Original Article

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# The Relationships Between Prenatal Smoking Exposure and Telomere Lengths in Fetuses, Infants, and Children

*A Systematic Literature Review*

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## Abstract

**Objective:** The aim of this study was to evaluate the relationships between prenatal smoking exposure and telomere lengths (TLs) in fetuses, infants, and children.

**Methods:** This is a systematic review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Databases searched were Biomedical Reference Collection, MEDLINE via PubMed, CINAHL, PsycINFO, and Google Scholar. The latest search was on October 18, 2019.

**Results:** Seven studies met the inclusion criteria and thus were reviewed. Five of the studies showed significant inverse relationships between prenatal tobacco exposure and TLs in fetuses, infants, and children. One study showed a modification effect of the postconceptual age, indicating that older fetuses with prenatal smoking exposure had shorter TLs than their counterparts. This effect was more prominent after 93 days of postconception. Another study reported a finding that was contrary to the above results, showing that the telomeres of newborns with prenatal smoking exposure were longer than those of their counterparts.

**Conclusion/Recommendations:** This review shows that the impact of prenatal smoking on the health of unborn fetuses, infants, and children is an understudied area. Because of the inconsistent findings and cross-sectional study designs, more research is required, especially longitudinally studies. Nonetheless, the findings of the review provide partial evidence that prenatal smoking can potentially impact the genetic biomarker, TLs, and, thus, health of fetuses, infants, and children. The evidence confirms the current practice that pregnant women should be encouraged to stop smoking as soon as they become pregnant.

**Keywords:** children health, maternal smoking, prenatal tobacco, telomere length

## INTRODUCTION

Smoking is known to be harmful to health. Inhaled tobacco smoke is an aerosol that comprises the mixtures of combustion gases, semivolatile compounds, and liquid droplets, the aggregation of which become mutagenic, cytotoxic, and proinflammatory (Morse & Rosas, 2014). Smoking can cause lung diseases, heart disease, cancer, stroke, diabetes, and chronic obstructive pulmonary diseases, such as emphysema and chronic bronchitis (Centers for Disease Control and Prevention [CDC], 2019). More than 16 million Americans are currently living with a disease that is caused by smoking (CDC, 2019). Tobacco smoking affects not only the people who smoke but also the ones surrounding them with secondhand smoke, including fetuses, infants, and children.

Smoking is also linked to damaging effects at the cellular level, such as accelerated telomere attrition and shortening (Astuti et al., 2017; Aviv et al., 2009; Verde et al., 2015). Telomeres are deoxyribonucleic acid repeat sequences located at each end of chromosomes, assembled in complex structures to form a cap protecting chromosomes. Telomeres are progressively shortened by each cell division, and when telomeres reach a critically short length, cellular senescence (the process of cellular deterioration) occurs (Aviv et al., 2015; Blackburn et al., 2015).

Telomeres are considered to play an important role in maintaining human genomic integrity and health. Epidemiological studies find that shorter telomere length (TL) is associated with an increased risk of some common diseases, such as cardiovascular disease, diabetes, and some cancer (Barrett et al., 2015). Besides the natural process of aging that leads to telomere shortening, other factors can accelerate telomere shortening. One of the factors is oxidative stress, the imbalance between stressors that are toxic to living cells and the body's antioxidant defense mechanisms (Aviv & Shay, 2018;

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Coluzzi et al., 2019). Cigarette smoking is known to increase oxidative stress and associated with telomere shortening in adults.

It is known that exposures in early life can impact adult chronic illnesses. Prenatal smoking or tobacco use during pregnancy has been identified as a significant risk factor for developing fetuses, resulting in fetal growth restriction, congenital defects, low birth weight, and premature birth, and also for newborns and children, leading to health issues such as neurodevelopmental issues and diabetes (Banderali et al., 2015). The question is whether maternal smoking exposure during pregnancy can affect the TL in fetuses, infants, and children. Changes in TL during early lives may be indicative of an increased incidence of chronic disease in adulthood (Bezruchka, 2015; Price et al., 2013).

Knowledge about the impact of prenatal smoking on the health of unborn fetuses, infants, and children is important because it can provide evidence for clinical practice and interventions. Two review articles (Oerther & Lorenz, 2019; Werlang et al., 2019) have been published about the impact of various maternal exposures on child telomere attritions, which, however, were not specifically about smoking. Therefore, the purpose of this review was to evaluate the relationships between prenatal smoking exposures and TL in fetuses, infants, and children.

## METHODS

### Design

This is a systematic literature review. The process of literature search was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009). The strategies of the search were developed by the first author and university research librarians.

### Search Process

The literature search was performed using the first author's university library website. Databases searched were Biomedical Reference Collection, MEDLINE via PubMed, CINAHL, PsycINFO, and Google Scholar, with the following search terms and keywords: "telomere*," "telomere length," "maternal," "newborn or neonate or infant or baby," "child*," "tobacco," "smoke," "pregnant," "pregnancy," and "prenatal smoking." In PubMed, the following MeSH headings were used to conduct the search: "Telomere" [Mesh] and "Telomere Shortening" [Mesh]; (("Smoking"[Mesh] OR "Tobacco Smoking" [Mesh] OR "Cigarette Smoking" [Mesh]) AND ("Pregnancy" [Mesh] OR "Mothers" [Mesh] OR "Maternal Exposure" [Mesh] OR "Maternal Behavior" [Mesh] OR "Maternal Health" [Mesh]); "Fetus" [Mesh] "Infant, Newborn" [Mesh] "Infant" [Mesh] "Child" [Mesh]. The keywords and terms were entered into the databases in various combinations to ensure an exhaustive search, with no time limit applied.

Records were deduplicated using the built-in mechanisms of the university library system and further completed manually. Articles were then assessed by their titles and abstracts for inclusion. Final selections were determined after the full-text reading of the articles. A supplementary search was performed in Google Scholar to locate gray literature and any articles not captured in database searches. Because of Google Scholar's relevance ranking, the first five pages (about 50 results) were reviewed to identify potential articles for full-text review. A subsequent reference list search was performed to identify other possible articles. The latest search was conducted on October 18, 2019, with no time limit applied. To be included, the studies should be empirical studies that reported TLs of fetuses, infants, and children younger than 18 years old who were exposed to smoking during pregnancy. Exclusion criteria were articles focused on the effects of tobacco on adults older than 18 years old.

### Data Analysis

We conducted the data analysis following the processes of extracting, compiling, and summarizing data recommended by Garrard (2017). The following information was extracted from the studies: purpose, country where the study was conducted, population, sample size, method of maternal smoking evaluation, source of telomere sample, method of TL measurement, and major findings regarding TL. Data extraction was conducted by two of the authors (H. W. and P. S.). The results of the extraction were cross-checked by the two authors. Disagreements were resolved by reading and discussing the original studies. The findings relevant to the impact of prenatal smoking on TL were compiled in Table 1 and summarized in the Results section. Because of the heterogeneity of the source of the telomeres extracted, we synthesized the findings narratively based on the age of the offspring.

### Quality Assessment

The quality of the articles was assessed based on the following five criteria: (a) the relevance of the sampling strategy to address the research question, (b) the representation of the sample on the target population, (c) the appropriateness of the measurements, (d) the risk of nonresponse bias, and (e) the suitability of the statistical analysis to answer the research question (Hong et al., 2018). Each criterion was worth 20%, for a total of 100%. The higher an article scored, the better the quality. The scores are reported in Table 2.

## RESULTS

After a thorough search, seven articles met the inclusion criteria and were included in this review. As shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses chart (see Figure 1), the initial search generated 128 studies. Seventy-four articles remained after duplicates were removed. After titles and abstracts were screened, 10 articles were left for full-text review, after which seven studies met the inclusion criteria and were included in the review. Because of the heterogeneity of the tissue sources for telomere measures, we could not conduct a meta-analysis, and thus, we organized and described the findings narratively according to the target population: fetuses (Mirzakhani et al.,

**TABLE 1 Data Extracted From the Studies in the Review**

| First Author (Year), Country | Purpose of the Study | Study Design and Sample | Tissue Source and Telomere Measure | Findings Related to Telomere |
|---|---|---|---|---|
| Almanzar et al. (2013), Austria | To analyze the peripheral lymphocyte of smoking and nonsmoking mothers and their newborns' relative telomere lengths and the serum cytokine concentrations | • Cross-sectional study<br>• Sample:<br>○ 169 newborn infants<br>○ Nonsmoking mothers: 111<br>○ Smoking mothers: 58<br>○ Smoking and nonsmoking mothers and their newborns were recruited at the Department of Gynecology and Obstetrics. | Lymphocytes from venous blood or cord blood<br>qPCR | • The newborns had significantly longer telomeres than their mothers.<br>• The newborns of smoking mothers had significantly longer telomeres than newborns of nonsmoking mothers ($p < .01$). |
| Bosquet Enlow et al. (2018), United States | To test the associations of maternal risk and protective factors in childhood and in pregnancy and newborn telomere length. | • Cross-sectional study<br>• Sample:<br>○ 151 sociodemographically diverse mother–infant dyads<br>○ Maternal cigarette smoking in pregnancy: 32 (21%) | Cord blood<br>qPCR | • Newborns' cord blood relative telomere length was negatively associated with maternal smoking in pregnancy and positively associated with maternal familial emotional support in childhood. |
| Ip et al. (2017); Hong Kong, China | To investigate the impact of prenatal tobacco exposure on a child's telomere length | • Cross-sectional study<br>• Sample:<br>○ 196 children recruited from the Hong Kong Child Health Survey<br>○ Children with tobacco exposure: 98<br>○ Children of age- and gender-matched controls: 98<br>○ The overall mean age: 6.33 ± 3.85 years | Buccal epithelial cells qPCR | • Telomere length in children who were exposed to prenatal smoking was significantly shorter than that in children who had no exposure to prenatal smoking.<br>• There was a negative dose–response relationship between the T/S ratio and the duration of tobacco exposure: the longer the duration of prenatal smoking, the shorter the child's telomere length. |
| Liu et al. (2019), China | To examine the association between prenatal secondhand smoke exposure and newborn telomere length | • Cross-sectional study<br>• Sample:<br>○ 746 mother–newborn pairs from a children's hospital between November 2013 and March 2015<br>○ With exposure to secondhand smoke: $n = 244$ (32.7%)<br>○ Without exposure to secondhand smoke: $n = 502$ (67.3%)<br>○ Information on secondhand smoke exposure was obtained via questionnaires. | Umbilical cord blood<br>qPCR assays | • Prenatal secondhand smoke exposure resulted in 9.7% shorter newborn telomere length than the newborns with no secondhand smoke exposure.<br>• Boys had lower estimates than girls, but there were no interactions between newborn gender and prenatal secondhand smoke ($p = .751$). |

*(continues)*

**TABLE 1 Data Extracted From the Studies in the Review, Continued**

| First Author (Year), Country | Purpose of the Study | Study Design and Sample | Tissue Source and Telomere Measure | Findings Related to Telomere |
|---|---|---|---|---|
| Mirzakhani et al. (2017), United States | To investigate the association of intrauterine fetal exposure to tobacco smoking during the early weeks of pregnancy and the relative telomere length (T/S ratio) as compared with fetuses without exposure to tobacco smoking | • Cross-sectional study<br>• Sample:<br>○ 207 fetal lung tissue collected from elective abortions between 2 and 6 hours postmortem<br>○ With intrauterine tobacco exposure: 96<br>○ Without intrauterine tobacco exposure: 111<br>• Maternal smoking status was determined by placenta cotinine levels, with the cutoff level being set at 7.53 ng/g.<br>• The postconception ages for the samples ranged from 54 to 137 days (7–19 weeks) of gestation. | Fetal lung tissues qPCR | • When comparing the samples as a whole, the T/S ratio was not significantly different between those with and without smoking exposures.<br>• However, there was a significant modification effect of the postconception age on the association of smoking exposure on T/S ratio, which was after 93 days of postconceptual age.<br>• Shorter relative telomere lengths were observed with the increase of postconception age between 93 and 137 days. |
| Salihu et al. (2015), United States | To investigate whether maternal smoking during pregnancy affects telomere length of the fetus | • Cross-sectional study<br>• 86 newborn infants<br>○ Infants of nonsmoking mothers: 25<br>○ Infants of passive smoking mothers: 31<br>○ Infants of active smoking mothers: 30<br>• Mothers of the newborns were >18 years old and delivered singleton full-term live births with no evidence of congenital and/or chromosomal anomalies.<br>• Maternal smoking was determined by a questionnaire and a salivary cotinine test. | Cord blood qPCR | • There was a reverse relationship between maternal smoking and fetal telomere length, with a dose–response effect.<br>• Maternal tobacco exposure was likely associated with the early intrauterine programming for accelerated aging. |

*(continues)*

**TABLE 1 Data Extracted From the Studies in the Review, Continued**

| First Author (Year), Country | Purpose of the Study | Study Design and Sample | Tissue Source and Telomere Measure | Findings Related to Telomere |
|---|---|---|---|---|
| Theall et al. (2013), United States | To examine the association between telomere length and prenatal tobacco exposure in children | • Cross-sectional study<br>• 101 children of African American descendants aged 4–14 years<br>○ Children with prenatal tobacco exposure: 19<br>○ Children with no prenatal tobacco exposure: 82<br>• Children were recruited from the public schools in New Orleans, Louisiana. | Saliva<br>qPCR | • The relative salivary telomere length was 7.3 ± 2.4, ranging from 2.5 to 18.0.<br>• Overall, 61.4% of the children had low relative salivary telomere length. Among these children, 19 (18.8%) children were prenatally exposed to tobacco smoke at home, and seven (6.8%) children were also exposed to maternal smoking.<br>• The mean salivary telomere length was significantly shorter among children exposed to smoke during pregnancy than their counterparts.<br>• Children exposed to prenatal tobacco exposure were nearly 3 times more likely to have short salivary telomere length than those not exposed to smoke prenatally. |

*Note.* qPCR = quantitative polymerase chain reaction; T/S = telomere-to-single copy.

2017), newborn infants (Almanzar et al., 2013; Bosquet Enlow et al., 2018; Liu et al., 2019; Salihu et al., 2015), and children (Ip et al., 2017; Theall et al., 2013).

## The Effects of Prenatal Smoking on Fetuses' TLs

Mirzakhani et al. (2017) examined the relationships between tobacco exposure during early pregnancy and fetal TLs measured as the fetal telomere-to-single copy (T/S) ratio. The researchers extracted telomeres from the lung tissues of the fetuses of elective abortions and measured the telomeres using quantitative real-time polymerase chain reaction. The study included 207 epithelial lung samples, 47.37% of which were female. The postconception ages for the samples were estimated to be between 54 and 137 days. Maternal cotinine exposure status was determined and confirmed by the test of placental cotinine levels (nanograms per gram of total placental tissue) in the whole-cell extracts from the placenta samples. The cutoff placenta cotinine level was set at 7.53 ng/g. On the basis of the cutoff value, 96 fetal samples were identified as positive with intrauterine tobacco exposure, and 111 fetal samples were below the cutoff level. There were no significant differences in demographics, such as gender and postconception age, between the groups of smoking exposure and nonexposure.

The researchers of the study (Mirzakhani et al., 2017) tested the TL (T/S ratio) at the baseline age, postconception age of 54–59 days, and did not find significant differences between the two groups ($p = .7$). The postconceptual age, however, had a modification effect on the relationship between fetal smoking exposure and T/S ratio (adjusted estimate = −0.008, 95% CI [−0.016, −0.0003]). Older fetuses with smoking exposure showed shorter TLs than their counterparts, and the effect was more prominent after 93 days postconception, which elucidated the potential impact of the duration of smoking exposure on TL.

## The Effects of Prenatal Smoking on Newborn Infants' TLs

Four studies (Almanzar et al., 2013; Bosquet Enlow et al., 2018; Liu et al., 2019; Salihu et al., 2015) examined the effects of maternal prenatal tobacco use on newborn infants' TLs, the

**TABLE 2 Quality Assessment**

| Quality Assessment Criteria | Almanzar et al. (2013), Austria | Bosquet Enlow et al. (2018), United States | IP et al. (2017), Hong Kong, China | Liu et al. (2019), China | Mirzakhani et al. (2017), United States | Salihu et al. (2015), United States | Theall et al. (2013), United States |
|---|---|---|---|---|---|---|---|
| 1. The relevance of the sampling strategy to address the research question | 20% | 20% | 20% | 20% | 20% | 20% | 20% |
| 2. The representation of the sample on the target population | 15% Only Whites were enrolled | 20% | 20% | 20% | 20% | 20% | 20% |
| 3. The appropriateness of the measurements | 20% | 20% | 20% | 20% | 20% | 20% | 20% |
| 4. The risk of nonresponse bias | Could not be found in the article | 20% | Could not be found in the article | Could not be found in the article | Could not be found in the article | Could not be found in the article | Could not be found in the article |
| 5. The suitability of statistical analysis to answer the research question | 20% | 20% | 20% | 20% | 20% | 20% | 20% |
| Total scores of each article | 75% | 100% | 80% | 80% | 80% | 80% | 80% |

The quality of the articles was assessed based on the following five criteria: (a) the relevance of the sampling strategy to address the research question, (b) the representation of the sample on the target population, (c) the appropriateness of the measurements, (d) the risk of nonresponse bias, and (e) the suitability of the statistical analysis to answer the research question. Each criterion was worth 20%, for a total of 100%. The higher an article scored, the better the quality.

results of which, however, were contradictive. Almanzar et al. (2013) analyzed the relative TL of smoking and nonsmoking mothers and their newborns. The researchers included 169 mother–infant dyads (111 nonsmoking mothers and 58 smoking mothers). The study did not find significant effects of smoking on TL when comparing the newborns of mothers who smoked or who did not smoke during pregnancy. Surprisingly, the telomeres of the newborns of smoking mothers were found to be significantly longer than those of their counterparts. In a multiple regression analysis, the results of TL did not change by the entry or removal of other variables such as mothers' age at delivery, gestational age, newborns' gender, birth weight and length, infants' head circumference, and appearance, pulse, grimace, activity, and respiration scores (1 and 5 minutes).

Bosquet Enlow et al. (2018) tested maternal risk and protective factors in their childhood and pregnancy that were linked to newborn TL. The data analysis of the study included 151 mother–infant dyads with diverse sociodemographical background, with 32 (21%) mothers reporting cigarette smoking in pregnancy. Newborn TL was tested via cord blood at birth. Among the risk/protective factors, only maternal smoking during pregnancy and familial emotional support in childhood were significant predictors of newborn TL. Among male newborns, maternal smoking, higher body mass index, and elevated depressive symptoms during pregnancy, as well as maternal sexual abuse in childhood, were correlated with shorter newborn TL. Higher maternal education and household income and greater family emotional support in childhood were related to longer newborn TL. However, female newborn TL was not affected by any of the risk and protective factors.

Liu et al. (2019) examined the relationship between prenatal secondhand smoke exposure and newborn TL. The researchers recruited 762 mother–newborn dyads between November 2013 and March 2015. Relative TL was measured via umbilical cord blood. The data analysis was based on 746 samples, 244 (32.7%) with exposure to secondhand smoke and 502 (67.3%) without exposure to secondhand smoke. Sixteen participants' samples were excluded because DNA samples were not available for telomere measurement. The results showed that prenatal secondhand smoke exposure resulted in 9.7% shorter newborn TL (percent difference:

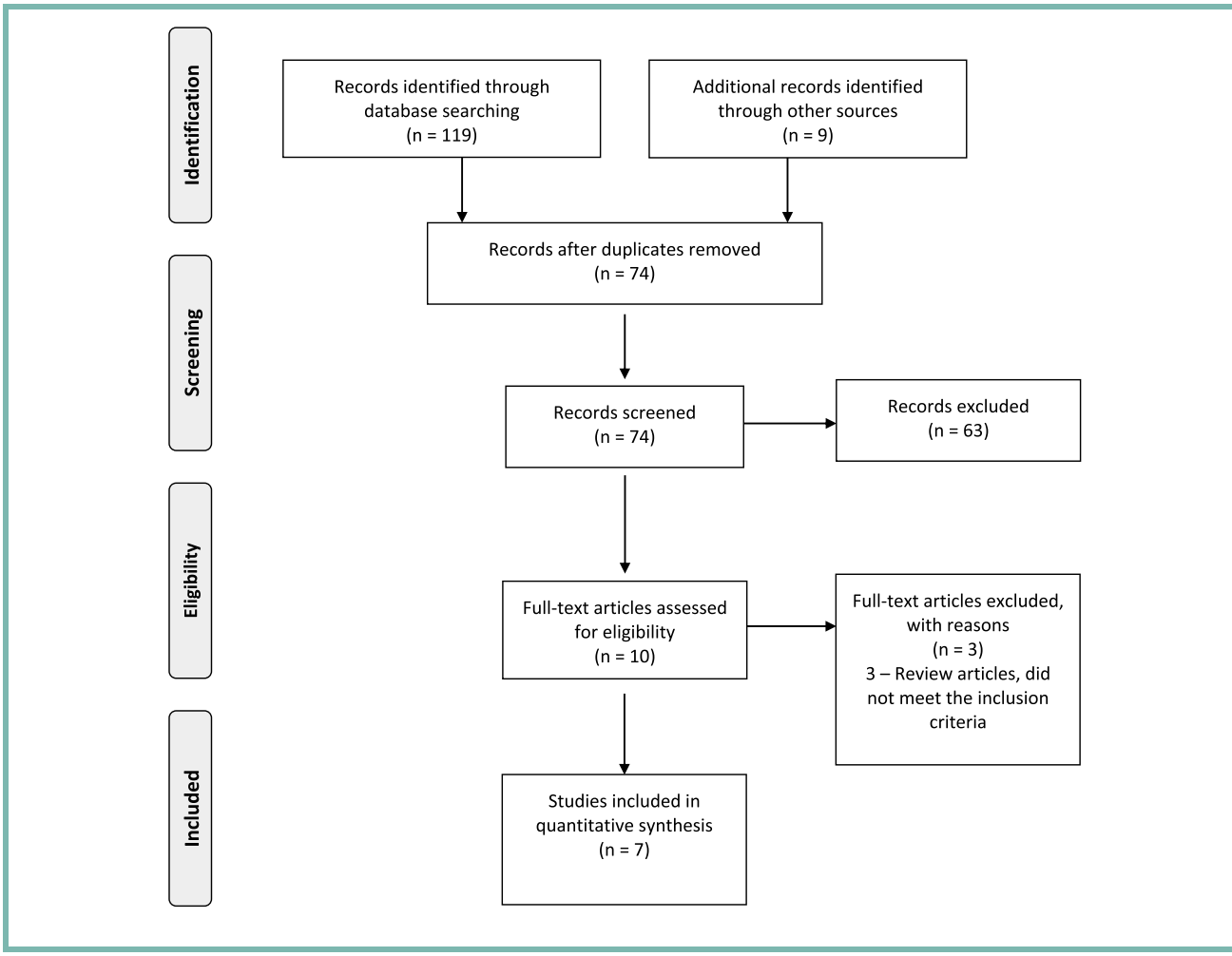


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the process of literature search.

−9.7%, 95% CI [−15.0, −4.0]) than the newborns with no secondhand smoke exposure. Boys had lower TL estimates than girls, but there were no interactions between newborn sex and prenatal secondhand smoke ($p = .751$).

Salihu et al. (2015) examined cord blood of 86 newborn infants, including 25 of nonsmoking mothers, 31 of passive smoking mothers, and 30 of active smoking mothers. In this study, the researchers found an inverse relationship between maternal smoking during pregnancy and fetal TL. Furthermore, the effects of maternal prenatal smoking had a negative dose–response pattern, meaning that TL (T/S ratio) of the newborn infants of nonsmokers was longer than that of passive smoking mothers, which was longer than that of active smoking mothers. According to the pairwise comparisons, the greatest difference of TL was between the newborns of nonsmoking and active smoking mothers.

## The Effects of Prenatal Smoking on Children's TLs

Ip et al. (2017) investigated the impact of tobacco exposure during pregnancy on the TL of children under 15 years old. The researchers of the study recruited 196 Hong Kong Chinese children from the Hong Kong Child Health Survey, a population-based household survey. Among the 196 children, 98 had prenatal tobacco exposure, and 98 were age- and gender-matched controls. The children had a mean age of 6.33 ± 3.85 years. The recruitment took place between September 2005 and August 2006. The study reported a significant difference in TL between the two groups of children. TL was significantly shorter in children with prenatal tobacco exposure than the ones without (mean T/S ratio = 24.9 ± 8.58 in children with tobacco exposure vs. 28.97 ± 14.15 in controls; $p = .02$). There was an inverse dose–response relationship between the extent of tobacco exposure prenatally and the T/S ratio: The longer the time of prenatal tobacco exposure, the shorter the children's TL. The inverse dose–response relationship stayed significant after other factors were taken into consideration, such as family socioeconomic status and environmental tobacco exposure prenatally and during childhood.

Theall et al. (2013) studied the relationship between mothers' tobacco exposure during pregnancy and TL in African American children aged 4–14 years. The researchers recruited 92 children from the public schools in New Orleans, Louisiana, from January through May 2010. Among the 92

children, 19 were exposed to secondhand smoking at home, and seven were exposed to maternal smoking during pregnancy. They collected children's sputum and extracted DNA to measure TL in children's salivary cells. They reported the average relative TL as T/S ratio. The mean relative salivary TL in children exposed to prenatal smoke was significantly shorter than that of their counterparts ($p < .05$). In addition, a higher proportion of children exposed to prenatal smoking had short salivary telomeres than those not exposed, 79% versus 57.3%, respectively ($p < .05$). Finally, children exposed to prenatal smoking were about 3 times more likely to have shorter salivary TL than those who were not exposed to prenatal smoking (crude odds ratio = 2.47, 95% CI [0.81, 7.51], $p = .11$).

## DISCUSSION

Cigarette smoking has long been known as a risk factor to health. Studies in this review, however, had controversial findings of the effects of prenatal smoking on the TL in newborns. Five of the seven studies reviewed showed significant inverse relationships between prenatal exposure to smoking and the TL in newborn infants (Bosquet Enlow et al., 2018; Liu et al., 2019; Salihu et al., 2015) and children (Ip et al., 2017; Theall et al., 2013). The study by Mirzakhani et al. (2017) revealed no overall differences between in-utero exposed and unexposed groups but reported a modification effect of postconceptual age on fetuses' TLs, showing that older fetuses with smoking exposure showed shorter TLs than their counterparts, and the effect was more prominent after 3 months postconception. In addition, one study (Almanzar et al., 2013) had an opposite finding, which reported that newborns of mothers who smoked during pregnancy had longer TLs than their counterparts. The authors contended that other confounding factors could be responsible for the observed discrepancies, such as different populations and different tissues to measure TL—lymphocytes from venous blood or cord blood.

This review indicated an understudied area related to the impact of prenatal smoking on the telomeres in fetuses, infants, and children and a need for more studies assessing effects at different stages of child development. Nonetheless, this review aggregated some evidence that prenatal smoking could start to have negative effects on fetuses' TLs from 3 months postconception. The impact of prenatal smoking exposure could be seen in infants, children, and teenage years. These findings were consistent with the findings in adult studies that telomeres were found shorter in adult ever-smokers than never-smokers (Astuti et al., 2017; Verde et al., 2015). The findings of this review went upstream and helped us see the progressive effects of the impact of prenatal smoking exposure across childhood, which could be a support for the findings in adult studies and provided evidence from a DNA level to support the initiative of no-smoking during pregnancy.

Smoking affects not only the people who smoke but also the ones exposed to it. This review, although the results were not conclusive, did find a direct relationship between prenatal smoking exposure and telomere attrition in fetuses, infants, and children. Reducing smoking and encouraging smoking cessation during pregnancy has been a national goal for Healthy People initiatives through the years (HealthyPeople.gov, 2019). Although great strides have been made in recent years, smoking continues to be a significant factor in population health. A report released by the CDC of the United States shows that the average rate of prenatal smoking is 7.2%; however, in some areas of the country, this number can be as high or more than 20% (Drake et al., 2018; North Carolina State Center for Health Statistics, 2019). According to the CDC report by Drake et al. (2018), the prevalence of prenatal smoking was highest for women between 20 and 24 years old (10.7%) and followed by women between 15 and 19 years old (8.5%) and between 25 and 29 years old (8.2%). Promoting pregnant women's and children's health is a significant goal of population health.

This review has extended the knowledge gained from adult smoking studies and indicated additional evidence of the negative impact of maternal prenatal smoking and maternal–child transmission at the cellular level. Accelerated telomere shortening has been connected to several human illnesses, mortality, and aging. Maternal prenatal smoking could set the trajectory for shortened telomeres early in life. Human health and illnesses are determined by many factors, including genetics and epigenetics, in addition to which, environmental factors play a significant role by altering TL (Savage, 2018; Slatter et al., 2014). The intrauterine milieu is the immediate environment for fetuses. Thus, it is important for pregnant women to understand the importance to cease smoking as soon as they know that they are pregnant (Drake et al., 2018; North Carolina State Center for Health Statistics, 2019). In addition to the negative impact on cellular telomere attrition, maternal prenatal smoking is also linked to preterm birth, fetal growth retardation, sudden infant death syndrome, and other illnesses such as children's neurodevelopmental and behavioral issues, obesity, hypertension, diabetes, lung dysfunction, wheezing, and asthma (Banderali et al., 2015).

### Limitations

One limitation of the review is the variety of the studies reviewed. The studies in this review included diverse populations of races and ethnicities; measured telomeres from different biofluids, including saliva, sputum, buccal epithelial cells, and blood; and compiled various age groups in childhood. The variety might have contributed to the varied findings. Nonetheless, most of the studies reviewed showed that TL was inversely correlated to the duration of maternal smoking. The longer the duration mothers smoked during pregnancy, the shorter the TL of the fetuses, newborns, and children (Ip et al., 2017; Mirzakhani et al., 2017; Salihu et al., 2015). The findings could provide evidence that pregnant women should be advised and encouraged to stop smoking as soon as they become pregnant.

Although we conducted an exhaustive search for literature on the effects of smoking on TL in infants and children, only seven studies emerged. A meta-analysis could not be performed

because of the heterogeneity of the tissues used to extract telomeres—fetal lung tissue (1/7), cord blood (4/7), buccal epithelial cells (1/7), and saliva (1/7). The main design of the studies was cross-sectional, making it hard to determine the cause–effect relationships between prenatal tobacco use/exposure and TL in fetuses, infants, and children. We recommend that future studies follow up with children who are exposed to smoking prenatally and examine their TL and health longitudinally. Another way to move this area forward is to have more studies using the same source for telomere extraction, in which case, meta-analyses could be conducted to provide stronger evidence for practice.

## CONCLUSIONS/RECOMMENDATION

This review shows that the impact of prenatal smoking on the health of unborn fetuses, infants, and children is an understudied area. Although cigarette smoking has been recognized as a significant source of illnesses for adults, no conclusive results can be reached that prenatal smoking leads to telomere shortening in fetuses, especially. Because of the inconsistent findings and cross-sectional designs, more research is needed, especially longitudinally studies. Nonetheless, the findings of the review can provide partial evidence that prenatal smoking could potentially impact the genetic biomarker, TL, and health of fetuses and children. Thus, the evidence confirms the current practice that pregnant women should be encouraged to stop smoking as soon as they become pregnant.

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