; Lee et al., 2020; Harnung Scholten et al., 2021; Song et al., 2019, 2022; Perera et al., 2018; Mandakh et al., 2021) using a singleplex quantitative polymerase chain reaction (qPCR) method while the other five (Rosa et al., 2019; Kaali et al., 2021; Durham et al., 2022; Isaevska et al., 2022; Bijnens et al., 2015) used multiplex qPCR to measure newborn TL. Nine studies (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Harnung Scholten et al., 2021; Song et al., 2019, 2022; Durham et al., 2022; Isaevska et al., 2022; Mandakh et al., 2021) assessed modeled ambient air pollution exposures at maternal residential addresses, one study (Kaali et al., 2021) assessed household air pollution exposure using personal monitors, one study (Perera et al., 2018) used an internal biomarker to assess prenatal air pollution exposure and one study (Bijnens et al., 2015) used a geographic information system to assess maternal traffic exposure. Air pollution assessment details are presented in Supplementary Tables 2 and 3 Three studies included Chinese participants (Song et al., 2019, 2022; Perera et al., 2018) and two studies were from cohorts in U.S.A.-one comprised participants with African-American and Dominican ethnicities (Durham et al., 2022) and one mainly comprised Black and Hispanic participants (PRISM: PRogramming of Intergenerational Stress Mechanisms study) (Lee et al., 2020). Five studies were from cohorts comprising European mothers of white ethnicity (Martens et al., 2017; Harnung Scholten et al., 2021; Isaevska et al., 2022; Mandakh et al., 2021; Bijnens et al., 2015), one had Mexican participants (PROGRESS: Programming Research in Obesity, Growth, Environment and Social Stressors study) (Rosa et al., 2019) and one included Ghanaian participants(GRAPHS: Ghana Randomized Air Pollution and Health Study) (Kaali et al., 2021). In what follows, we summarize the findings for the associations between newborn TL and specific air pollutants.

3.3.1. Particulate matter

Seven studies investigated the association between prenatal exposure to $PM_{2.5}$ and TL at birth (Table 2) (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Kaali et al., 2021; Harnung Scholten et al., 2021; Song et al., 2019; Durham et al., 2022). Mean $PM_{2.5}$ concentrations ranged between 8.8 μg/m^3 during the entire gestation (PRISM study, USA) (Lee et al., 2020) to 79.7 μg/m^3 during the first trimester (in China) (Song et al., 2019). In six studies, modeled $PM_{2.5}$ exposures were used while in the study by Kaali et al. (2021), personal 72-h indoor $PM_{2.5}$ exposure was assessed using monitors affixed to the clothing of study participants during three equally spaced instances throughout gestation (Supplementary Tables 2 and 3). In two studies (n = 793 in total), modeled prenatal $PM_{2.5}$ exposure during the entire period of gestation was associated with shorter cord blood TL (Martens et al., 2017; Lee et al., 2020). This observation was confirmed in the study of Kaali et al. (2021) which used personally monitored $PM_{2.5}$ exposures. None of these studies found any associations with exposures during the first trimester of gestation. One study (Martens et al., 2017) observed a negative association during the second trimester and two studies (Harnung Scholten et al., 2021; Song et al., 2019) found an inverse association during the third trimester. Two studies (Martens et al., 2017; Harnung Scholten et al., 2021) additionally evaluated placental TL as an outcome, but in only one study (Martens et al., 2017) negative associations were observed with exposure during the entire period of gestation and second trimester. Two studies did not report any significant associations between prenatal $PM_{2.5}$ exposure and newborn TL (Rosa et al., 2019; Durham et al., 2022).

Three studies (Harnung Scholten et al., 2021; Song et al., 2019; Isaevska et al., 2022) investigated the association between prenatal exposure to PM_{10} and cord blood TL of which one study (Harnung Scholten et al., 2021) additionally investigated associations with placental TL (Supplementary Table 4). All studies used modeled exposures (Supplementary Table 2). The lowest concentration of PM_{10} exposure during the entire gestation period was reported in the study (Harnung Scholten et al., 2021) from Denmark (mean exposure of 17.8 μg/m^3) where no association between PM_{10} exposure and TL in cord blood and placenta was observed. The highest concentration of PM_{10} was observed during the second trimester in the study from China (Song et al., 2019) (mean exposure of 142.9 μg/m^3) where an inverse association was found between PM_{10} exposure during the third trimester and cord blood TL. Finally, Isaevska et al. (2022) did not find any association between PM_{10} and cord blood TL during any period of gestation (mean exposure during entire gestation: 32.2 μg/m^3).

3.3.2. Nitrogen oxides

Three studies evaluated the potential effects of prenatal exposure to nitrogen oxides on newborn TL (Harnung Scholten et al., 2021; Song et al., 2019; Mandakh et al., 2021) (Table 3). All three studies used modeled air pollution exposures, as described in Supplementary Table 2. The highest NO_2 levels (mean exposure up to 50.4 μg/m^3 during the

Table 2
Newborn telomere length and prenatal exposure to particulate matter ($PM_{2.5}$).

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference or β (95% C.I.)	Adjustments[b]
Martens et al., 2017	ENVIRONAGE	641	50.40%	Cord blood	Entire pregnancy	13.4 (4.3–32.5)	5	**−8.8% (-14.1% to -3.1%)**	1,2,3,4,5,6,7,8,9,10, 11[c]
	Belgium				Trimester 1			−2.3% (−6.1% to 1.7%)	
					Trimester 2			**−9.4 (-13.1% to -5.6%)**	
					Trimester 3			3.1% (−1.8% to 8.3%)	
				Placenta	Entire pregnancy	13.4 (4.3–32.5)	5	**−13.2 (-19.3% to -6.7%)**	1,2,3,4,5,6,7,8,9,10, 11[c]
					Trimester 1			−1.4% (−6% to 3.5%)	
					Trimester 2			**−7.1% (-11.6% to -2.4%)**	
					Trimester 3			−5.3% (−10.8% to 0.5%)	
Rosa et al., 2019*,*	PROGRESS	423	54.10%	Cord blood	Entire pregnancy	22.8 (20.5–24.5)	10	−0.9% (−11.3% to 11.6%)	2,3,4,5,12
	Mexico				Trimester 1			−6.7% (−14.7% to 1.0%)	
					Trimester 2			6.1% (−5.8% to 20.9%)	
					Trimester 3			0 (−6.7% to 8.3%)	
Song et al., 2019	China	743	51.40%	Cord blood	Entire pregnancy		10	−3.5% (−7.3% to 0.4%)	1,2,3,4,5,7,8,13
					Trimester 1	79.7 (28.7)		0.04% (−1.7% to 1.8%)	
					Trimester 2	78.0 (27.3)		−0.4% (−2.8% to 1.9%)	
					Trimester 3	69.1 (33.6)		**−3.7% (-6.0% to -1.3%)**	
Lee et al., 2020	PRISM	152	47.30%	Cord blood	Entire pregnancy	8.8 (8.2–9.2)	1	**−0.29 (-0.49 to -0.10)**	1,6[d]
	USA								
Harnung Scholten et al., 2021	Denmark	296	48.90%	Cord blood	Entire pregnancy	11.5 (4.4)	IQR	11% (−9% to 36%)	1,2,3,4,5,7,8,10,13[e]
					Trimester 1			7% (−10% to 27%)	
					Trimester 2			18% (−5% to 46%)	
					Trimester 3			**−23% (-35% to -9%)**	
				Placenta	Entire pregnancy	11.5 (4.4)	IQR	4% (−16% to 28%)	1,2,3,4,5,7,8,10,13[e]
					Trimester 1			4% (−11% to 22%)	
					Trimester 2			−2% (−22% to 23%)	
					Trimester 3			7% (−11% to 29%)	
Kaali et al., 2021	GRAPHS	60	53.30%	Cord blood	Entire pregnancy	58.3 (37.3–84.3)	10	**−4.9% (-8.6% to -0.4%)**	1,2,6,9
	Ghana								
Durham et al., 2022,*	CCCEH MN	193	42.40%	Cord blood	Entire pregnancy	16.5 (15.7–17.7)		−0.005 (−0.03 to 0.02)	1,3,6,9[f]
	USA				Trimester 1	16.7 (15.3–18.8)		0.002 (−0.01 to 0.02)	
					Trimester 2	16.6 (14.7–18.3)		−0.01 (−0.02 to 0.002)	
					Trimester 3	16.8 (14.9–18.5)		0.005 (−0.01 to 0.02)	

Abbreviations: ENVIRONAGE = ENVIRonmental influence *ON* AGEing in early life study; PROGRESS= Programming Research in Obesity, Growth, Environment and Social Stressors study; PRISM= PRogramming of Intergenerational Stress Mechanisms study, GRAPHS = Ghana Randomized Air Pollution and Health Study, CCCEH MN= Columbia Center for Children's Environmental Health Mothers and Newborns study.
*Effect estimates not presented in published manuscript and were requested from authors.
[a]Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in μg/m.^{3}.
[b]All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 4 = season of delivery; 5 = prenatal smoke exposure; 6 = newborn ethnicity; 7 = parity; 8 = pregnancy complications (including hypertension, diabetes, pre-eclampsia); 9 = samples storage; 10 = ambient temperature; 11 = date of delivery; 12 = batch; 13 = birthweight.
Additional adjustments in:
[c]For paternal age.
[d]For maternal lifetime stress, marital status and antioxidant status.
[e]For indoor exposure, mode of delivery, newborn length and head circumference.
[f]Conception season.

second trimester) were observed in China (Song et al., 2019), although no association with cord blood TL was observed. Scholten et al. (Harnung Scholten et al., 2021) evaluated NO_2 (mean exposure of 16.9 μg/m^3 during entire gestation) and NO_x (mean exposure of 21.0 μg/m^3 during entire gestation) exposures with cord blood and placental TL. Both NO_2 and NO_x were positively associated with cord blood TL during the second trimester and only NO_2 was inversely associated with cord blood TL during the third trimester. No associations with placental TL were observed (Harnung Scholten et al., 2021). Mandakh et al. (2021) did not find any association between NO_x exposure (mean exposure during entire gestation: 14.8 μg/m^3) and placental TL.

3.3.3. *Carbon monoxide*

Three studies investigated the association between prenatal CO exposure and newborn TL (Table 4), of which two used modeled exposure (Harnung Scholten et al., 2021; Song et al., 2019) and one used personally monitored exposures (Kaali et al., 2021) (Supplementary Tables 2 and 3). The highest CO exposure was observed in China (1019.9 μg/m^3 during second trimester) and in this study cord blood TL was inversely associated with prenatal CO exposure during the third trimester of gestation, but not during other gestational periods. In line with this, Scholten et al. (Harnung Scholten et al., 2021), also observed a negative association between cord blood TL and prenatal CO exposure (mean gestational exposure of 173.6 μg/m^3) during the third trimester, but a positive association during the second trimester of gestation. In

Table 3
Newborn telomere length and prenatal exposure to nitrogen oxides.

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference or β (95% C.I.)	Adjustments[b]
Song et al., 2019	China	743	51.40%	Cord blood	Entire pregnancy		10	−1.5% (−6.6% to 3.8%)	1,2,3,4,5,7,8,13
(NO_2)					Trimester 1	49.3 (16.2)		−1.2% (−4.7% to 2.4%)	
					Trimester 2	50.4 (16.9)		1.1% (−2.7% to 5.0%)	
					Trimester 3	46.6 (15.4)		−2.1% (−5.8% to 1.7%)	
Harnung Scholten et al., 2021	Denmark	296	48.90%	Cord blood	Entire pregnancy	16.9 (9.5)	IQR	9% (−6% to 27%)	1,2,3,4,5,7,8,10,13[c]
(NO_2)					Trimester 1			−5% (−17% to 7%)	
					Trimester 2			**20% (3% to 39%)**	
					Trimester 3			**−20% (-31% to -6%)**	
				Placenta	Entire pregnancy	16.9 (9.5)	IQR	2% (−11% to 17%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			2% (−10% to 14%)	
					Trimester 2			2% (−13% to 18%)	
					Trimester 3			25 (−11% to 18%)	
Mandakh et al., 2021	Sweden	137	53.30%	Placenta	Entire pregnancy	14.8 (8.4)		0.08 (−0.06 to 0.21)	2,3,4,7
(NO_x)					Trimester 1	14.0 (7.6)		0.03 (−0.11 to 0.17)	
					Trimester 2	16.2 (12.4)		0.07 (−0.08 to 0.21)	
					Trimester 3	14.7 (8.6)		0.07 (−0.06 to 0.21)	
Harnung Scholten et al., 2021	Denmark	296	48.90%	Cord blood	Entire pregnancy	21.0 (14.7)	IQR	9% (−5% to 25%)	1,2,3,4,5,7,8,10,13[c]
(NO_x)					Trimester 1			**−12% (-22% to 0)**	
					Trimester 2			**19% (3% to 37%)**	
					Trimester 3			−9% (−22% to 6%)	
				Placenta	Entire pregnancy	21.0 (14.7)	IQR	4% (−8% to 18%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			0 (−10% to 12%)	
					Trimester 2			5% (−9% to 20%)	
					Trimester 3			2% (−11% to 17%)	

Abbreviations: NO_2 = nitrogen dioxide; NO_x = nitrogen oxides.
[a]Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in μg/m.^{3}.
[b]All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 4 = season; 5 = prenatal smoke exposure; 7 = parity; 8 = pregnancy complications (including hypertension, diabetes, pre-eclampsia); 10 = ambient temperature; 13 = birthweight.
Additional adjustments in:
[c]For indoor exposure, mode of delivery, newborn length and head circumference.

Table 4
Newborn telomere length and prenatal exposure to carbon monoxide.

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference (95% C.I.)	Adjustments[b]
Song et al., 2019	China	743	51.40%	Cord blood	Entire pregnancy		10	−1.0% (−4.9% to 2.9%)	1,2,3,4,5,7,8,13
					Trimester 1	983.6 (284.7)		0.5% (−1.1% to 2.1%)	
					Trimester 2	1019.9 (324.6)		0.4% (−1.7% to 2.7%)	
					Trimester 3	988.0 (283.1)		**−3.6% (-6.2% to -1%)**	
Harnung Scholten et al., 2021	Denmark	296	48.90%	Cord blood	Entire pregnancy	173.6 (72.5)	IQR	28% (−7% to 78%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			−13% (−33% to 13%)	
					Trimester 2			**70% (24% to 132%)**	
					Trimester 3			**−29% (-48% to -5%)**	
				Placenta	Entire pregnancy	173.6 (72.5)	IQR	−8% (−34% to29%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			−1% (−22 to 25%)	
					Trimester 2			−12% (−37% to 22%)	
					Trimester 3			20% (−12% to 63%)	
Kaali et al., 2021	GRAPHS, Ghana	97	53.30%	Cord blood	Entire pregnancy	0.85 (0.49–1.42) in ppm	1 ppm	−3.0% (−9.5% to 4.1%)	1,2,6,9

Abbreviations: GRAPHS = Ghana Randomized Air Pollution and Health Study; ppm = parts per million.
[a]Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in μg/m.^{3}.
[b]All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 4 = season; 5 = prenatal smoke exposure; 6 = newborn ethnicity; 7 = parity; 8 = pregnancy complications (including hypertension, diabetes, pre-eclampsia); 9 = samples storage; 10 = ambient temperature; 13 = birthweight.
Additional adjustments in:
[c]For indoor exposure, mode of delivery, newborn length and head circumference.

Table 5
Newborn telomere length and prenatal exposure to sulfur dioxide.

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference (95% C.I.)	Adjustments[b]
Song et al., 2019	China	743	51.40%	Cord blood	Entire pregnancy		10	**−16.8% (-29.8% to -1.3%)**	1,2,3,4,5,7,8,13
					Trimester 1	16.5 (14.0)		−0.4% (−6.1% to 5.6%)	
					Trimester 2	16.2 (11.3)		−2.5% (−10.0% to 5.6%)	
					Trimester 3	14.5 (9.7)		**−11.1% (-18.8% to -2.5%)**	
Harnung Scholten et al., 2021	Denmark	296	48.90%	Cord blood	Entire pregnancy	1.2 (0.7) in ppb	IQR	−20% (−38% to 3%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			58% (25% to 98%)	
					Trimester 2			**−36% (-52% to -25%)**	
					Trimester 3			**−33% (-47% to -16%)**	
				Placenta	Entire pregnancy	1.2 (0.7) in ppb	IQR	6% (−18% to 35%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			−12% (−29% to 9%)	
					Trimester 2			20% (−10% to 59%)	
					Trimester 3			−3% (−22% to 22%)	

Abbreviations: ppb = parts per billion.
[a]Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in μg/m.^{3}.
[b]All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 4 = season; 5 = prenatal smoke exposure; 7 = parity; 8 = pregnancy complications (including hypertension, diabetes, pre-eclampsia); 10 = ambient temperature; 13 = birthweight.
Additional adjustments in:
[c]For indoor exposure, mode of delivery, newborn length and head circumference.

this study, no associations were observed with placental TL. No association was observed between cord blood TL and personally monitored CO exposure during the entire gestation (Kaali et al., 2021).

3.3.4. *Sulfur dioxide*

Song et al. (2019) and Scholten et al. (Harnung Scholten et al., 2021) were the only studies evaluating prenatal modeled SO_2 exposure in China and Denmark, respectively (Table 5). Exposure assessment methods are described in Supplementary Table 2. Cord blood TL was negatively associated with SO_2 exposure during the entire gestation (borderline in the study by Scholten et al. (Harnung Scholten et al., 2021)) and the third trimester of gestation in both studies. Furthermore, a strong negative association during the second trimester was observed in the Danish study (mean gestational exposure of 1.2 parts per billion) but not in the Chinese study (mean exposure up to 16.5 μg/m^3 in the first trimester). No association between SO_2 exposure and placental TL was observed (Harnung Scholten et al., 2021).

3.3.5. *Ozone*

In line with SO_2, only the studies by Song et al. (2022) and Scholten et al. (Harnung Scholten et al., 2021) investigated prenatal O_3 exposure (Table 6). A positive association with cord blood TL was observed during the second trimester of gestation in both studies. Additionally, in the Chinese study (mean gestational exposure of 111.6 μg/m^3) a positive association was observed for O_3 exposure during the entire gestation and third trimester, but a negative association was found during the first trimester (Song et al., 2019). Similar to the other pollutants described above, Scholten et al. (Harnung Scholten et al., 2021), did not observe any associations with placental TL (mean gestational exposure of 64.4 μg/m^3).

Table 6
Newborn telomere length and prenatal exposure to ozone.

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference (95% C.I.)	Adjustments[b]
Song et al., 2022	China	743	51.40%	Cord blood	Entire pregnancy	111.6 (8.3)	10	**7.1% (4.4% to 10.2%)**	1,2,3,4,5,7
					Trimester 1	104.6 (45.0)		**−8.3% (-12.9% to -3.6%)**	
					Trimester 2	107.3 (42.4)		**6.0% (1.5% to 10.6%)**	
					Trimester 3	123.1 (55.5)		**12.6% (7.5% to 18%)**	
Harnung Scholten et al., 2021	Denmark	296	48.90%	Cord blood	Entire pregnancy	64.4 (21.1)	IQR	22% (−6% to 58%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			−17% (−35% to 5%)	
					Trimester 2			**60% (24% to 107%)**	
					Trimester 3			−13% (−38% to22%)	
				Placenta	Entire pregnancy	64.4 (21.1)	IQR	−12% (−31% to 12%)	1,2,3,4,5,7,8,10,13[c]
					Trimester 1			0% (−19% to 25%)	
					Trimester 2			−21% (−37% to −1%)	
					Trimester 3			19% (−11% to 59%)	

[a]Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in μg/m.^{3}.
[b]All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 4 = season; 5 = prenatal smoke exposure; 7 = parity; 8 = pregnancy complications (including hypertension, diabetes, pre-eclampsia); 10 = ambient temperature; 13 = birthweight.
Additional adjustments in:
[c]For indoor exposure, mode of delivery, newborn length and head circumference.

3.3.6. Air pollutants reported by single studies

In addition to the above-mentioned air pollutants, Scholten et al. (Harnung Scholten et al., 2021) additionally evaluated the associations between prenatal BC, OC and ammonium NH_4^+ exposure and cord blood as well as placental TL (Supplementary Table 5). Although no associations were observed with placental TL, both BC and OC were positively associated with cord blood TL during the second trimester, and negatively during the third trimester. Exposure to NH_4^+ was positively associated with cord blood TL in the first trimester, but negatively during the third.

Perera et al. (2018) evaluated differences in cord blood TL from newborns born before and after the closure of a coal-burning facility. Polycyclic aromatic hydrocarbons (PAH exposure, as evaluated by cord blood PAH-DNA adducts was negatively associated with cord blood TL (Supplementary Table 6). Newborns born after the closure of the coal-burning facility had longer TL than those born before the closure.

Finally, Bijnens et al. (2015) evaluated the association between geocoded exposure to traffic at the maternal residential addresses and newborn TL. others living further away from major roads had longer placental TL (Supplementary Table 6).

3.4. Prenatal exposure to air pollution and newborn mtDNA content

Eight studies, with a total of 3081 participants were identified that investigated the association between prenatal exposure to air pollution and mtDNA content at birth (Janssen et al., 2012, 2015; Brunst et al., 2018; Clemente et al., 2016; Mandakh et al., 2021; Rosa et al., 2017; Kaali et al., 2018; Hu et al., 2020). The study with the smallest sample size included 120 participants (Kaali et al., 2018) and the study with the largest sample size had 743 participants (Hu et al., 2020). Three studies (Rosa et al., 2017; Kaali et al., 2018; Hu et al., 2020) investigated cord blood mtDNA content, three studies (included four independent cohorts) investigated placental mtDNA content (Clemente et al., 2016; Mandakh et al., 2021; Janssen et al., 2015) and two studies (Janssen et al., 2012; Brunst et al., 2018) investigated both cord blood as well as placental mtDNA content. Mitochondrial DNA content was assessed using qPCR in all studies (five studies (Janssen et al., 2012; Clemente et al., 2016; Mandakh et al., 2021; Janssen et al., 2015; Hu et al., 2020) used singleplex qPCR and three studies (Brunst et al., 2018; Rosa et al., 2017; Kaali et al., 2018) used a multiplex technique). Seven studies (Janssen et al., 2012, 2015; Brunst et al., 2018; Clemente et al., 2016; Mandakh et al., 2021; Rosa et al., 2017; Hu et al., 2020) used modeled air pollution assessment methods and one study (Kaali et al., 2018) used personally monitored air pollution exposure. Details on the assessment of air pollution exposures are provided in Supplementary Tables 2 and 3 The studies were mainly conducted across several countries in Europe, including Belgium (Janssen et al., 2012, 2015; Clemente et al., 2016), Sweden (Mandakh et al., 2021) and Spain (Clemente et al., 2016), while one study each was based in China (Hu et al., 2020), Mexico (PROGRESS cohort) (Rosa et al., 2017) and Ghana (GRAPHS cohort) (Kaali et al., 2018). One American study included participants from White, Black and Hispanic ethnicities (PRISM cohort) (Brunst et al., 2018).

3.4.1. Particulate matter

Four studies (Janssen et al., 2015; Rosa et al., 2017; Hu et al., 2020; Brunst et al., 2018) investigated the association between prenatal $PM_{2.5}$ exposure and mtDNA content at birth (Table 7). All four studies used modeled exposures, details of which are provided in Supplementary Table 2. Janssen et al. (2015) reported an inverse association between prenatal $PM_{2.5}$ exposure and placental mtDNA content during the entire period of gestation and the third trimester (mean gestational exposure of 16.7 $\mu g/m^3$). Brunst et al. (2018) did not find any association between $PM_{2.5}$ exposure and placental mtDNA content but observed an inverse association with cord blood mtDNA content during the entire period of gestation (mean exposure of 7.9 $\mu g/m^3$). Finally, Hu et al. (2020) reported an inverse association during the third trimester (mean gestational exposure of 79.6 $\mu g/m^3$) with cord blood mtDNA content. However, Rosa et al. (2017) did not find any significant associations between prenatal $PM_{2.5}$ exposure and mtDNA content during the entire gestation or any of the trimesters.

Table 7
Newborn mitochondrial DNA content and prenatal exposure to $PM_{2.5}$.

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference or β (95% C.I.)	Adjustments[b]
Janssen et al., 2015	ENVIRONAGE	381	49.30%	Placenta	Entire pregnancy	16.7 (15.2–18.2)	IQR	**−15.6% (-23.9% to -6.4%)**	1,3,5,6,7[c]
	Belgium				Trimester 1	16.0 (11.8–19.6)		−7.6% (−20.8% to 7.9%)	
					Trimester 2	16.9 (12.2–20.4)		−15.2% (−28.3% to 0.4%)	
					Trimester 3	17.3 (11.9–21.7)		**−23.6% (-36.3% to -8.4%)**	
Rosa et al., 2016,f	PROGRESS	456	55.20%	Cord blood	Entire pregnancy	23.1 (20.8–24.5)	10	Approx. −2%; p > 0.05	1,5[d]
	Mexico				Trimester 1			Approx. −1%; p > 0.05	
					Trimester 2			Approx. 4.5%; p > 0.05	
					Trimester 3			Approx. −5%; p > 0.05	
Brunst et al., 2018	PRISM	126	50.00%	Cord blood	Entire pregnancy	7.9 (0.69)	1	**−0.78 (-1.41 to -0.16)**	1,6,9[e]
	USA	140	52.10%	Placenta	Entire pregnancy	7.9 (0.67)	1	−0.07 (−0.23 to 0.04)	1,6[e]
Hu et al., 2020	China	743	51.40%	Cord blood	Entire pregnancy	79.6 (74.7–83.9)	10	−2.4% (−11.6% to 7.6%)	1,2,3,5,7,8
					Trimester 1			0.3% (−2.1% to 2.8%)	
					Trimester 2			5.4% (−0.04% to 11.3%)	
					Trimester 3			**−8.5% (-13.3% to -3.5%)**	

[a]Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in $\mu g/m.^3$.
[b]All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 5 = prenatal smoke exposure; 6 = newborn ethnicity; 7 = parity; 8 = pregnancy complications (including hypertension, diabetes); 9 = cell type proportions. Additional adjustments in:
[c]For conception season.
[d]For year of birth and batch.
[e]For maternal lifetime trauma.
[f]Estimates were not numerically presented in the original manuscript and could only be estimated on presented figures, for interpretation we refer to the original publications. Abbreviations: ENVIRONAGE = ENVIRonmental influence ON AGEing in early life study; PROGRESS= Programming Research in Obesity; Growth, Environment and Social Stressors study; PRISM= Programming of Intergenerational Stress Mechanisms study.

Two studies (Janssen et al., 2012; Hu et al., 2020) investigated modeled prenatal PM_{10} exposure and mtDNA content (Supplementary Tables 2 and 7). A considerable difference was observed in the mean gestational PM_{10} concentrations at the two study settings (Janssen et al., 2012; Hu et al., 2020) (22.7 μg/m^3 in Belgium versus 140.4 μg/m^3 in China). Janssen et al. (2012) did not find any associations between PM_{10} exposures during any period of gestation and cord blood mtDNA content but found an inverse association with placental mtDNA content only during the third trimester. Contrarily, Hu et al. (2020) reported a positive association during the second trimester for cord blood mtDNA content.

3.4.2. Nitrogen oxides

One study (Mandakh et al., 2021) evaluated prenatal exposure to NO_x and placental mtDNA content and observed an inverse association during the entire period of gestation as well as the first trimester (mean gestational exposure level of 14.8 μg/m^3) (Table 8). This is in line with observations made by Clemente et al. (2016), who reported findings on NO_2 exposures and mtDNA content in two independent European birth cohorts (INMA, Spain and ENVIR*ON*AGE, Belgium) separately and combined. Prenatal exposure to NO_2 was associated with lower placental mtDNA content during all trimesters of gestation in the INMA study (mean gestational exposure of 25.5 μg/m^3) and during the second and third trimesters in the ENVIR*ON*AGE cohort (mean gestational exposure of 21.1 μg/m^3) (Clemente et al., 2016) (Table 8).

3.4.3. Air pollutants reported by single studies

One study evaluated personally monitored CO exposure during gestation and cord blood mtDNA content and found no overall associations (Kaali et al., 2018). (Supplementary Tables 3 and 8).

3.5. Sex-specific effects between prenatal air pollution and newborn TL and mtDNA content

As both biomarkers of aging and air pollution exposure effects may be sex-dependent (Liu et al., 2018), we additionally evaluated whether prenatal air pollution exposures showed sex-specific associations with newborn TL and mtDNA content from the studies which reported these associations. Of the nineteen included studies, nine (Martens et al., 2017; Lee et al., 2020; Brunst et al., 2018; Rosa et al., 2017, 2019; Kaali et al., 2018, 2021; Song et al., 2019; Hu et al., 2020) reported sex-specific associations and ten (Janssen et al., 2012, 2015; Clemente et al., 2016; Harnung Scholten et al., 2021; Song et al., 2022; Perera et al., 2018; Durham et al., 2022; Isaevska et al., 2022; Mandakh et al., 2021; Bijnens et al., 2015) did not. Five studies (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Kaali et al., 2021; Song et al., 2019) reported analyses stratified by sex for newborn TL (Supplementary Table 9) and four studies (Brunst et al., 2018; Rosa et al., 2017; Kaali et al., 2018; Hu et al., 2020) stratified by sex for mtDNA content (Supplementary Table 10). Sex-specific differences for the association between prenatal $PM_{2.5}$ exposure and newborn TL can be summarized as follows: 1) Martens et al. (2017) did not observe any different associations by sex, 2) Rosa et al. (2019) showed a slightly stronger association in females as compared to males, and 3) the other three studies (Lee et al., 2020; Kaali et al., 2021; Song et al., 2019) observed stronger associations in males as compared to females. However, no study reported a significant interaction by infant sex. Stratified analysis by sex for the association between newborn TL and prenatal PM_{10}, SO_2, NO_2, and CO exposure was performed by Song et al. (2019) with slightly stronger associations in males compared to females, but none showed a significant interaction.

For the studies on prenatal PM air pollution and mtDNA content, two studies (Brunst et al., 2018; Hu et al., 2020) found no differences in the association between $PM_{2.5}$ and PM_{10} and cord blood mtDNA content by sex. Rosa et al. (2017) reported significant associations only in males for $PM_{2.5}$ exposure and reduced mtDNA content during 37–40 weeks of gestation, but found no significant interaction by newborn sex in their posthoc analyses. The results from GRAPHS showed significant reductions in cord blood mtDNA content due to prenatal CO exposure in males (Kaali et al., 2018). (Supplementary Table 10).

4. Discussion

Exposure to air pollution is an inevitable phenomenon during daily life. Fetal development is considered a sensitive window for such exposures in the course of human life since any biological alterations at this stage may lead to undesirable health outcomes later in life (Luyten et al., 2018). Previous reviews have shown a potential negative association between long-term exposure to $PM_{2.5}$ and TL in adults (Miri et al., 2019; Assavanopakun et al., 2022), while no consensus has ever been reached for the effect of exposure to environmental pollutants on mtDNA content in adults (Avilés-Ramírez et al., 2022). However, studies investigating such associations in newborns specifically remain limited and this is the first systematic review evaluating the effect of prenatal air pollution exposure on these two critical markers of cellular aging with established links to multiple future health risks. This review

Table 8
Newborn mitochondrial DNA content and prenatal exposure to nitrogen oxides.

Authors	Cohort, Country	N	% Male	Sample	Exposure window	Exposure concentrations[a]	Pollutant increment	% difference or β (95% C.I.)	Adjustments[b]
Clemente et al., 2016	INMA	376	51.60%	Placenta	Entire pregnancy	25.5 (11.4)	10	**−5.5% (-8.8% to -2.1%)**	1,2,3,4,5,6,7
(NO_2)	Spain				Trimester 1	26.1 (12.9)		**−4.1% (-7.1% to -1.1%)**	
					Trimester 2	25.6 (11.6)		**−5.0% (-8.0% to -2.0%)**	
					Trimester 3	25.7 (12.1)		**−4.9% (-7.9% to -1.8%)**	
	ENVIR*ON*AGE	550	50.40%	Placenta	Entire pregnancy	21.1 (4.2)	10	−10.1% (−20.1% to 1.2%)	1,2,3,4,5,6,7
	Belgium				Trimester 1	20.7 (6.1)		−5.1% (−15.5% to 6.6%)	
					Trimester 2	20.8 (6.0)		**−11.1% (-19.9% to -1.2%)**	
					Trimester 3	21.4 (6.1)		**−13.5% (-20.1% to -6.4%)**	
Mandakh et al., 2021	Sweden	137	53.30%	Placenta	Entire pregnancy	14.8 (8.4)		**−0.14 (-0.31 to -0.02)**	2,3,4,7
(NO_x)					Trimester 1	14.0 (7.6)		**−0.20 (-0.36 to -0.04)**	
					Trimester 2	16.2 (12.4)		−0.16 (−0.33 to 0.01)	
					Trimester 3	14.7 (8.6)		−0.15 (−0.31 to 0.01)	

Abbreviations: NO_2 = nitrogen dioxide; NO_x = nitrogen oxides; INMA= INfancia y Medio Ambiente, Environment and Childhood birth cohort; ENVIR*ON*AGE = ENVIRonmental influence ON AGEing in early life study.

[a] Exposure concentrations presented as mean (SD) or as median (25th percentile to 75th percentile) in μg/m.^{3}.

[b] All studies adjusted for maternal age and newborn sex. Other adjustment variables include 1 = maternal education; 2 = maternal pre-pregnancy BMI; 3 = gestational age; 4 = season of birth; 5 = prenatal smoke exposure; 6 = newborn ethnicity; 7 = parity.

systematically explored the current evidence on the potential impact of prenatal exposure to ambient air pollution on TL and mtDNA content as early-life aging markers at birth.

The findings of this systematic research can be summarized as follows. First, we found that more studies (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Harnung Scholten et al., 2021; Song et al., 2019, 2022; Durham et al., 2022; Isaevska et al., 2022; Mandakh et al., 2021) evaluated the association between prenatal ambient air pollution exposure and newborn TL (of which most studies (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Kaali et al., 2021; Harnung Scholten et al., 2021; Song et al., 2019; Song et al., 2022; Perera et al., 2018; Durham et al., 2022; Isaevska et al., 2022) used cord blood as a biological matrix) compared to studies (Janssen et al., 2012, 2015; Brunst et al., 2018; Clemente et al., 2016; Mandakh et al., 2021; Rosa et al., 2017; Hu et al., 2020) evaluating newborn mtDNA content (of which more studies (Janssen et al., 2012; Brunst et al., 2018; Clemente et al., 2016; Mandakh et al., 2021; Janssen et al., 2015) used placenta as a biological matrix). Second, for newborn TL, most studies were conducted on prenatal $PM_{2.5}$ exposure and five (Martens et al., 2017; Lee et al., 2020; Kaali et al., 2021; Harnung Scholten et al., 2021; Song et al., 2019) out of seven (Martens et al., 2017; Lee et al., 2020; Rosa et al., 2019; Kaali et al., 2021; Harnung Scholten et al., 2021; Song et al., 2019; Durham et al., 2022) studies showed a negative association. However, no clear consensus could be established for the trimester-specific effects observed for the associations. Studies that evaluated PM_{10} (including the larger fraction of ambient particles) were less conclusive, in which only one (Song et al., 2019) out of three (Harnung Scholten et al., 2021; Song et al., 2019; Isaevska et al., 2022) studies reported on a negative association with newborn TL. The latter may indicate the stronger toxic impact of smaller particles ($PM_{2.5}$) on biological processes (Feipeng et al., 2023), including telomere biology. Based on the findings of the currently limited studies on prenatal exposure to nitrogen oxide species and newborn TL there is currently no strong evidence of an association. For prenatal CO and SO_2 exposure it is shown in two independent cohorts (Harnung Scholten et al., 2021; Song et al., 2019) that exposure in trimester 3 is negatively associated with cord blood TL. Finally, for newborn TL, two studies (Harnung Scholten et al., 2021; Song et al., 2022) evaluated prenatal ozone exposures and tended to report positive associations. Third, for newborn mtDNA content, prenatal $PM_{2.5}$ exposure during entire pregnancy and trimester 3 of pregnancy tends to be negatively associated with newborn mtDNA (negative associations confirmed in $3^{23,35,38}$ out of 4 studies). As in line with newborn TL, no clear association was observed with prenatal PM_{10} (one study (Hu et al., 2020) showing a positive and one study (Janssen et al., 2012) showing a negative association). Finally, for mtDNA, two studies (Clemente et al., 2016; Mandakh et al., 2021) evaluating in total 3 independent cohorts all showed a negative association between prenatal exposure to nitrogen oxygen species and placental mtDNA content. Fourth, a relative high inconsistency in findings between these studies, especially in the context of trimester-specific associations for mtDNA content, was observed. Additionally, no moderating effect of the sample sizes of the included studies was observed on the findings for both these biomarkers in newborns.

The inconsistent findings could be attributable to the following reasons: 1) The geographical differences between studies imply differences in air pollution levels and genetic differences in the study population. The highest air pollution levels were observed in the study (Song et al., 2019, 2022; Hu et al., 2020) from Wuhan, China, followed by the participants from the study conducted in Africa (Kaali et al., 2021) and Mexico (Rosa et al., 2017, 2019). The studies based on cohorts in Europe (Martens et al., 2017; Janssen et al., 2012, 2015; Clemente et al., 2016; Harnung Scholten et al., 2021; Mandakh et al., 2021) and U.S.A. (Lee et al., 2020; Brunst et al., 2018) had comparatively lower concentrations of air pollutants for their respective study periods. Although associations were observed for different concentration levels across various study settings, genetic differences may additionally underly differences in susceptibility and adaptability to environmental stressors across population groups (O'Neill et al., 2012). 2) The sociodemographic characteristics of the studies were not similar. For example, the participants from the PROGRESS (Rosa et al., 2017, 2019) and GRAPHS (Kaali et al., 2018, 2021) belonged to low socio-economic status (SES) groups while the PRISM (Lee et al., 2020; Brunst et al., 2018) and ENVIR*O*NAGE (Martens et al., 2017; Janssen et al., 2012, 2015) cohorts were based on voluntary participation, indicating a majority of the participants were well-educated and presumably had a higher socio-economic position. As such, SES differences may further confound or complicate the relation between exposure and TL and mtDNA, as a recent meta-analysis confirmed an association between TL and SES in children and individuals from more 'at risk' SES levels are often exposed to multiple environmental toxins (Francis et al., 2023). 3) All studies, except four (Kaali et al., 2018, 2021; Perera et al., 2018; Bijnens et al., 2015), used modeled exposures for the air pollutants investigated in their studies. However, the findings based on modeled prenatal exposures could be confirmed by studies investigating internal biomarkers of exposures and personally monitored exposures, as reported by Perera et al. (2018) and Kaali et al., 2018, 2021 respectively. 4) All studies measured TL and mtDNA content using qPCR which shows more variability and measurement error as compared to methods such as Telomere Restriction Fragment analysis (Lin et al., 2019). 5) PM is a mixture of several particles which, based on the constitution, may have different toxic effects, that could not be described in the current papers. These reasons could explain the diffuseness in study results despite the similarities in study design and methodology.

In total, four studies (Martens et al., 2017; Janssen et al., 2012; Brunst et al., 2018; Harnung Scholten et al., 2021) measured TL or mtDNA content in both cord blood and placental tissue, of which two studies (Martens et al., 2017; Janssen et al., 2012) found stronger associations for both biomarkers in placental tissue as compared to cord blood for exposures to PM pollution. These findings may be explained by the presence of a potential compensatory mechanism in cord blood, that is absent in the placenta (Martens et al., 2017). The stronger effect observed in the placenta may furthermore be explained by the development of the placental barrier, which is fully developed and functional by the end of the first trimester, but becomes a thinner barrier with fewer cell layers by the third trimester (Burton and Jauniaux, 2018). This allows for the translocation of fine PM from the mother's lungs into the placenta which could cause oxidative stress-induced inflammatory reactions in the fetus (Bové et al., 2019). Some positive associations observed for prenatal air pollution exposures with newborn TL may be due to the fact that such exposure can cause an inflammatory reaction leading to alterations in the leukocyte composition, further leading to an increase in the number of neutrophils; which are positively associated with leukocyte TL (Harnung Scholten et al., 2021; Mollica et al., 2009). The observations for TL and mtDNA content in both cord blood and placental tissues followed a similar trend in three studies (Martens et al., 2017; Janssen et al., 2012; Brunst et al., 2018), which could be explained by the recent establishment that TL in cord blood and placenta is positively associated with mtDNA content in the respective tissues (Van Der Stukken et al., 2022). However, a direct comparison of observations for the two biomarkers among these studies could not be made due to analytical differences in methodology. Furthermore, while TL measurements show high correlations in different tissues, mtDNA content shows high tissue-specific variability within individuals; thus, the dissimilarity in correlations between TL and mtDNA content across diverse matrices or tissues might not be consistent. Tissue-specific regulatory factors and methodological nuances may contribute to observed discrepancies. Nevertheless, research shows a reciprocal relationship between mtDNA content and TL. Imbalances in one parameter may influence the other, indicating a cross-talk between mitochondrial function and nuclear genomic stability (Sahin et al., 2011).

It is also notable to acknowledge the findings from the study published by Van der Stukken et al. (Van Der Stukken et al., 2023), which, to

date, is the only study that investigated the impact of prenatal $PM_{2.5}$ exposure on both these biomarkers of aging in cord blood, as well as placenta, in newborns within the ENVIRONAGE birth cohort. The authors concluded that prenatal $PM_{2.5}$ exposures during the entire gestation and second trimester were associated with shorter placental TL while $PM_{2.5}$ exposure during the third trimester was associated with reduced placental mtDNA content. Furthermore, the authors also showed that placental TL is a potential mediator in the association between prenatal $PM_{2.5}$ exposure and placental mtDNA content and cord blood p53. Their results showed that for prenatal $PM_{2.5}$ exposures, placental TL mediated 65% of the negative association with placental mtDNA content and 17% of the positive association with cord plasma p53 protein levels, thus providing more clarity on the mechanisms underlying the effect of prenatal air pollution exposure on the biomarkers of aging at birth.

From the limited number of studies reporting sex-stratified analyses, slightly stronger associations were found between $PM_{2.5}$ and TL in newborn males compared to newborn females, albeit some inconsistency was found. No sex-specific differences were found for the effect of prenatal PM air pollution exposure on newborn mtDNA content from the limited evidence available, while reduced cord blood mtDNA content was found to be associated with higher prenatal CO exposure in males. This is probably attributable to the endocrine-disrupting properties of air pollutants (Darbre, 2018). Newborn males may be more vulnerable to oxidation-induced stress on biological mechanisms which could be responsible for sex-specific differences in health outcomes in adulthood as well (Minghetti et al., 2013). Besides air pollution, other prenatal exposures to factors such as stress (Rosa et al., 2016), cadmium (Taylor et al., 2016) and also metal mixtues (Signes-Pastor et al., 2019) have been shown to lead to sex-specific differences in outcomes.

We report the following limitations and important considerations for interpreting the current findings. We did not conduct a meta-analysis as 1) the included studies used different modeling methods for exposure assessments, with different validation techniques that could influence measurement errors and be a source of potential bias, 2) some studies reported week-specific effects of prenatal exposures using distributed lag models (Martens et al., 2017; Rosa et al., 2019) while others used average exposures over longer periods (Lee et al., 2020) and some used personal exposures (Kaali et al., 2018, 2021) making their comparison and standardization difficult, 3) qPCR was used in all studies, which due to different normalization and expression strategies cannot be combined when no clear summary statistics are provided that could be used to obtain standardized effect estimates. While a risk of potential publication bias may be suspected here, the non-uniform reporting formats also made it difficult to statistically assess it. Meta-analyses (Avilés-Ramírez et al., 2022; Zong et al., 2023) conducted on this topic so far remain methodologically inaccurate since they do not consider the differences in statistical and laboratorial analyses among studies. Additionally, these meta-analyses do not report standardized regression estimates; making them out of line with the Cochrane guidelines for meta-analyses. 4) While this systematic review relied on trimesters to identify sensitive windows of exposure during gestation, these windows could actually span multiple trimesters or be narrower. The use of distributed lag models (DLMs) is an efficient way to explore sensitive windows based on weekly exposures. Since only a few included studies applied DLMs (Supplementary Table 2) whereas most studies reported trimester-specific effects, the present review only summarized trimester-specific associations. Further detailed exposure assessments are necessary to shed light on sensitive windows of exposure during gestation in the context of air pollution-TL/mtDNA content associations. 5) While the study conducted by Van der Stukken et al. (Van Der Stukken et al., 2023), was the only one till date that evaluated the association between prenatal air pollution exposure and both the biomarkers of aging at birth, it could not be included in the review in adherence with the Cochrane guidelines. Nonetheless, this study strongly highlights the need for future epidemiological studies to integrate multiple biomarkers of the telomere-mitochondrial axis of aging simultaneously to gain a more detailed insight into the prenatal air pollution induced telomere-mitochondrial effects.

It is important to take into consideration that some studies reviewed here investigated multiple air pollutants (using the same modeling approach), and therefore one specific pollutant may be largely reflective of the other pollutants, showing similar results for these pollutants (Harnung Scholten et al., 2021; Song et al., 2019). In addition, the molecular mechanisms by which different pollutants impact health risk may differ and there is growing evidence, particularly for TL, describing impacts that could significantly shorten and also significantly lengthen TL, causing future health risks (Wu et al., 2012; Bhattacharjee et al., 2020). Therefore, a clear distinction between the effector pollutants cannot be made and the use of more agnostic and/or complex analytic models that account for mixed exposures are likely needed to enhance our understanding of the lasting health effects of prenatal exposures to different agents of air pollution. This holds for studies investigating single air pollutants as well as only measuring one pollutant does not exclude the potential that other unmeasured pollutants that are highly correlated are driving the observed relationship in epidemiological studies. Here greater integration with preclinical animal models where exposures can be directly measured and controlled would be expected to enhance the ability to truly define causal pathways.

Finally, the findings from this systematic review further support the hypothesis on the air pollution-induced connection between telomeres and mitochondria, whose interplay impacts the aging phenotype. The interplay of these biomolecular markers underlies health outcomes in later life, especially for the age-related onset of disease and mortality (Li et al., 2021; Dolcini et al., 2020). Moving forward, future longitudinal studies with larger populations, investigating personal exposures for shorter periods instead of averaging entire gestational exposures with uniform reporting formats would allow for the generalizability of study findings and truly unravel the nature of associations between prenatal exposures and these two biomolecular markers of aging at birth.

5. Conclusion

This review summarized the current and most updated evidence available on the association between prenatal air pollution exposure and newborn TL and mtDNA content from relevant epidemiological studies with somewhat similar, yet unique study designs. In general, the available evidence suggests that prenatal exposure to ambient air pollution, especially PM, was negatively associated with newborn TL and mtDNA content. Currently available evidence remains far too limited to reach overall conclusions regarding the impact of air pollution exposures across the three gestational trimesters, as well as the evaluation of the effects of multiple air pollutants. Future studies should aim to further unravel the impact of prenatal air pollution on biomolecular markers of aging at birth; along with the potential impact on later-life health consequences. This would pave the way for future public health measures to protect pregnant women and the fetus from air pollution exposures, especially during crucial periods of gestation.

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Funding

This study has received funding from the European Union's Horizon 2020 research and innovation programme 'SURREAL' under grant agreement No 956780. TSN holds funding by Methusalem. SD holds funding by National Institutes of Health (NIH U24AG066528). DSM

holds a postdoctoral grant by the Flemish Scientific Fund (FWO12X9623N).

CRediT authorship contribution statement

Shradha Mishra: Conceptualization, Investigation, Methodology, Writing - original draft. **Charlotte Van Der Stukken:** Writing - review & editing. **Stacy Drury:** Writing - review & editing. **Tim S. Nawrot:** Conceptualization, Writing - review & editing. **Dries S. Martens:** Conceptualization, Investigation, Methodology, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

We thank Dr Maria Jose Rosa and Dr Teresa Durham for providing additional data from their studies' analyses for associations between continuous prenatal $PM_{2.5}$ exposure and newborn TL.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117990.

References

Assavanopakun, P., Sapbamrer, R., Kumfu, S., Chattipakorn, N., Chattipakorn, S.C., 2022. Effects of air pollution on telomere length: evidence from in vitro to clinical studies. Environ. Pollut. 312, 120096.
Avilés-Ramírez, C., Moreno-Godínez, M.E., Bonner, M.R., et al., 2022. Effects of exposure to environmental pollutants on mitochondrial DNA copy number: a meta-analysis. Environ. Sci. Pollut. Control Ser. 29 (29), 43588–43606.
Bhattacharjee, P., Das, A., Giri, A.K., 2020. Epigenetic regulations in alternative telomere lengthening: understanding the mechanistic insight in arsenic-induced skin cancer patients. Sci. Total Environ. 704, 135388.
Bijnens, E., Zeegers, M.P., Gielen, M., et al., 2015. Lower placental telomere length may be attributed to maternal residential traffic exposure; a twin study. Environ. Int. 79, 1–7.
Bové, H., Bongaerts, E., Slenders, E., et al., 2019. Ambient black carbon particles reach the fetal side of human placenta. Nat. Commun. 10 (1), 3866.
Brunst, K.J., Sanchez-Guerra, M., Chiu, Y.M., et al., 2018. Prenatal particulate matter exposure and mitochondrial dysfunction at the maternal-fetal interface: effect modification by maternal lifetime trauma and child sex. Environ. Int. 112, 49–58.
Burton, G.J., Jauniaux, E., 2018. Development of the human placenta and fetal Heart: Synergic or independent? Front. Physiol. 9, 373.
Byun, H.M., Colicino, E., Trevisi, L., Fan, T., Christiani, D.C., Baccarelli, A.A., 2016. Effects of air pollution and blood mitochondrial DNA methylation on markers of Heart rate variability. J. Am. Heart Assoc. 5 (4).
Clemente, D.B., Casas, M., Vilahur, N., et al., 2016. Prenatal ambient air pollution, placental mitochondrial DNA content, and birth Weight in the INMA (Spain) and ENVIRONAGE (Belgium) birth cohorts. Environ. Health Perspect. 124 (5), 659–665.
Darbre, P.D., 2018. Overview of air pollution and endocrine disorders. Int. J. Gen. Med. 11, 191–207.
Dolcini, J., Wu, H., Nwanaji-Enwerem, J.C., et al., 2020. Mitochondria and aging in older individuals: an analysis of DNA methylation age metrics, leukocyte telomere length, and mitochondrial DNA copy number in the VA normative aging study. Aging (Albany NY) 12 (3), 2070–2083.
Durham, T., Guo, J., Cowell, W., et al., 2022. Prenatal PM(2.5) exposure in relation to maternal and newborn telomere length at delivery. Toxics 10 (1).
Feipeng, C., Yu, S., Junqing, X., et al., 2023. Air pollutants, genetic susceptibility and risk of incident idiopathic pulmonary fibrosis. Eur. Respir. J. 61 (2), 2200777.
Francis, M., Lindrose, A., O'Connell, S., Tristano, R.I., McGarvey, C., Drury, S., 2023. The interaction of socioeconomic stress and race on telomere length in children: a systematic review and meta-analysis. SSM Popul Health 22, 101380.
Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (10258), 2020, 1223–1249.
Grooten, W.J.A., Tseli, E., Äng, B.O., et al., 2019. Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS—aspects of interrater agreement. Diagnostic and Prognostic Research 3 (1), 5.
Harnung Scholten, R., Møller, P., Jovanovic Andersen, Z., et al., 2021. Telomere length in newborns is associated with exposure to low levels of air pollution during pregnancy. Environ. Int. 146, 106202.
Higgins, J.P.T.T.J., Chandler, J., Cumpston, M., Li, T., Page, M.J., 2022. Welch VA Cochrane Handbook for Systematic Reviews of Interventions Version 6.3. February 2022. www.training.cochrane.org/handbook.
Hu, C., Sheng, X., Li, Y., et al., 2020. Effects of prenatal exposure to particulate air pollution on newborn mitochondrial DNA copy number. Chemosphere 253, 126592.
Ide, T., Tsutsui, H., Hayashidani, S., et al., 2001. Mitochondrial DNA damage and dysfunction associated with oxidative stress in Failing Hearts after Myocardial Infarction. Circ. Res. 88 (5), 529–535.
Isaevska, E., Fiano, V., Asta, F., et al., 2022. Prenatal exposure to PM(10) and changes in DNA methylation and telomere length in cord blood. Environ. Res. 209, 112717.
Janssen, B.G., Munters, E., Pieters, N., et al., 2012. Placental mitochondrial DNA content and particulate air pollution during in utero life. Environ. Health Perspect. 120 (9), 1346–1352.
Janssen, B.G., Byun, H.M., Gyselaers, W., Lefebvre, W., Baccarelli, A.A., Nawrot, T.S., 2015. Placental mitochondrial methylation and exposure to airborne particulate matter in the early life environment: an ENVIRONAGE birth cohort study. Epigenetics 10 (6), 536–544.
Kaali, S., Jack, D., Delimini, R., et al., 2018. Prenatal household air pollution Alters cord blood Mononuclear cell mitochondrial DNA copy number: sex-specific associations. Int J Environ Res Public Health 16 (1).
Kaali, S., Jack, D., Opoku-Mensah, J., et al., 2021. Prenatal household air pollution exposure, cord blood Mononuclear cell telomere length and age four blood Pressure: evidence from a Ghanaian pregnancy cohort. Toxics 9 (7).
Kwon, E.J., Kim, Y.J., 2017. What is fetal programming?: a lifetime health is under the control of in utero health. Obstet Gynecol Sci 60 (6), 506–519.
Lee, A.G., Cowell, W., Kannan, S., et al., 2020. Prenatal particulate air pollution and newborn telomere length: effect modification by maternal antioxidant intakes and infant sex. Environ. Res. 187, 109707.
Li, Y., Sundquist, K., Wang, X., et al., 2021. Association of mitochondrial DNA copy number and telomere length with Prevalent and incident cancer and cancer mortality in women: a prospective Swedish population-based study. Cancers 13 (15).
Lin, J., Smith, D.L., Esteves, K., Drury, S., 2019. Telomere length measurement by qPCR - summary of critical factors and recommendations for assay design. Psychoneuroendocrinology 99, 271–278.
Ling, X., Zhang, G., Chen, Q., et al., 2016. Shorter sperm telomere length in association with exposure to polycyclic aromatic hydrocarbons: results from the MARHCS cohort study in Chongqing, China and in vivo animal experiments. Environ. Int. 95, 79–85.
Liu, H., Chen, Q., Lei, L., et al., 2018. Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances affects leukocyte telomere length in female newborns. Environ. Pollut. 235, 446–452.
López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2023. Hallmarks of aging: an expanding universe. Cell 186 (2), 243–278.
Luyten, L.J., Saenen, N.D., Janssen, B.G., et al., 2018. Air pollution and the fetal origin of disease: a systematic review of the molecular signatures of air pollution exposure in human placenta. Environ. Res. 166, 310–323.
Mandakh, Y., Oudin, A., Erlandsson, L., et al., 2021. Association of prenatal ambient air pollution exposure with placental mitochondrial DNA copy number, telomere length and Preeclampsia. Front Toxicol 3, 659407.
Martens, D.S., Nawrot, T.S., 2016. Air pollution stress and the aging Phenotype: the telomere connection. Current Environmental Health Reports 3 (3), 258–269.
Martens, D.S., Cox, B., Janssen, B.G., et al., 2017. Prenatal air pollution and newborns' Predisposition to accelerated biological aging. JAMA Pediatr. 171 (12), 1160–1167.
Minghetti, L., Greco, A., Zanardo, V., Suppiej, A., 2013. Early-life sex-dependent vulnerability to oxidative stress: the natural twining model. J. Matern. Fetal Neonatal Med. 26 (3), 259–262.
Miri, M., Nazarzadeh, M., Alahabadi, A., et al., 2019. Air pollution and telomere length in adults: a systematic review and meta-analysis of observational studies. Environ. Pollut. 244, 636–647.
Mollica, L., Fleury, I., Belisle, C., Provost, S., Roy, D.C., Busque, L., 2009. No association between telomere length and blood cell counts in elderly individuals. J Gerontol A Biol Sci Med Sci 64 (9), 965–967.
O'Neill, M.S., Breton, C.V., Devlin, R.B., Utell, M.J., 2012. Air pollution and health: emerging information on susceptible populations. Air Qual Atmos Health 5 (2), 189–201.
Organization, W.H., 2021. WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide: Executive Summary.
Orru, H., Ebi, K.L., Forsberg, B., 2017. The interplay of Climate change and air pollution on health. Current Environmental Health Reports 4 (4), 504–513.
Perera, F., Lin, C.J., Qu, L., Tang, D., 2018. Shorter telomere length in cord blood associated with prenatal air pollution exposure: Benefits of intervention. Environ. Int. 113, 335–340.
Rosa, M.J., Just, A.C., Tamayo y Ortiz, M., et al., 2016. Prenatal and postnatal stress and wheeze in Mexican children: sex-specific differences. Ann. Allergy Asthma Immunol. 116 (4), 306–312.e1.

Rosa, M.J., Just, A.C., Guerra, M.S., et al., 2017. Identifying sensitive windows for prenatal particulate air pollution exposure and mitochondrial DNA content in cord blood. Environ. Int. 98, 198–203.
Rosa, M.J., Hsu, H.L., Just, A.C., et al., 2019. Association between prenatal particulate air pollution exposure and telomere length in cord blood: effect modification by fetal sex. Environ. Res. 172, 495–501.
Sahin, E., Depinho, R.A., 2010. Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature 464 (7288), 520–528.
Sahin, E., DePinho, R.A., 2012. Axis of ageing: telomeres, p53 and mitochondria. Nat. Rev. Mol. Cell Biol. 13 (6), 397–404.
Sahin, E., Colla, S., Liesa, M., et al., 2011. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 470 (7334), 359–365.
Shamseer, L., Moher, D., Clarke, M., et al., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ Br. Med. J. (Clin. Res. Ed.) 349, g7647.
Signes-Pastor, A.J., Doherty, B.T., Romano, M.E., et al., 2019. Prenatal exposure to metal mixture and sex-specific birth outcomes in the New Hampshire Birth Cohort Study. Environ Epidemiol 3 (5).
Song, L., Zhang, B., Liu, B., et al., 2019. Effects of maternal exposure to ambient air pollution on newborn telomere length. Environ. Int. 128, 254–260.
Song, L., Wu, M., Wang, L., et al., 2022. Ambient ozone exposure during pregnancy and telomere length in newborns: a prospective investigation in Wuhan, China. Environ. Sci. Pollut. Res. Int. 29 (41), 62662–62668.
Stroup, D.F., Berlin, J.A., Morton, S.C., et al., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 283 (15), 2008–2012.
Taylor, C.M., Golding, J., Emond, A.M., 2016. Moderate prenatal cadmium exposure and adverse birth outcomes: a role for sex-specific differences? Paediatr. Perinat. Epidemiol. 30 (6), 603–611.
Van Der Stukken, C., Nawrot, T.S., Alfano, R., et al., 2022. The telomere-mitochondrial axis of aging in newborns. Aging (Albany NY) 14 (4), 1627.
Van Der Stukken, C., Nawrot, T.S., Wang, C., et al., 2023. The association between ambient particulate matter exposure and the telomere–mitochondrial axis of aging in newborns. Environ. Int. 171, 107695.
Vardoulakis, S., Giagloglou, E., Steinle, S., et al., 2020. Indoor exposure to selected air pollutants in the Home environment: a systematic Review. Int J Environ Res Public Health 17 (23).
Ward-Caviness, C.K., Nwanaji-Enwerem, J.C., Wolf, K., et al., 2016. Long-term exposure to air pollution is associated with biological aging. Oncotarget 7 (46), 74510.
Wong, J.Y., De Vivo, I., Lin, X., Christiani, D.C., 2014. Cumulative PM2. 5 exposure and telomere length in workers exposed to welding fumes. J. Toxicol. Environ. Health, Part A 77 (8), 441–455.
Wu, Y., Liu, Y., Ni, N., Bao, B., Zhang, C., Lu, L., 2012. High lead exposure is associated with telomere length shortening in Chinese battery manufacturing plant workers. Occup. Environ. Med. 69 (8), 557–563.
Xue, Y., Tian, H., Yan, J., et al., 2016. Temporal trends and spatial variation characteristics of primary air pollutants emissions from coal-fired industrial boilers in Beijing, China. Environ. Pollut. 213, 717–726.
Zong, Z.Q., Chen, S.W., Wu, Y., Gui, S.Y., Zhang, X.J., Hu, C.Y., 2023. Ambient air pollution exposure and telomere length: a systematic review and meta-analysis. Publ. Health 215, 42–55.