air

MDPI

Article

Exposure to Ambient Particulate Matter during Pregnancy: Implications for Infant Telomere Length

Nina E. Ahlers [1,*], Jue Lin [2] and Sandra J. Weiss [1]

[1] Department of Community Health Systems, University of California, San Francisco, CA 94143, USA; sandra.weiss@ucsf.edu
[2] Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143, USA; jue.lin@ucsf.edu
* Correspondence: nina.ahlers@ucsf.edu

Abstract: Background: Growing evidence suggests that air pollution may influence fetal development, with potential consequences for later health. Alteration of telomere length (TL) is one possible mediating mechanism for the link between fetal exposure to air pollution and the development of disease. However, the few studies exploring associations between prenatal pollution and infant TL have assessed varied trimesters of pregnancy and shown mixed results. The aim of this study was to examine the differential relationships between prenatal exposure to air pollutant $PM_{2.5}$ during the first, second, and third trimesters of pregnancy with infant TL at one month of age. Methods: Women (n = 74) were recruited in obstetric clinics during their third trimester. Data on $PM_{2.5}$ exposure for each woman's residential area during each trimester was acquired from the regional Air Quality Management District. At one month postnatal, a salivary sample was collected from the infant, which provided DNA for the telomere assay. Women completed questionnaires about stressors in their lives, perceived stress, depression, and sociodemographics for inclusion as covariates. Multiple linear regression was used to analyze the results. Results: $PM_{2.5}$ exposure during the second (β = 0.31, p = 0.003) and third (β = 0.24, p = 0.02) trimesters was associated with longer infant TL. Exposure in the first trimester was not related to TL. Covariates of maternal depression and age and infant female sex were also associated with longer TL. Variables in the model contributed to 34% of the variance in TL (F = 10.58, p = 0.000). Discussion: Fetal programming of longer telomeres in response to pollution may have adaptive value in preparing the neonate for a postnatal environment that is less than optimal in terms of air quality. Alternatively, longer telomeres may forecast later health risks, considering established links between longer TL and diseases such as cancer. Future research needs to address how prenatal pollution interacts with TL to influence health over time.

Keywords: air pollution; telomere length; prenatal exposure; fetal programming; pregnancy; infants

Citation: Ahlers, N.E.; Lin, J.; Weiss, S.J. Exposure to Ambient Particulate Matter during Pregnancy: Implications for Infant Telomere Length. *Air* **2024**, *2*, 24–37. https://doi.org/10.3390/air2010002

Received: 15 November 2023
Revised: 16 January 2024
Accepted: 31 January 2024
Published: 3 February 2024

1. Introduction

Air pollution is an established cause of respiratory and cardiovascular diseases, reproductive and central nervous system dysfunctions, and cancer [1–3]. There is growing evidence that adverse impacts of air pollution can begin as early as pregnancy [4–6] and have long-term impacts in later life [7,8]. These findings reinforce the validity of a widely recognized theory, the Developmental Origins of Health and Disease (DOHaD), which proposes that in utero exposures program fetal development to influence health outcomes throughout life [9,10]. Fetal exposure to air pollutants can occur through cross-placental transfer of particulate matter or metabolized molecules of air pollutants [11–13].

Shortening of telomere length (TL) is one possible mediating mechanism for the link between fetal exposure to air pollution and the later development of disease [14]. As shown in Figure 1, telomeres are protective caps at the ends of chromosomes, which reduce their risk of erosion [15]. These caps are regions of repetitive DNA sequences that safeguard the

ends of the chromosome from becoming frayed or tangled. A recent systematic review and meta-analysis indicated that 94.8% of participants from 19 studies experienced shorter TL from exposure to air pollution [16]. However, few studies have examined the association between air pollution and TL in utero or among infants.

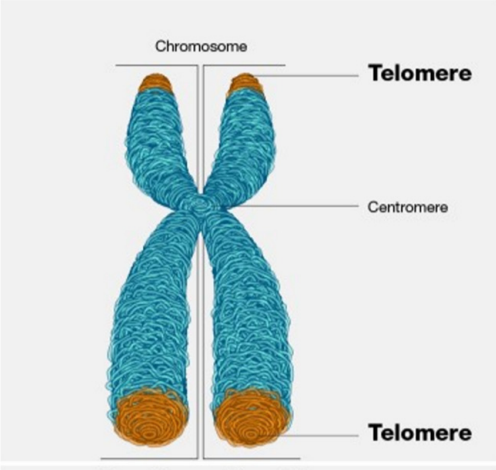

Figure 1. Protective telomere caps on the end of a chromosome.

Previous research points to a key role for oxidative stress (OS) in the adverse effects of air pollution [17,18]. Telomeres are sensitive to OS given their guanine-rich structure, with increased OS eliciting site-specific damage to telomeres at the triple guanine nucleotide sequence [19]. Li et al. [17] propose that particulate matter may induce OS through processes such as the direct generation of reactive oxygen species or inflammatory activation. Because of its underdeveloped antioxidant defenses, the fetus is especially susceptible to oxidative stress [20,21].

Research suggests that the integrity of telomeres can affect the way in which DNA unfolds, with early-life programming of an individual's telomere biology accounting for a large proportion of later health and disease [22–24]. Programming of adult TL may begin as early as embryogenesis [25] and is strongly predicted by newborn TL [23]. However, newborn telomere length appears to be highly variable [26,27], implicating the prenatal stage as a critical window of vulnerability to early life exposures.

Particulate matter with aerodynamic diameter $\leq$ 2.5 μm ($PM_{2.5}$) has been the primary type of pollution studied during pregnancy. One study examining the first trimester of pregnancy found that increased $PM_{2.5}$ was associated with shorter TL in the cord blood of newborns [28]. Three studies of the second trimester reported mixed results, with two of these finding that higher $PM_{2.5}$ exposure was related to shorter TL in the cord blood of newborns [18,29]. The third study found that higher $PM_{2.5}$ levels during the second trimester were associated with longer TL [28]. For third-trimester $PM_{2.5}$ exposure, three studies also reported mixed findings from cord blood, with two noting that higher pollution predicted shorter TL [30,31] and a third study finding pollution was associated with longer TL [28]. Clearly, research to date indicates no consensus regarding the nature of the relationships between air pollution during various trimesters of pregnancy and infant TL.

The purpose of this study was to advance existing knowledge of the effects of pollution exposure during different trimesters on infant TL (Figure 2). Our specific aim was to assess the differential relationships between prenatal exposure to air pollutant $PM_{2.5}$ during the first, second, and third trimesters of pregnancy on infant telomere length at one month of age.

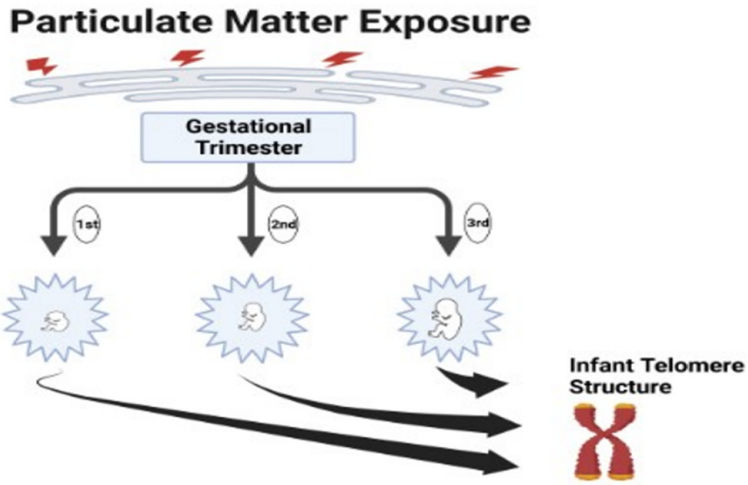

Figure 2. Potential programming effects of prenatal $PM_{2.5}$ exposure on infant telomeres.

2. Materials and Methods

2.1. Sample and Procedures

Our sample included pregnant women (n = 74) enrolled in a longitudinal cohort study funded by the National Institutes of Health (R01 HD081188). English- and Spanish-speaking women from obstetric clinics affiliated with a large university medical center were eligible to participate if they were ≥18 years old and ≥28 weeks' gestation between 2015 and 2019. Based on the requirements of the larger cohort study, exclusion criteria included ongoing steroid use, a history of endocrine conditions, smoking, serious medical problems, or cognitive impairment.

Archived data and sample specimens were accessed 5 January 2023, for the purpose of this study. We acquired data on particulate matter ($PM_{2.5}$) within each woman's residential area from public records of the air quality control district in the region, identifying levels present during each trimester of the woman's pregnancy. Salivary samples for telomere analysis were collected from the infant at one month of age. Women also completed measures of their demographics, perceived stress, the stressors they experienced, and their depression as potential covariates. All participants provided written consent, and the study was approved by the University of California at San Francisco's (UCSF) Institutional Review Board for Human Research Protection before it began.

2.2. Air Pollutant ($PM_{2.5}$) Exposure during Pregnancy

The pregnancy air pollution measures are based on data from the Bay Area Air Quality Management District (BAAQMD). BAAQMD sites were determined after analyzing preliminary air quality measurements collected from field studies, temporary monitoring studies, and mobile monitoring data [32]. Our participants resided within 4 BAAQMD counties, and data from 6 monitors were used to collect 24 h average $PM_{2.5}$ levels. $PM_{2.5}$ measures were estimated for each participant according to the nearest monitoring station to their residence at the time of enrollment, which was geocoded with Google Earth. Kim et al. [33] implicated that central fixed-site measurements of $PM_{2.5}$ can be treated as a proxy measure for personal exposure to $PM_{2.5}$ within a 15.5-mile radius. The average distance between the maternal residence and the nearest $PM_{2.5}$ monitoring station in our study was 2.39 miles and ranged between 0.28 and 5.63 miles. Four air pollution measures were calculated for the analyses, including the woman's average $PM_{2.5}$ exposure across the entire pregnancy period and estimates for each clinically defined trimester (1st trimester: 1–13 weeks, 2nd trimester: 14–27 weeks, 3rd trimester: 28 weeks delivery).

2.3. Infant Telomere Length

Saliva for DNA was collected from infants at approximately one month of age using an Oragene DNA Collection Kit (DNA Genotek, Inc, Stittsville, ON, Canada). The kit contained 5 small sponges, which were each inserted sequentially for one minute in the infant's mouth. Each sponge was moved around the upper and lower cheek pouches for approximately 30 s on each side of the mouth, and then placed in a collection tube with stabilizing solution at room temperature until assayed for telomere length. Research has validated saliva samples as a high-quality source of DNA for genomic applications that is equivalent to DNA from blood for downstream applications [34–36]. Salivary telomere length correlates with leukocyte telomere length and known correlates of telomere length (e.g., age and adversity) as measured by blood leukocytes [16,37,38].

Genomic DNA was purified from 500 µL of saliva with the DNA Agencourt DNAdvance kit (cat# A48705, Beckman Coulter Genomics Inc., Brea, CA, USA). DNA was quantified by measuring OD260 with a NanoDrop 2000c Spectrophotometer (Nanodrop Products, Wilmington, DE, USA) and run on 0.8% agarose gels to check the integrity. Samples that passed the quality control of OD260/OD280 between 1.7–2.0, concentration greater than 10 ng/µL, and no degradation were used for telomere length measurement. All except one sample passed quality control. Further information regarding the protocol can be found in Supplementary Materials File S1.

Relative telomere length was measured by quantitative polymerase chain reaction (qPCR), expressed as the ratio of telomere to single-copy gene abundance (T/S ratio) [39,40]. The reaction was carried out in a Roche LightCycler 480 in 384-well plates, with triplicate wells for each sample. The Dixon Q test was used to exclude outliers from the triplicates. The average of the T and S triplicate wells after outlier removal was used to calculate the T/S ratio for each sample.

The inter-assay coefficient of variation (CV) for this study is 2.3% ± 1.6%. The intraclass correlation of duplicate DNA extraction was not estimated for this specific study but was reported to be 0.95 (CI: 0.911–0.972) from another study using saliva samples collected in the same DNA extraction kit and the same telomere length assay [41]. A detailed protocol can be found on the Telomere Research Network's website (https://trn.tulane.edu/wp-content/uploads/sites/445/2021/07/Lin-qPCR-protocol-01072020.pdf) accessed on 20 September 20223.

2.4. Covariates

Data were collected on 9 covariates to control for their effects if needed in the testing of the aims: maternal age, educational level, income, perceived stress, exposure to stressors, and depression, as well as infant sex, gestational age, and birth weight. Infant sex, gestational age, and birth weight were identified from medical records, while maternal demographic data was acquired from a sociodemographic questionnaire. The three other covariates (stressors, stress, and depression) were measured with standardized questionnaires. Exposure to stressors was measured by The Crisis in Family Systems (CRISYS) Questionnaire [42,43]. The CRISYS Questionnaire consists of 64 stressful events that represent 11 key stressor domains: home safety, neighborhood safety, financial challenges, legal problems, career setbacks, relationship difficulties, medical problems (self and others), housing issues, prejudice, and troubles with authority. Women identified all events they experienced over the prior 6 months. The greater the number of events, the higher the woman's stressor score. Maternal perceived stress was evaluated using the Perceived Stress Scale (PSS; [44]). The PSS measured the degree to which women felt that their lives were unpredictable, uncontrollable, and overloaded with stressors within the last month. Each of the 10 items was rated on a 5-point Likert scale, with a total higher score indicating greater perceived stress. Maternal depression was assessed with the 9-item Patient Health Questionnaire (PHQ-9). Women reported the frequency of 9 depressive symptoms during the past two weeks, ranging from "not at all" to "nearly every day", with the sum of individual symptom scores yielding the total. The following score ranges reflect the

progressive seriousness of depression: 1–4 = minimal depression, 5–9 = mild depression, 10–14 = moderate depression, 15–19 = moderately severe depression, and 20+ = severe symptoms of depression. A diagnosis of major depression is indicated (at both a sensitivity and specificity of 88%) when an individual has a score of >10 [45].

2.5. Analysis

The sample was characterized using descriptive statistics. Assumptions of linearity and normality were examined, resulting in log transformations for telomere scores to assure a normal distribution. We employed stepwise multiple linear regression to assess the relationship between prenatal exposure to air pollution and infant telomere length, including which covariates to retain in the final models. Two separate models were tested, with the T/S ratio for telomere length as the dependent variable in each model. In the first model, average $PM_{2.5}$ exposure across all trimesters was the primary predictor of interest, while in the second model, specific $PM_{2.5}$ estimates of exposure during each of the trimesters were all entered as predictors. Covariates were entered into the model through a stepwise regression procedure. The default for entry and removal of each covariate was $p = 0.15$. The first variable entered into the model was the variable with the smallest p-value, then the variable with the next smallest p-value, and so forth until all variables meeting the criteria for entry were included. If any variable exceeded the $p = 0.15$ threshold for retention after the inclusion of additional variables, it was removed from the model. The final models included only those variables that met the criteria for entry and were retained. Analyses were conducted using Stata version 16 (StataCorp, College Station, TX, USA).

3. Results

3.1. Sample Characteristics

Sample characteristics and distributions for key covariates are displayed in Table 1. 74 women were included in the study (M = 33 yrs), with ~41% reporting an annual household income of USD 51,000 or less (32% reported USD 21,000 or less). About 55% were from diverse racial and ethnic backgrounds, including 20% who identified as Black/African American and 20% as Hispanic/Latina. The average prenatal $PM_{2.5}$ exposure was 8.8 $\mu g/m^3$, with exposure estimates ranging between 5.5 and 14.4 $\mu g/m^3$ across the pregnancy. Infant telomere T/S ratios had a mean value of 2.71 and ranged between 2.07 and 3.63.

3.2. Relationships between Prenatal $PM_{2.5}$ Exposures and Infant Telomere Length

Table 2 shows a significant effect of average $PM_{2.5}$ exposure across pregnancy on infant TL length ($\beta = 0.466$, $p = 0.000$). According to our findings, per every 1 $\mu g/m^3$ increase in $PM_{2.5}$ exposure across pregnancy, infant TL increased by 0.466 log units ($p = 0.000$). Maternal depressive symptoms ($\beta = 0.225$, $p = 0.025$) and maternal age ($\beta = 0.218$, $p = 0.032$) had significant positive associations with TL. In addition, male infants had a significantly shorter TL than female infants ($\beta = -0.258$, $p = 0.010$). The variables in the model contributed to 34% of the variance in TL ($F = 10.58$, $p = 0.000$). All covariates were included in the preliminary model testing, but only maternal depression, age, and infant sex were retained during stepwise regression procedures. Preliminary bivariate correlation coefficients for all variables in the study are presented in Supplementary Materials Table S1.

Table 3 presents differential effects for each of the trimester $PM_{2.5}$ exposures, adjusted for significant covariates. First-trimester exposure to $PM_{2.5}$ was not significantly related to infant TL in either bivariate correlations or after adjusting for covariates. Second and third trimester exposure to $PM_{2.5}$ had significant positive associations with TL ($\beta = 0.310$, $p = 0.003$; $\beta = 0.241$, $p = 0.021$; respectively). Like the effects shown in Table 2, prenatal depressive symptoms, maternal age, and infant female sex were positively associated with longer infant TL. Figure 3 highlights the differential effects of $PM_{2.5}$ exposure on infant TL in each trimester and across the entire gestational period.

Table 1. Sample characteristics and covariates.

Variable	Unit or Category	Mean (Range) or N (%)
Maternal age	Years	33 (21–44)
Maternal education		
	Elementary school	3 (4%)
	High school or GED	15 (20%)
	Some college	15 (20%)
	Bachelor's degree	16 (22%)
	Master's degree	10 (14%)
	Advanced degree	15 (20%)
Household income		
	Less than USD 15,000	14(19%)
	USD 15,000–30,999	14 (19%)
	USD 31,000–50,999	3 (4%)
	USD 51,000–100,999	2 (3%)
	USD 101,000–149,999	10 (13%)
	USD 150,000+	31 (42%)
Stressors	Number of events	6.8 (0–39)
Perceived stress	Continuous score	14.6 (3–31)
Maternal depression	Continuous score	5.8 (0–18)
Infant sex		
	Male	38 (51%)
	Female	36 (49%)
Infant gestational age	Weeks	36.4 (27.3–41.6)
Infant birth weight	Grams	2771.6 (700–4650)
Infant telomere length	T/S ratios *	2.71 (2.07–3.63)
$PM_{2.5}$ exposure		
First trimester exposure	$\mu g/m^3$	9.4 (4.2–22.7)
Second trimester exposure	$\mu g/m^3$	8.8 (3.9–21.1)
Third trimester exposure	$\mu g/m^3$	8.3 (4.2–19.7)
Average pregnancy exposure	$\mu g/m^3$	8.8 (5.5–14.4)

* Telomere length ratio values were log transformed.

Table 2. Regression model for effects of average prenatal $PM_{2.5}$ exposure on infant telomere length [a].

	Effects on Infant Telomere Length		
Model Covariates	**β (95% CI)**	**Standard Error**	***p*-Value**
Average Prenatal $PM_{2.5}$	0.466 (0.275–0.657)	0.096	0.000
Depressive Symptoms	0.225 (0.029–0.421)	0.098	0.025
Maternal Age	0.218 (0.020–0.417)	0.099	0.032
Infant Male Sex	−0.258 (−0.451–−0.065)	0.097	0.010

[a] R-adj = 0.34.

Table 3. Regression model for effects of prenatal $PM_{2.5}$ exposure in each trimester on infant telomere length [a].

	Effects on Infant Telomere Length		
Model Covariates	**β (95% CI)**	**Standard Error**	***p*-Value**
T1 $PM_{2.5}$	0.184 (−0.015–0.382)	0.099	0.069
T2 $PM_{2.5}$	0.310 (0.110–0.509)	0.099	0.003
T3 $PM_{2.5}$	0.241 (0.038–0.443)	0.101	0.021
Depressive Symptoms	0.207 (0.004–0.410)	0.102	0.046
Maternal Age	0.211 (−0.011–0.412)	0.101	0.039
Infant Male Sex	−0.245 (−0.442–−0.049)	0.098	0.015

[a] R-adj = 0.20.

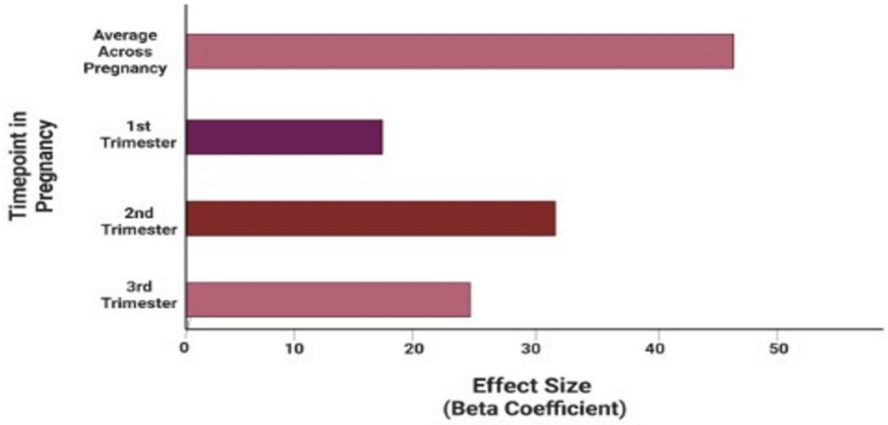

Figure 3. Differential effects of prenatal $PM_{2.5}$ exposure on infant telomere length at one month of age.

4. Discussion

The results of this study indicate that fetal exposure to particulate matter in the air ($PM_{2.5}$) is significantly associated with longer infant TL at one month of age. The strongest effect of $PM_{2.5}$ was found for overall pregnancy exposure. However, results suggest that exposure during the second trimester may account for the greatest contribution to infant TL, followed by exposure during the third trimester. Although average $PM_{2.5}$ exposure was highest during the first trimester, air pollution during this trimester was not associated with TL. These differential findings among trimesters suggest that the first trimester may not be the time of greatest fetal vulnerability to particulate matter. In addition, based on our results and previous findings, the amount of $PM_{2.5}$ exposure does not appear to provide a primary explanation for variation in TL [18,28,31].

4.1. Exposure to $PM_{2.5}$ during Pregnancy and Infant Telomere Length

Women in our study experienced an average $PM_{2.5}$ exposure level of 8.8 $\mu g/m^3$ throughout their pregnancy. Although this exposure level was actually below the standardized safety limit of 12.0 $\mu g/m^3$ (National Ambient Air Quality Standards, 2020 [46]), it was still associated with telomere length. However, it is important to note that concentration levels peaked as high as 23 $\mu g/m^3$, 21 $\mu g/m^3$, and 18 $\mu g/m^3$ during each progressive trimester, respectively. Our findings are consistent with other studies that have identified the second and third trimesters of pregnancy as critical windows of vulnerability to $PM_{2.5}$ exposure. Rosa et al. [28] also found significant associations between increased $PM_{2.5}$ exposure during the second and third trimesters and elongated infant TL. Scholten et al. [30] found a positive association between second-trimester exposure and longer infant TL, but shorter infant TL was associated with exposure during the third trimester.

Despite previous support for our findings, there are some notable differences between our study and other studies examining these relationships. Other research examined TL in cord blood cells collected from the infant after delivery [18,28–31], in contrast to our study, which analyzed infant salivary samples during the first month of life. Thus, comparison is difficult because of the differing developmental timepoints and the use of different tissue sources. While most studies have found shorter telomeres in blood from the effect of air pollution on adults [16], one study examining salivary TL among children 8–9 years of age found that greater $PM_{2.5}$ exposure was associated with longer TL [47]. In addition, three of the five studies examining the effect of prenatal exposure to particulate matter on cord blood TL among newborns reported elongated telomeres. Although mixed findings do exist, our study adds to growing evidence supporting the hypothesis that air pollution exposure during pregnancy may lead to longer TL during early life.

Our fetal exposure levels to air pollution were on average mild, potentially resulting in low-grade systemic inflammation. Low-grade inflammation might explain the effects of air pollution on telomere length. Maternal inhaled particulate matter can directly cross the placental barrier into the placenta or fetal circulation [48], resulting in the production of DNA-damaging reactive oxygen species (ROS) from the surface of the particles [15,49] and the activation of inflammation in cells [50]. Both processes may cause mutations and shortening of telomeres. However, inflammation-inducing particulate matter may not always cross through the placenta [51] but instead stimulate the placenta in ways that result in low-grade inflammatory fetal reactions [52]. These low-grade inflammatory reactions have been associated with elongated telomeres [53–55]. As noted by Scholten et al. [30], alterations caused by low-grade systemic inflammation may reflect both the expansion of cellular subpopulations with longer telomeres (T and B lymphocytes), as those proliferate faster, and a greater number of leukocytes from the bone marrow, which typically produces longer telomeres due to their immaturity ([54,56]).

Up-regulation of telomerase (an enzyme that extends telomeres by adding new DNA sequences to the ends of chromosomes) may also be involved as a mechanism to counteract the erosive effects of inflammation or air pollutants on telomeres [57,58]. Increased exposure to $PM_{2.5}$ could stimulate increased production of placental telomerase, with the resulting elongation of developing fetal telomeres. Up-regulation of telomerase has been proposed by others as a potential mechanism underlying the associations they found between pollutant exposure and longer telomeres at birth and in childhood [47,59]. Telomerase may also help to explain the lack of association we found between first trimester particulate matter exposure and telomere length. Research indicates that, in normative pregnancies, telomerase activity is greater in the first trimester [60], potentially enhancing its buffering role against any adverse effects of pollution on telomeres. However, as gestation proceeds, telomerase activity typically decreases [61].

Some early alterations in biological systems, such as the telomere system, may have adaptive value in preparing the infant for potential adversities in the environment after birth [62]. It has been suggested that mild to moderate levels of early life adversity may have positive, adaptive effects on fetal programming by creating longer telomere length at birth [63,64]. In this way, longer telomeres could provide a compensatory and protective foundation for postnatal health when potentially adverse air quality is expected.

Alternatively, it is important to note that longer telomeres are not always indicative of a protective health status or advantageous outcomes. For example, multiple studies have reported that exposure to carcinogens is associated with longer telomeres [65–68] and that longer telomeres are a risk factor for many types of cancer [69,70]. With this view in mind, exposure to particulate matter in utero may place the infant at future risk for later health problems. The developmental trajectory of health outcomes stemming from the interaction between prenatal pollution exposure and TL will be essential to study.

4.2. Associations of Covariates with Infant Telomere Length

Although not a focus of our research aims, results indicate that increased prenatal depressive symptoms, older maternal age, and infant female sex were also associated with longer infant telomeres. Few studies to date have examined the relationship between prenatal depression and infant TL, with mixed findings. Ammala et al. [71] and Wojcicki et al. [72] found no relationship between prenatal maternal depression and infant TL. In other studies, prenatal depressive symptoms have been associated with shorter cord blood TL among male infants [73] and shorter placental TL in female infants [74]. In a final study, prenatal depression was associated with longer TL among males only (Bosquet et al. [63]).

While paternal age is a well-established predictor of newborn TL [75], maternal age has shown no significant effects on infant TL [76,77]. We found one study reporting an association between maternal age at birth and longer infant TL [78].

Our findings regarding infant sex are consistent with other studies reporting shorter telomeres among males versus females in the association to increased prenatal $PM_{2.5}$ exposure [18,31] and other environmental exposures [79]. However, one previous study found that prenatal $PM_{2.5}$ exposure was associated with shorter TL for female infants than males [28], and another reported no sex differences [29]. Sex differences in telomere dynamics may be associated with sex-related hormonal conditions during intrauterine life [80], but these conditions have not been carefully studied. More research is clearly needed to understand how maternal depression, maternal age, and infant sex may influence infant TL and interact with air pollution in determining effects on telomere length.

In contrast to some previous research, we found no association of TL with educational level, income, perceived stress, exposure to stressors, gestational age, or birth weight. These variables will need further study with a larger sample size. There is also a need to examine other potential covariates in future research. Risk factors such as maternal smoking, a higher body mass index in pregnancy, and childhood trauma have been linked to TL [36,80], as well as behavioral factors such as healthy nutrition (including antioxidant intake), exercise, sleep, and leisure time [18,81].

4.3. Implications

The results of this study have implications for future research. One of our very interesting findings was that $PM_{2.5}$ exposure during the first trimester was not associated with infant TL, in contrast to significant associations between TL and $PM_{2.5}$ exposure during the second and third trimesters. This finding was particularly unexpected since infants incurred greater average $PM_{2.5}$ exposure during the first trimester. Considering these results, it will be important to further examine the effects of exposure dosage on TL and to separate out any effects of $PM_{2.5}$ dose from the increased versus decreased developmental vulnerability that may exist in different trimesters of pregnancy.

The variables we identified as contributing to TL across pregnancy explained approximately one-third of the variance in infant telomere length. While providing an important foundation for future research, these results indicate that other factors clearly influence TL as well. Studies should examine both mediating and moderating factors that may explain more of the variance in TL. In particular, the direct and mediating effects of telomerase activity and inflammation will be essential to assess. As noted earlier, telomerase is a ribonucleoprotein enzyme that regulates telomere length by adding new DNA sequences to the ends of chromosomes [82]. Through this process, it prevents continued erosion and maintains the length of the telomeres. Thus, a greater capacity to express telomerase could lead to longer telomeres [83]. Regarding inflammation, prenatal biomarkers such as C-Reactive Protein, Tumor Necrosis Factor (TNF-α) and Interleuken (IL-6, IL-10) have shown robust associations with neonatal TL [84,85]. These markers warrant further examination for their influence on TL. In addition, the direct and moderating effects of diet and exercise should also be examined since there is growing evidence that they may play key roles, including effects on placental TL [86,87].

Lastly, our results raise important questions about the health implications of neonates having shorter versus longer telomeres when exposed to prenatal air pollutants such as $PM_{2.5}$. Although it is often assumed that longer telomeres are health-protective, as we noted in the discussion above, elongated telomeres have been linked to both positive and negative health outcomes. It will be essential to conduct longitudinal studies that follow infants over the first few years of life to assess how exposure to prenatal particulate matter affects their telomeres over time and the actual impact of elongated telomeres on their health status. Ultimately, such knowledge may inform the use of telomeres as a marker of health risk or resilience as well as guide potential changes in standards for $PM_{2.5}$ exposure.

4.4. Strengths and Limitations

The strengths of our study include a diverse sample, the high temporal resolution of the $PM_{2.5}$ estimates, examination of pollution across all trimesters, and adjustment for salient covariates. Given that our exposure estimates are extracted from the nearest single site monitor from a network of ground monitors, a limitation of our study is that we do not account for further personalized exposure estimates for each participant from the workplace or indoor household exposure levels that can affect exposure variation. Because of the lack of correlation between exposure to ambient air pollution and non-ambient exposure, such as indoor air pollution [88], both components should be separately examined. We also did not include other air pollutants in our analysis that could potentially modify or confound the associations we observed. Our small sample size may hinder the generalizability of the findings to populations not well represented in the study. Lastly, our ability to understand any long-term effects is limited by the cross-sectional design of our study.

4.5. Conclusions

Our findings indicate that fetal exposure to greater air pollution during pregnancy is related to longer telomeres among infants at 1 month of age. Fetal programming of longer telomeres in response to pollution may have adaptive value in preparing the neonate for a postnatal environment that may be less than optimal in air quality. Alternatively, longer telomeres may not be indicative of a protected health status, considering what is known about the link between longer telomeres and cancer risk. In this context, elongated telomeres could place the neonate at future risk for later health problems. It will be essential to better understand mechanisms responsible for pollution-related programming effects on TL, such as telomerase up-regulation, inflammation, oxidative stress, or epigenetic alterations. Future research also needs to address how prenatal pollution exposure interacts with telomere length to influence health outcomes over time. A clearer understanding of the mechanistic pathways underlying air pollution exposure and its effects across the life course will assist with the development of interventions and targeted therapeutics needed to combat any negative effects on telomeres at both the clinical and public health levels.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/air2010002/s1, Table S1: Bivariate Correlations between Key Study Variables and Covariates and File S1: qPCR Protocols.

Author Contributions: N.E.A. conceived and designed the experiments; performed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools, and data; and wrote the paper. J.L. performed all qPCR procedures and telomere assays and reviewed and contributed to the paper. S.J.W.: conceived and designed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools, and data; wrote the paper; and provided administration and funding for the project. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by NICHD, RO1 HD081188-05 (S.J.W., Principal Investigator), and the Robert and Delphine Wentland Eschbach Endowment.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the University of California of San Fransico's (UCSF) Institutional Review Board (IRB) for Human Research Protection (14-13516 and 25 August 2016).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: We thank Sandra Niemann for her contributions to study coordination and data management. Figures were created with BioRender.com accessed on 10 January 2024.

Conflicts of Interest: The authors have no conflicts to disclose.

References

1. Dominski, F.H.; Lorenzetti Branco, J.H.; Buonanno, G.; Stabile, L.; Gameiro da Silva, M.; Andrade, A. Effects of air pollution on health: A mapping review of systematic reviews and meta-analyses. *Environ. Res.* **2021**, *201*, 111487. [CrossRef]
2. Johnson, N.M.; Hoffmann, A.R.; Behlen, J.C.; Lau, C.; Pendleton, D.; Harvey, N.; Shore, R.; Li, Y.; Chen, J.; Tian, Y.; et al. Air pollution and children's health-a review of adverse effects associated with prenatal exposure from fine to ultrafine particulate matter. *Environ. Health Prev. Med.* **2021**, *26*, 72. [CrossRef] [PubMed]
3. Manisalidis, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Health* **2020**, *8*, 14. [CrossRef] [PubMed]
4. Bai, W.; Li, Y.; Niu, Y.; Ding, Y.; Yu, X.; Zhu, B.; Duan, R.; Duan, H.; Kou, C.; Li, Y.; et al. Association between ambient air pollution and pregnancy complications: A systematic review and meta-analysis of cohort studies. *Environ. Res.* **2020**, *185*, 109471. [CrossRef] [PubMed]
5. Proietti, E.; Röösli, M.; Frey, U.; Latzin, P. Air pollution during pregnancy and neonatal outcome: A review. *J. Aerosol. Med. Pulm. Drug Deliv.* **2013**, *26*, 9–23. [CrossRef]
6. Yan, M.; Liu, N.; Fan, Y.; Ma, L.; Guan, T. Associations of pregnancy complications with ambient air pollution in China. *Ecotoxicol. Environ. Saf.* **2022**, *241*, 113727. [CrossRef] [PubMed]
7. Iglesias-Vázquez, L.; Binter, A.C.; Canals, J.; Hernández-Martínez, C.; Voltas, N.; Ambròs, A.; Fernández-Barrés, S.; Pérez-Crespo, L.; Guxens, M.; Arija, V. Maternal exposure to air pollution during pregnancy and child's cognitive, language, and motor function: ECLIPSES study. *Environ. Res.* **2022**, *212*, 113501. [CrossRef] [PubMed]
8. Lubczyńska, M.J.; Muetzel, R.L.; El Marroun, H.; Hoek, G.; Kooter, I.M.; Thomson, E.M.; Hillegers, M.; Vernooij, M.W.; White, T.; Tiemeier, H.; et al. Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. *Environ. Res.* **2021**, *198*, 110446. [CrossRef] [PubMed]
9. Lacagnina, S. The Developmental Origins of Health and Disease (DOHaD). *Am. J. Lifestyle Med.* **2019**, *14*, 47–50. [CrossRef]
10. Swanson, J.M.; Entringer, S.; Buss, C.; Wadhwa, P.D. Developmental origins of health and disease: Environmental exposures. *Semin. Reprod. Med.* **2009**, *27*, 391–402. [CrossRef]
11. Bové, H.; Bongaerts, E.; Slenders, E.; Bijnens, E.M.; Saenen, N.D.; Gyselaers, W.; Van Eyken, P.; Plusquin, M.; Roeffaers, M.B.J.; Ameloot, M.; et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat. Commun.* **2019**, *10*, 3866. [CrossRef]
12. Kim, D.; Chen, Z.; Zhou, L.F.; Huang, S.X. Air pollutants and early origins of respiratory diseases. *Chronic Dis. Transl. Med.* **2018**, *4*, 75–94. [CrossRef] [PubMed]
13. Liu, N.M.; Miyashita, L.; Maher, B.A.; McPhail, G.; Jones, C.J.P.; Barratt, B.; Thangaratinam, S.; Karloukovski, V.; Ahmed, I.A.; Aslam, Z.; et al. Evidence for the presence of air pollution nanoparticles in placental tissue cells. *Sci. Total Environ.* **2021**, *751*, 142235. [CrossRef] [PubMed]
14. Hermanova, B.; Riedlova, P.; Dalecka, A.; Jirik, V.; Janout, V.; Sram, R.J. Air pollution and molecular changes in age-related diseases. *Int. J. Environ. Health Res.* **2022**, *32*, 772–790. [CrossRef] [PubMed]
15. Blackburn, E.H.; Epel, E.S.; Lin, J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science* **2015**, *350*, 1193–1198. [CrossRef] [PubMed]
16. Zhao, B.; Ha, V.; Johnston, F.; Negishi, K. Air pollution and telomere length: A systematic review of 12,058 subjects. *Cardiovasc. Diagn. Ther.* **2018**, *8*, 480–492. [CrossRef] [PubMed]
17. Li, Z.; Tang, Y.; Song, X.; Lazar, L.; Li, Z.; Zhao, J. Impact of ambient pm 2.5 on adverse birth outcome and potential molecular mechanism. *Ecotoxicol. Environ. Saf.* **2019**, *169*, 248–254. [CrossRef]
18. Rao, X.; Zhong, J.; Brook, R.D.; Rajagopalan, S. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. *Antioxid. Redox Signal.* **2018**, *28*, 797–818. [CrossRef]
19. Lee, A.G.; Cowell, W.; Kannan, S.; Ganguri, H.B.; Nentin, F.; Wilson, A.; Coull, B.A.; Wright, R.O.; Baccarelli, A.; Bollati, V.; et al. Prenatal particulate air pollution and newborn telomere length: Effect modification by maternal antioxidant intakes and infant sex. *Environ. Res.* **2020**, *187*, 109707. [CrossRef] [PubMed]
20. Grzeszczak, K.; Łanocha-Arendarczyk, N.; Malinowski, W.; Ziętek, P.; Kosik-Bogacka, D. Oxidative Stress in Pregnancy. *Biomolecules* **2023**, *13*, 1768. [CrossRef]
21. Panfoli, I.; Candiano, G.; Malova, M.; De Angelis, L.; Cardiello, V.; Buonocore, G.; Ramenghi, L.A. Oxidative Stress as a Primary Risk Factor for Brain Damage in Preterm Newborns. *Front. Pediatr.* **2018**, *6*, 369. [CrossRef]
22. Bosquet Enlow, M.; Sideridis, G.; Bollati, V.; Hoxha, M.; Hacker, M.R.; Wright, R.J. Maternal cortisol output in pregnancy and newborn telomere length: Evidence for sex-specific effects. *Psychoneuroendocrinology* **2019**, *102*, 225–235. [CrossRef]
23. Entringer, S.; de Punder, K.; Buss, C.; Wadhwa, P. The fetal programming of telomere biology hypothesis: An update. *Phil. Trans. R. Soc.* **2018**, *373*, 20170151. [CrossRef]
24. Shalev, I.; Entringer, S.; Wadhwa, P.D.; Wolkowitz, O.M.; Puterman, E.; Lin, J.; Epel, E.S. Stress and telomere biology: A lifespan perspective. *Psychoneuroendocrinology* **2013**, *38*, 1835–1842. [CrossRef] [PubMed]
25. Schaetzlein, S.; Lucas-Hahn, A.; Lemme, E.; Kues, W.A.; Dorsch, M.; Manns, M.P.; Niemann, H.; Rudolph, K.L. Telomere length is reset during early mammalian embryogenesis. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 8034–8038. [CrossRef] [PubMed]
26. Factor-Litvak, P.; Susser, E. The importance of early life studies of telomere attrition. *Paediatr. Perinat. Epidemiol.* **2015**, *29*, 144–145. [CrossRef] [PubMed]

27. Okuda, K.; Bardeguez, A.; Gardner, J.P.; Rodriguez, P.; Ganesh, V.; Kimura, M.; Skurnick, J.; Awad, G.; Aviv, A. Telomere length in the newborn. *Pediatr. Res.* **2002**, *52*, 377–381. [CrossRef]
28. Rosa, M.J.; Hsu, H.L.; Just, A.C.; Brennan, K.J.; Bloomquist, T.; Kloog, I.; Pantic, I.; García, A.M.; Wilson, A.; Coull, B.A.; et al. Association between prenatal particulate air pollution exposure and telomere length in cord blood: Effect modification by fetal sex. *Environ. Res.* **2019**, *172*, 495–501. [CrossRef]
29. Martens, D.S.; Cox, B.; Janssen, B.G.; Clemente, D.; Gasparrini, A.; Vanpoucke, C.; Lefebvre, W.; Roels, H.A.; Plusquin, M.; Nawrot, T.S. Prenatal Air Pollution and Newborns' Predisposition to Accelerated Biological Aging. *JAMA Pediatr.* **2017**, *171*, 1160–1167. [CrossRef] [PubMed]
30. Scholten, R.; Møller, P.; Andersen, Z.; Dehlendorff, C.; Khan, J.; Brandt, J.; Ketzel, M.; Knudsen, L.; Mathiesen, L. Telomere length in newborns is associated with exposure to low levels of air pollution during pregnancy. *Environ. Int.* **2021**, *146*, 106202. [CrossRef] [PubMed]
31. Song, L.; Zhang, B.; Liu, B.; Wu, M.; Zhang, L.; Wang, L.; Xu, S.; Cao, Z.; Wang, Y. Effects of maternal exposure to ambient air pollution on newborn telomere length. *Environ. Int.* **2019**, *128*, 254–260. [CrossRef]
32. Knoderer, C.; Nguyen, D.; Alrick, D.; Hoag, K. *2016 Air Monitoring Network plan*; Bay Area Air Quality Management District: San Francisco, CA, USA, 2019.
33. Kim, D.; Sass-Kortsak, A.; Purdham, J.; Dales, R.; Brook, J. Associations between personal exposures and fixed-site ambient measurements of fine particulate matter, nitrogen dioxide, and carbon monoxide in Toronto, Canada. *J. Expo. Sci. Environ. Epidemiol.* **2005**, *16*, 172–183. [CrossRef]
34. Hu, Y.; Ehli, E.A.; Nelson, K.; Bohlen, K.; Lynch, C.; Huizenga, P.; Kittlelsrud, J.; Soundy, T.J.; Davies, G.E. Genotyping Performance between Saliva and Blood-Derived Genomic DNAs on the DMET Array: A Comparison. *PLoS ONE* **2012**, *7*, e33968. [CrossRef]
35. Tomiyama, A.J.; O'Donovan, A.; Lin, J.; Puterman, E.; Lazaro, A.; Chan, J.; Dhabhar, F.S.; Wolkowitz, O.; Kirschbaum, C.; Blackburn, E.; et al. Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. *Physiol. Behav.* **2012**, *106*, 40–45. [CrossRef]
36. Van den Bergh, B.R.H.; van den Heuvel, M.I.; Lahti, M.; Braeken, M.; de Rooij, S.R.; Entringer, S.; Hoyer, D.; Roseboom, T.; Räikkönen, K.; King, S.; et al. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neurosci. Biobehav. Rev.* **2017**, *117*, 26–64. [CrossRef]
37. von Zglinicki, T. Oxidative stress shortens telomeres. *Trends Biochem. Sci.* **2002**, *27*, 339–344. [CrossRef]
38. Wikgren, M.; Maripuu, M.; Karlsson, T.; Nordfjall, K.; Bergdahl, J.; Hultdin, J.; Del-Favero, J.; Roos, G.; Nilsson, L.-G.; Adolfsson, R.; et al. Short telomeres in depression and the general population are associated with a hypocortisolemic state. *Biol. Psychiatry* **2012**, *71*, 294–300. [CrossRef]
39. Cawthon, R.M. Telomere measurement by quantitative PCR. *Nucleic Acids Res.* **2002**, *30*, e47. [CrossRef]
40. Lin, J.; Epel, E.; Cheon, J.; Kroenke, C.; Sinclair, E.; Bigos, M.; Wolkowitz, O.; Mellon, S.; Blackburn, E. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: Insights for epidemiology of telomere maintenance. *J. Immunol. Methods.* **2010**, *352*, 71–80. [CrossRef]
41. Smith, D.L.; Wu, C.; Gregorich, S.; Dai, G.; Lin, J. Impact of DNA Extraction Methods on Quantitative PCR Telomere Length Assay Precision in Human Saliva Samples. *Int. J. Methodol.* **2022**, *1*, 44–57. [CrossRef]
42. Berry, C.; Shalowitz, M.; Quinn, K.; Wolf, R. Validation of the Crisis in Family Systems-Revised, a contemporary measure of life stressors. *Psychol. Rep.* **2001**, *88 Pt 1*, 713–724. [CrossRef]
43. Berry, C.A.; Quinn, K.A.; Portillo, N.; Shalowitz, M.U. Reliability and validity of the Spanish version of the Crisis in Family Systems—Revised. *Psychol. Rep.* **2006**, *98*, 123–132. [CrossRef]
44. Cohen, S.; Kamarck, T.; and Mermelstein, R. A global measure of perceived stress. *J. Health Soc. Behav.* **1983**, *24*, 385–396. [CrossRef]
45. Kroenke, K.; Spitzer, R.; Williams, J. The PHQ-15: Validity of a New Measure for Evaluating the Severity of Somatic Symptoms. *Psychosom. Med.* **2002**, *64*, 258–266. [CrossRef]
46. National Ambient Air Quality Standards (NAAQS) for, PM. Available online: https://www.epa.gov/pm-pollution/national-ambient-air-quality-standards-naaqs-pm (accessed on 20 January 2020).
47. Walton, R.T.; Mudway, I.S.; Dundas, I.; Marlin, N.; Koh, L.C.; Aitlhadj, L.; Vulliamy, T.; Jamaludin, J.B.; Wood, H.E.; Barratt, B.M.; et al. Air pollution, ethnicity and telomere length in east London schoolchildren: An observational study. *Environ. Int.* **2016**, *96*, 41–47. [CrossRef]
48. Wick, P.; Malek, A.; Manser, P.; Meili, D.; Maeder-Althaus, X.; Diener, L.; Diener, P.A.; Zisch, A.; Krug, H.F.; von Mandach, U. Barrier capacity of human placenta for nanosized materials. *Environ. Health Perspect.* **2010**, *118*, 432–436. [CrossRef]
49. Kawanishi, S.; Oikawa, S. Mechanism of telomere shortening by oxidative stress. *Ann. N. Y. Acad. Sci.* **2004**, *1019*, 278–284. [CrossRef]
50. Risom, L.; Møller, P.; Loft, S. Oxidative stress-induced DNA damage by particulate air pollution. *Mutat. Res.* **2005**, *592*, 119–137. [CrossRef]
51. Hawkins, S.J.; Crompton, L.A.; Sood, A.; Saunders, M.; Boyle, N.T.; Buckley, A.; Minogue, A.M.; McComish, S.F.; Jiménez-Moreno, N.; Cordero-Llana, O.; et al. Nanoparticle-induced neuronal toxicity across placental barriers is mediated by autophagy and dependent on astrocytes. *Nat. Nanotechnol.* **2018**, *13*, 427–433. [CrossRef]

52. van den Hooven, E.H.; de Kluizenaar, Y.; Pierik, F.H.; Hofman, A.; van Ratingen, S.W.; Zandveld, P.Y.; Lindemans, J.; Russcher, H.; Steegers, E.A.; Miedema, H.M.; et al. Chronic air pollution exposure during pregnancy and maternal and fetal C-reactive protein levels: The Generation R Study. *Environ. Health Perspect.* **2012**, *120*, 746–751. [CrossRef]
53. Dioni, L.; Hoxha, M.; Nordio, F.; Bonzini, M.; Tarantini, L.; Albetti, B.; Savarese, A.; Schwartz, J.; Bertazzi, P.A.; Apostoli, P.; et al. Effects of short-term exposure to inhalable particulate matter ontelomere length, telomerase expression, and telomerase methylation in steel workers. *Environ. Health Perspect.* **2011**, *119*, 622–627. [CrossRef]
54. Hodes, R.J.; Hathcock, K.S.; Weng, N.P. Telomeres in T and B cells. *Nat. Rev. Immunol.* **2002**, *2*, 699–706. [CrossRef]
55. Weng, N.P.; Granger, L.; Hodes, R.J. Telomere lengthening and telomerase activation during human B celldifferentiation. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10827–10832. [CrossRef]
56. Thiede, C.; Prange-Krex, G.; Freiberg-Richter, J.; Bornhäuser, M.; Ehninger, G. Buccal swabs but not mouthwash samples can be used to obtain pretransplant DNA fingerprints from recipients of allogeneic bone marrow transplants. *Bone Marrow Transplant.* **2000**, *25*, 575–577. [CrossRef]
57. Vasu, V.; Turner, K.J.; George, S.; Greenall, J.; Slijepcevic, P.; Griffin, D.K. Preterm infants have significantly longer telomeres than their term born counterparts. *PLoS ONE* **2017**, *12*, e0180082. [CrossRef]
58. Wang, C.; Wolters, P.J.; Calfee, C.S.; Liu, S.; Balmes, J.R.; Zhao, Z.; Koyama, T.; Ware, L.B. Long-term ozone exposure is positively associated with telomere length in critically ill patients. *Environ. Int.* **2020**, *141*, 105780. [CrossRef]
59. Liu, Y.; Song, L.; Wu, M.; Bi, J.; Wang, L.; Liu, Q.; Xiong, C.; Cao, Z.; Xu, S.; Wang, Y. Association between rare earth element exposure during pregnancy and newborn telomere length. *Environ. Sci. Pollut. Res. Int.* **2023**, *30*, 38751–38760. [CrossRef]
60. Fragkiadaki, P.; Tsoukalas, D.; Fragkiadoulaki, I.; Psycharakis, C.; Nikitovic, D.; Spandidos, D.A.; Tsatsakis, A.M. Telomerase activity in pregnancy complications (Review). *Mol. Med. Rep.* **2016**, *14*, 16–21. [CrossRef]
61. Gielen, M.; Hageman, G.; Pachen, D.; Derom, C.; Vlietinck, R.; Zeegers, M.P. Placental telomere length decreases with gestational age and is influenced by parity: A study of third trimester live-born twins. *Placenta* **2014**, *35*, 791–796. [CrossRef]
62. Gluckman, P.D.; Hanson, M.A.; Beedle, A.S. Early life events and their consequences for later disease: A life history and evolutionary perspective. *Am. J. Hum. Biol.* **2007**, *19*, 1–19. [CrossRef]
63. Bosquet Enlow, M.; Petty, C.R.; Hacker, M.R.; Burris, H.H. Maternal psychosocial functioning, obstetric health history, and newborn telomere length. *Psychoneuroendocrinology* **2021**, *123*, 105043. [CrossRef]
64. Ridout, K.K.; Syed, S.A.; Kao, H.; Porton, B.; Rozenboym, A.V.; Tang, J.; Fulton, S.; Perera, T.; Jackowski, A.P.; Kral, J.G.; et al. Relationships between telomere length, plasma glucagon-like peptide 1, and insulin in early-life stress–exposed nonhuman primates. *Biol. Psychiatry Glob. Open Sci.* **2022**, *2*, 54–60. [CrossRef]
65. Ameer, S.S.; Xu, Y.; Engström, K.; Li, H.; Tallving, P.; Nermell, B.; Boemo, A.; Parada, L.A.; Peñaloza, L.G.; Concha, G.; et al. Exposure to Inorganic Arsenic Is Associated with Increased Mitochondrial DNA Copy Number and Longer Telomere Length in Peripheral Blood. *Front. Cell Dev. Biol.* **2016**, *4*, 87. [CrossRef]
66. Bassig, B.A.; Zhang, L.; Cawthon, R.M.; Smith, M.T.; Yin, S.; Li, G.; Hu, W.; Shen, M.; Rappaport, S.; Barone-Adesi, F.; et al. Alterations in leukocyte telomere length in workers occupationally exposed to benzene. *Environ. Mol. Mutagen.* **2014**, *55*, 673–678. [CrossRef]
67. Mitro, S.D.; Birnbaum, L.S.; Needham, B.L.; Zota, A.R. Cross-sectional Associations between Exposure to Persistent Organic Pollutants and Leukocyte Telomere Length among, U.S. Adults in NHANES, 2001–2002. *Environ. Health Perspect.* **2016**, *124*, 651–658. [CrossRef]
68. Jimenez Villarreal, J.; Murillo Ortiz, B.; Martinez Garza, S.; Rivas Armendáriz, D.I.; Boone Villa, V.D.; Carranza Rosales, P.; Betancourt Martínez, N.D.; Delgado Aguirre, H.; Morán Martínez, J. Telomere length analysis in residents of a community exposed to arsenic. *J. Biochem. Mol. Toxicol.* **2018**, *33*, e22230. [CrossRef]
69. Haycock, P.C.; Burgess, S.; Nounu, A.; Zheng, J.; Okoli, G.N.; Bowden, J.; Wade, K.H.; Timpson, N.J.; Evans, D.M.; Willeit, P.; et al. Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. *JAMA Oncol.* **2017**, *3*, 636–651. [CrossRef]
70. Zhang, E.; Bell, A.J.; Wilkie, G.S.; Suárez, N.M.; Batini, C.; Veal, C.D.; Armendáriz-Castillo, I.; Neumann, R.; Cotton, V.E.; Huang, Y.; et al. Inherited Chromosomally Integrated Human Herpesvirus 6 Genomes Are Ancient, Intact, and Potentially Able To Reactivate from Telomeres. *J. Virol.* **2017**, *91*, e01137-17. [CrossRef]
71. Ämmälä, A.J.; Vitikainen, E.I.K.; Hovatta, I.; Paavonen, J.; Saarenpää-Heikkilä, O.; Kylliäinen, A.; Pölkki, P.; Porkka-Heiskanen, T.; Paunio, T. Maternal stress or sleep during pregnancy are not reflected on telomere length of newborns. *Sci. Rep.* **2020**, *10*, 13986. [CrossRef]
72. Wojcicki, J.M.; Heyman, M.B.; Elwan, D.; Shiboski, S.; Lin, J.; Blackburn, E.; Epel, E. Telomere length is associated with oppositional defiant behavior and maternal clinical depression in Latino preschool children. *Transl. Psychiatry* **2015**, *5*, e581. [CrossRef]
73. Bosquet Enlow, M.; Bollati, V.; Sideridis, G.; Flom, J.D.; Hoxha, M.; Hacker, M.R.; Wright, R.J. Sex differences in effects of maternal risk and protective factors in childhood and pregnancy on newborn telomere length. *Psychoneuroendocrinology* **2018**, *95*, 74–85. [CrossRef]
74. García-Martín, I.; Penketh, R.; Garay, S.; Jones, R.; Grimstead, J.; Baird, D.; John, R. Symptoms of Prenatal Depression Associated with Shorter Telomeres in Female Placenta. *Int. J. Mol. Sci.* **2021**, *22*, 7458. [CrossRef]
75. Eisenberg, D.T.A.; Kuzawa, C.W. The paternal age at conception effect on offspring telomere length: Mechanistic, comparative and adaptive perspectives. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2018**, *373*, 20160442. [CrossRef] [PubMed]

76. Chen, L.; Tan, K.M.L.; Gong, M.; Chong, M.F.F.; Tan, K.H.; Chong, Y.S.; Meaney, M.J.; Gluckman, P.D.; Eriksson, J.G.; Karnani, N. Variability in newborn telomere length is explained by inheritance and intrauterine environment. *BMC Med.* **2022**, *20*, 20. [CrossRef] [PubMed]
77. Lee, S.P.; Hande, P.; Yeo, G.S.; Tan, E.C. Correlation of cord blood telomere length with birth weight. *BMC Res. Notes* **2017**, *10*, 469. [CrossRef] [PubMed]
78. Verner, G.; Epel, E.; Lahti-Pulkkinen, M.; Kajantie, E.; Buss, C.; Lin, J.; Blackburn, E.; Räikkönen, K.; Wadhwa, P.D.; Entringer, S. Maternal Psychological Resilience During Pregnancy and Newborn Telomere Length: A Prospective Study. *Am. J. Psychiatry* **2021**, *178*, 183–192. [CrossRef]
79. Herlin, M.; Broberg, K.; Igra, A.M.; Li, H.; Harari, F.; Vahter, M. Exploring telomere length in mother-newborn pairs in relation to exposure to multiple toxic metals and potential modifying effects by nutritional factors. *BMC Med.* **2019**, *17*, 77. [CrossRef] [PubMed]
80. Aviv, A. Telomeres, sex, reactive oxygen species, and human cardiovascular aging. *J. Mol. Med.* **2002**, *80*, 689–695. [CrossRef]
81. Revesz, D.; Verhoeven, J.E.; Milaneschi, Y. Penninx BW Depressive and anxiety disorders and short leukocyte telomere length: Mediating effects of metabolic stress and lifestyle factors. *Psychol. Med.* **2016**, *46*, 2337–2349. [CrossRef]
82. Colatto, B.N.; de Souza, I.F.; Schinke, L.A.A.; Noda-Nicolau, N.M.; da Silva, M.G.; Morceli, G.; Menon, R.; Polettini, J. Telomere Length and Telomerase Activity in Foetal Membranes from Term and Spontaneous Preterm Births. *Reprod. Sci.* **2020**, *27*, 411–417. [CrossRef]
83. Houminer-Klepar, N.; Bord, S.; Epel, E.; Baron-Epel, O. Are pregnancy and parity associated with telomere length? A systematic review. *BMC Pregnancy Childbirth* **2023**, *23*, 733. [CrossRef]
84. Cheng, S.-B.; Davis, S.; Sharma, S. Maternal-fetal cross talk through cell-free fetal, D.N.A.; telomere shortening, microchimerism, and inflammation. *Am. J. Reprod. Immunol.* **2018**, *79*, e12851. [CrossRef]
85. Lazarides, C.; Epel, E.S.; Lin, J.; Blackburn, E.H.; Voelkle, M.C.; Buss, C.; Simhan, H.N.; Wadhwa, P.D.; Entringer, S. Maternal pro-inflammatory state during pregnancy and newborn leukocyte telomere length: A prospective investigation. *Brain Behav. Immun.* **2019**, *80*, 419–426. [CrossRef]
86. Balan, E.; Decottignies, A.; Deldicque, L. Physical Activity and Nutrition: Two Promising Strategies for Telomere Maintenance? *Nutrients* **2018**, *10*, 1942. [CrossRef] [PubMed]
87. Lis, N.; Lamnisos, D.; Bograkou-Tzanetakou, A.; Hadjimbei, E.; Tzanetakou, I.P. Preterm Birth and Its Association with Maternal Diet, and Placental and Neonatal Telomere Length. *Nutrients* **2023**, *15*, 4975. [CrossRef] [PubMed]
88. Wilson, W.E.; Mage, D.T.; Grant, L.D. Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: Why and how. *J. Air Waste Manag. Assoc.* **2000**, *50*, 1167–1183. [CrossRef] [PubMed]