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POPULATION STUDY ARTICLE

Prenatal second-hand smoke exposure and newborn telomere length

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BACKGROUND: Cigarette smoking is associated with shorter telomere lengths in adults, but evidence on the effect of prenatal tobacco exposure is limited. We aimed to investigate the association between prenatal second-hand smoke exposure and newborn telomere length.

METHODS: We recruited 762 mother–newborn pairs from Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital) between November 2013 and March 2015. Information on second-hand smoke exposure was obtained via questionnaires. Relative telomere length was measured in DNA extracted from umbilical cord blood. We used linear regression to assess the associations between prenatal second-hand smoke exposure and newborn telomere length.

RESULTS: In the fully adjusted model, prenatal second-hand smoke exposure was associated with 9.7% shorter newborn telomere length (percent difference: −9.7%; 95% confidence interval (CI): −15.0, −4.0). The estimate for boys was lower (percent difference: −10.9%; 95% CI: −18.6, −2.5) than that for girls (percent difference: −8.5%; 95% CI: −15.8, −0.5), but the interaction term between newborn sex and prenatal second-hand smoke was not significant ($P = 0.751$).

CONCLUSIONS: This study demonstrated that prenatal second-hand smoke exposure may be a preventable risk factor for accelerated biological aging in the intrauterine stage, and further suggested possible sex differences in the susceptibility to prenatal second-hand smoke.

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INTRODUCTION

Telomere is a nucleoprotein complex at the chromosome end, which maintains genomic DNA stability.[1] Telomere progressively shortens with each cell division and eventually reaches a critical length that triggers cellular senescence.[1] Because telomere attrition is a key mechanism of cellular senescence, telomere length (TL) has long been considered as a marker of biological aging. A substantial body of studies indicated that shortened TL in adulthood is associated with shorter lifespan and age-related diseases.[2,3] TLs are highly variable across individuals. It was reported that this inter-individual variation was originated early in life, while the lifestyle or environment in adulthood exerts a minor impact.[4] Therefore, understanding the determinants of initial TL (TL of newborns) might provide insights into possible mechanisms underlying relationships between prenatal exposures and later health outcomes.

Cigarette smoking is a major risk factor of age-related diseases,[5] and is associated with intensified oxidative stress and inflammation.[6,7] Both oxidative stress and inflammation are related to telomere shortening,[8,9] leading to the hypothesis that cigarette smoking accelerates telomere attrition. It has been well established that active smoking is associated with shorter TL in adults.[10] Compared with active smoking, second-hand smoke (SHS) exposure is a more common and avoidable public health threat. Findings about the relationship between SHS exposure and TL among adults are inconsistent.[11–13] Fetuses are more vulnerable to environmental threats than adults. However, the association between prenatal SHS exposure and newborn TL was poorly understood.

In China, the active smoking rate for women of childbearing age is very low (0.7–1.6%),[14] while researches showed that there were 38.9 to 75.1% non-smoking women exposed to SHS during pregnancy.[15] The high prevalence of SHS exposure during pregnancy indicates an urgent need for the illustration of adverse impact of SHS exposure on fetus. In this study, we investigated the association between prenatal SHS exposure and newborn TL, with the hypothesis that prenatal SHS exposure was associated with shorter newborn TL.

MATERIALS AND METHODS

Participants

We recruited 762 mother–newborn pairs from Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), a maternity hospital in Wuhan city, Hubei province, China, between November 2013 and March 2015. The following inclusion criteria were applied: (a) during the first trimester of pregnancy (<16 weeks); (b) singleton pregnancy; (c) residents of Wuhan City

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during pregnancy; (d) intention to have prenatal care and give birth at Wuhan Children's Hospital; (e) consent for participation in this study. After excluding 16 participants with DNA sample unavailable for TL measurement, there were 746 mother–newborn pairs included in the analysis.

The study protocol of this study was approved by the Medical Ethics Committee of Tongji Medical College and the Wuhan Children's Hospital. Signed informed consent was obtained from all participants.

Data collection

Maternal SHS exposure was collected via questionnaire, by asking "do you have SHS exposure during pregnancy?" SHS exposure was defined as non-smokers' exposure to the tobacco smoke for an average of at least 10 min per day. Active maternal smoking status was collected via questionnaires, by asking "do you have active cigarette smoking six months before pregnancy" and "do you have active cigarette smoking during pregnancy." Demographic information on age at delivery, education background (high school or below, college or above), and annual household income were collected via questionnaire. All the participants were interviewed face-to-face by trained nurses during the period of institutional delivery. Self-reported pre-pregnancy weight was collected at the first antenatal care visit (in the first trimester). Standing height was obtained by medical examination. Pre-pregnancy body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). The information on parity, gestational diabetes, and hypertensive disorders in pregnancy were obtained from medical records. Information on newborn sex, birth weight, and date of delivery were obtained from hospital delivery records. Low birth weight infant was defined as infant with birth weight <2500 g. Information on gestational age was estimated by women's last menstrual period, which was obtained from medical records. The preterm birth infant was defined as an infant with gestational age <37 weeks.

Umbilical cord blood collection and TL measurement

At birth, umbilical cord blood samples were drawn in EDTA tubes. DNA was extracted from stored umbilical cord blood samples using the Wizard® Genomic DNA Purification (Promega Corporation, Madison, WI) following the manufacturer's instructions. Quantitative real-time polymerase chain reaction (qPCR) was used for TL measurement. This method measured the relative TL by determining the T/S ratio of telomere repeat copy number (T) and single-copy nuclear gene copy number (human β-globin) (S), and the T/S ratio of the experimental sample was standardized with the reference pooled sample. The standard DNA pool consists of 50 DNA samples that were randomly selected from the 746 samples of this study. The four primers 5′−3′ were as follows: telomere forward, 5′-ACACTAAGGTTTGGGTTTGGGTTTGGGTT TGGGTTAGTGT-3′; telomere reverse, 5′-TGTTAGGTATCCCTATCCCT ATCCCTATCCCTATCCCTAACA-3′; reference gene forward, 5′-GT GCACCTGACTCCTGAGGAGA-3′; reference gene reverse, 5′-CCTT GATACCAACCTGCCCAG-3′. The reagents in the 10 μL PCR were 1 μL of extracted DNA (10 ng/μL), 5 μL of KAPA SYBR® FAST Master MIX 1× (KAPA Biosystems), and RNase free water. The final telomere primer concentrations were: telomere forward, 270 nM; telomere reverse, 900 nM. The final single copy gene primer concentrations were: HGB forward, 200 nM; HGB reverse, 200 nM. Samples were run in triplicate in a 384-well plate with the use of ViiA™ 7 Dx Real-Time PCR System (Applied Biosystems). The acceptable standard deviation (SD) for three Ct values was set at 0.3. If the SD of three Ct value was out of acceptable range, the measurement was repeated in a new 384-well plate. The thermal cycling profile were: 50 °C for 2 min, 95 °C for 3 min, followed by 40 cycles of 95 °C for 3 s, and 60 °C for 30 s. A melting-curve analysis was performed at the end of each run to ensure the amplification specificity and absence of primer dimer. For the standard curve, the standard DNA pool was four-fold serial diluted to generate five solutions with concentrations ranging from 0.4 to 104 ng/μL ($R^2 \geq 0.99$). In order to assess qPCR amplification efficiency, we run a five-point serial dilution of standard reference genomic DNA sample on each run. The qPCR amplification efficiency was 108% for telomere and 103% for single-copy gene. We calculated coefficient of variation (CV) to assess the variability. The CV was calculated using the following formula: $(\sigma \div \mu) \times 100\%$, where σ and μ are standard deviation and mean value of the Ct values of single-copy gene of standard reference sample, respectively. The inter-run CV was calculated using Ct values of single-copy gene of standard reference sample in all qPCR assays. And the intra-run CV was calculated using Ct values of three replicates for single-copy gene of the standard reference genomic DNA sample in each 384-well sample plate. The inter-run CV and mean intra-run CV were 4.1% and 3.0%, respectively.

Statistical analysis

Categorical variables were expressed as proportions (%), and continuous variables were expressed as means ± SD)for normal distribution, or geometric mean (GM) and 95% confidence interval (CI) for skewed distribution. Differences in means and proportions between two categories of prenatal SHS exposure were tested by the analysis of variance or χ^2 test. Linear regression models were employed to investigate the relationship between prenatal SHS exposure and ln-transformed T/S ratio. Newborns without prenatal SHS exposure were treated as the reference group, and the percent difference in newborn TL was estimated as $e^{\beta} - 1 \times 100\%$. An unadjusted model was used to assess the association between SHS and newborn TL without adjustment for any covariate. We selected covariates based on a priori knowledge, including maternal age, pre-pregnancy BMI, education background, annual household income, parity, gestational diabetes, hypertensive disorders in pregnancy, infant sex, gestational age, birth weight, and date of delivery.

Because previous studies have suggested sex-specific relationship between prenatal environmental pollutants exposure and newborn TL,[16] we inserted newborn sex × SHS as an interaction term in the regression models to obtain P value for interaction. The stratified analyses were employed to show the specific differences in percent changes of TL between boys and girls. To evaluate the robustness of our study, we performed sensitivity analyses excluding newborns with preterm birth and low birth weight, women ≥35 years old, women with gestational diabetes and hypertensive disorders in pregnancy, and women with active cigarette smoking before or during pregnancy. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). Statistical significance was set at $P < 0.05$.

RESULTS

Characteristics of the participants according to prenatal SHS exposure are shown in Table 1. Of 746 eligible women, 244 (32.7%) reported SHS exposure during pregnancy. Compared with women who had no exposure to SHS during pregnancy, women with SHS exposure were younger ($P = 0.002$) and had lower annual household income ($P = 0.024$). Compared with newborns without prenatal SHS exposure, those with SHS exposure had shorter umbilical cord blood TL ($P < 0.001$).

The distribution of fetal TL in two groups is shown in Fig. 1. The violin plot and box plot revealed that newborn TL was shorter in the non-SHS group, and the two groups had similar distribution of fetal TL.

We used two logistic regression models to assess the associations between prenatal SHS exposure and newborn TL (Table 2). In the unadjusted model, prenatal SHS exposure was associated with 10.5% shorter newborn TL (percent difference: −10.5%; 95% CI: −15.7, −5.0). After adjustment for potential

Table 1. Characteristics of the study participants according to prenatal second-hand smoke exposure

Characteristic	Prenatal second-hand smoke exposure		*P* value
	No	Yes	
	N = 502 (67.3%)	*N* = 244 (32.7%)	
Maternal			
Age (years)	28.9 ± 3.4	28.1 ± 3.1	0.002
Pre-pregnancy BMI (kg/m^2)	20.9 ± 2.8	21.0 ± 2.9	0.685
Education background			
High school or below	96 (19.1%)	61 (25.0%)	0.065
College or above	406 (80.9%)	183 (75.0%)	
Annual household income (Yuan)[a]			
<50,000	92 (18.4%)	52 (21.4%)	0.024
50,000–100,000	181 (36.1%)	106 (43.6%)	
≥100,000	228 (45.5%)	85 (35.0%)	
Number of parity			
1	427 (85.1%)	217 (88.9%)	0.148
≥2	75 (14.9%)	27 (11.1%)	
Smoking before pregnancy			
No	499 (99.4%)	243 (99.6%)	0.742
Yes	3 (0.6%)	1 (0.4%)	
Smoking during pregnancy			
No	502 (100%)	244 (100%)	
Yes	0 (0%)	0 (0%)	
GDM			
No	464 (92.4%)	229 (93.9%)	0.478
Yes	38 (7.6%)	15 (6.1%)	
HDP			
No	489 (97.4%)	238 (97.5%)	0.915
Yes	13 (2.6%)	6 (2.5%)	
Newborn			
TL[b], T/S ratio	0.77 (0.75, 0.80)	0.69 (0.66, 0.72)	<0.001
Sex			
Male	254 (50.6%)	129 (52.9%)	0.56
Female	248 (49.4%)	115 (47.1%)	
PB			
No	488 (97.2%)	240 (98.4%)	0.337
Yes	14 (2.8%)	4 (1.6%)	
LBW			
No	492 (98.0%)	239 (98.0%)	0.958
Yes	10 (2.0%)	5 (2.0%)	

BMI body mass index, *LBW* low birth weight, *PB* preterm birth, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorders in pregnancy
[a]One Yuan RMB is equal to 0.1477 US$
[b]Geometric mean (95% CI)

confounders, including maternal age, pre-pregnancy BMI, education status, annual household income, parity, gestational diabetes, hypertension disorders in pregnancy, infant sex, birth weight, gestational age, and date of delivery, this association was slightly attenuated, but still significant (percent difference: −9.7%; 95% CI: −15.0, −4.0).

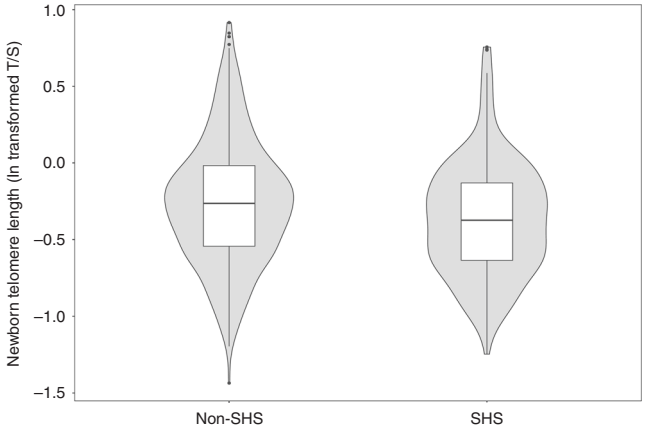

Fig. 1 The violin plot and box plot in distribution of newborn telomere length between two groups

We further did the stratified analysis by infant sex. After adjustment for potential confounders, the estimate for boys was lower (percent difference: −10.9%; 95% CI: −18.6, −2.5) than that for girls (percent difference: −8.5%; 95% CI: −15.8, −0.5) (Table 2), but the interaction term between newborn sex and prenatal SHS was not significant ($P = 0.751$).

To evaluate the robustness of our study, we performed sensitivity analyses excluding newborns with preterm birth and low birth weight, women ≥35 years, women with gestational diabetes and hypertensive disorders in pregnancy, and women with active cigarette smoking before or during pregnancy (Table 3). The associations between prenatal SHS exposure and umbilical cord blood TL did not materially changed.

DISCUSSION

In this study, we observed that compared with newborns without prenatal SHS exposure, those with SHS exposure had shorter umbilical cord blood TL. Besides, although the interaction term between newborn sex and prenatal SHS was not significant, the estimate for boys was lower than that for girls.

The association between active smoking and shorter TL has been well established in adults (Table 3). A meta-analysis included 30 studies have suggested an inverse relationship between pack-years of smoking and TL.[10] So far, there was only one study regarding the impact of prenatal tobacco exposure on cord blood TL. Salihu et al.[17] conducted a study among 86 mother–newborn pairs, and they found a dose–response pattern that newborn TL for nonsmokers was longest, which is followed by that for passive smokers, and the shortest was that for active smokers. It was noteworthy that Salihu et al.[17] did not control any potential confounders in their study. Besides, the small sample size, underprivileged study subjects with a high active smoking rate of Salihu's study might reduce the extension of these results to other population. There were two studies which investigated the association between prenatal tobacco exposure and early life TL among children population. Thall et al.[18] conducted a cross-sectional study among 104 children aged 4 to 14 years old, which suggested that children with prenatal tobacco exposure (maternal active and passive smoking during pregnancy) had shorter telomere than those without prenatal tobacco exposure. Consistent with Thall's study, a case–control study, which conducted among 196 Hong Kong Chinese children aged <15 years old, reported a negative dose–response relationship between the buccal epithelial cells TL and prenatal tobacco exposure duration.[19] Because TL in later life is mainly determined by initial TL,[20] these two studies might support our findings.

Table 2. Percent difference in newborn telomere length by prenatal second-hand smoke exposure

Groups	Unadjusted		Fully adjusted	
	Percent difference (95% CI)	*P* value	Percent difference (95% CI)	*P* value
Total population				
Non-SHS	Referent		Referent	
SHS	−10.5 (−15.7, −5.0)	<0.001	−9.7 (−15.0, −4.0)[a]	0.001
Boys				
Non-SHS	Referent		Referent	
SHS	−11.9 (−19.3, −3.9)	0.004	−10.9 (−18.6, −2.5)[b]	0.013
Girls				
Non-SHS	Referent		Referent	
SHS	−9.0 (−16.2, −1.0)	0.028	−8.5 (−15.8, −0.5)[b]	0.038

CI confidence interval, *SHS* second-hand smoke
[a]Adjusted for maternal age, pre-pregnancy BMI, education status, annual household income, parity, gestational diabetes, hypertensive disorders in pregnancy, infant sex, birth weight, gestational age, and date of delivery
[b]Adjusted for maternal age, pre-pregnancy BMI, education status, annual household income, parity, gestational diabetes, hypertensive disorders in pregnancy, birth weight, gestational age, and date of delivery

Table 3. Sensitivity analysis

Sensitivity analysis	*N*	Unadjusted		Fully adjusted	
		Percent difference (95% CI)	*P* value	Percent difference (95% CI)	*P* value
Newborns without LBW and PB[a]					
Non-SHS	488	Referent		Referent	
SHS	240	−10.3 (−15.9, −4.4)	<0.001	−9.8 (−15.2, −4.0)	0.001
Women <35 years[a]					
Non-SHS	464	Referent		Referent	
SHS	234	−10.6 (−16.0, −4.9)	<0.001	−10.2 (−15.7, −4.4)	0.001
Women without GDM and HDP[b]					
Non-SHS	454	Referent		Referent	
SHS	224	−10.9 (−16.1, −5.3)	0.001	−9.6 (−15.3, −3.5)	0.002
Women without active smoking[a]					
Non-SHS	499	Referent		Referent	
SHS	243	−10.4 (−15.6, −4.8)	<0.001	−9.3 (−14.7, −3.5)	0.002

CI confidence interval, *SHS* second-hand smoke, *LBW* low birth weight, *PB* preterm birth, *GDM* gestational diabetes mellitus, *HDP* hypertensive disorders in pregnancy
[a]Adjusted for maternal age, pre-pregnancy BMI, education status, annual household income, parity, GDM, HDP, infant sex, birth weight, gestational age, and date of delivery
[b]Adjusted for maternal age, pre-pregnancy BMI, education status, annual household income, parity, infant sex, birth weight, gestational age, and date of delivery

Oxidative stress might be a potential mechanism underlying the associations between prenatal SHS exposure and newborn TL. Because of the high guanine content, telomeres are vulnerable to oxidative stress. Oxidative stress induce DNA breakage and accelerate the rate of telomere shorten with each cell division.[21] SHS is a complex mixture containing various known carcinogens, teratogens, and toxins.[22] Some of these chemical contaminants, such as nicotine, CO, benzo(*a*)pyrene, lead, and cadmium, readily access to the fetus via placenta.[23–27] The exposure to these toxic chemicals in cigarette smoke would induce oxidative stress, which accelerate telomere shortening in the fetus. In addition, endothelial dysfunction caused by cigarette smoke would intensify the oxidative stress, resulting in shortened telomeres.[28]

In this study, we also observed that the estimate for boys was lower than that for girls. However, it should be noted that the interaction between newborn sex and prenatal SHS was not significant, which indicated that this sex-specific association between prenatal SHS and newborn TL might be attributed to chance. Compared with female fetuses, male fetuses have lower level estrogen.[29] Estrogen upregulates superoxide dismutase and glutathione peroxidase gene expression, resulting significantly higher antioxidant enzymes level in female fetus.[30] Therefore, male fetuses might be more susceptible to oxidative stress caused by prenatal SHS exposure.

There were several limitations in our study. First, one major limitation is that prenatal SHS exposure was self-reported, which might introduce recall bias. However, previous studies had shown good reliability and validity of self-reported exposure to SHS among adults.[31] Second, although extensive potential confounders were controlled in this study, we could not eliminate the unmeasured confounding caused by variables, such as maternal stress, nutritional status during pregnancy, and paternal age. These factors were reported to be related to offspring TL,[32–34] and might confound the relationship between SHS and TL. Further studies with these informations are needed to confirm the finding of this study.

In this study, we found out prenatal SHS exposure was related with shorter newborn TL. Because the effect of early-life TL persists over the life course, the prenatal SHS exposure might have a lasting harmful effect on offspring's health outcomes in childhood and adulthood.[20] China is the world's largest producer and consumer of tobacco. According Global Adult Tobacco Survey estimation in 2010, 52.9% Chinese men were current smokers, whereas only 2.4% women were current smokers.[14] The higher level of household smoking, poor ventilation, and overcrowding lead to widespread SHS exposure among Chinese women.[14] The findings of our study adds to the growing body of evidence that prenatal exposure to SHS lead to adverse health impact on fetus. Effective intervention programs, which prevent SHS exposure during pregnancy, might improve longevity and life quality of offspring.

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AUTHOR CONTRIBUTIONS

B.L. contributed to conception and design of the study, analysis and interpretation of data, and writing and revising the manuscript. L.S. contributed to collecting and analyzing data and revising the manuscript. L.Z., L.W., M.W., Z.C., B.Z., C.X., Y.L., W.X. and S.X. contributed to data collection and manuscript revising. Y.W. contributed to design of the study and revising the manuscript. All authors approved this manuscript to be published and agreed to be accountable for all aspects of this work.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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REFERENCES

1. Blackburn, E. H., Epel, E. S. & Lin, J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. *Science* **350**, 1193–1198 (2015).
2. Bojesen, S. E. Telomeres and human health. *J. Intern. Med.* **274**, 399–413 (2013).
3. Xi, H., Li, C., Ren, F., Zhang, H. & Zhang, L. Telomere, aging and age-related diseases. *Aging Clin. Exp. Res.* **25**, 139–146 (2013).
4. Benetos, A. et al. Tracking and fixed ranking of leukocyte telomere length across the adult life course. *Aging Cell* **12**, 615–621 (2013).
5. Glantz, S. & Gonzalez, M. Effective tobacco control is key to rapid progress in reduction of non-communicable diseases. *Lancet* **379**, 1269–1271 (2012).
6. Burke, A. & Fitzgerald, G. A. Oxidative stress and smoking-induced vascular injury. *Prog. Cardiovasc Dis.* **46**, 79–90 (2003).
7. Goncalves, R. B. et al. Impact of smoking on inflammation: overview of molecular mechanisms. *Inflamm. Res.* **60**, 409–424 (2011).
8. von Zglinicki, T. Oxidative stress shortens telomeres. *Trends Biochem. Sci.* **27**, 339–344 (2002).
9. Jurk, D. et al. Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nat. Commun.* **2**, 4172 (2014).
10. Astuti, Y., Wardhana, A., Watkins, J., Wulaningsih, W. & Network, P. R. Cigarette smoking and telomere length: a systematic review of 84 studies and meta-analysis. *Environ. Res.* **158**, 480–489 (2017).
11. Lu, L. et al. Association between exposure to second-hand smoke and telomere length: cross-sectional study of 1303 non-smokers. *Int J. Epidemiol.* **46**, 1978–1984 (2017).
12. Hoxha, M. et al. Association between leukocyte telomere shortening and exposure to traffic pollution: a cross-sectional study on traffic officers and indoor office workers. *Environ. Health* **8**, 41 (2009).
13. Wulaningsih, W., Serrano, F. E., Utarini, A., Matsuguchi, T. & Watkins, J. Smoking, second-hand smoke exposure and smoking cessation in relation to leukocyte telomere length and mortality. *Oncotarget* **7**, 60419–60431 (2016).
14. Li, Q., Hsia, J. & Yang, G. Prevalence of smoking in China in 2010. *N. Engl. J. Med.* **364**, 2469–2470 (2011).
15. Zhang, L. et al. Exposure to secondhand tobacco smoke and interventions among pregnant women in China: a systematic review. *Prev. Chronic Dis.* **12**, E35 (2015).
16. Liu, H. et al. Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances affects leukocyte telomere length in female newborns. *Environ. Pollut.* **235**, 446–452 (2018).
17. Salihu, H. M. et al. Impact of intrauterine tobacco exposure on fetal telomere length. *Am. J. Obstet. Gynecol.* **212**, 205 e1–205 e8 (2015).
18. Theall, K. P., McKasson, S., Mabile, E., Dunaway, L. F. & Drury, S. S. Early hits and long-term consequences: tracking the lasting impact of prenatal smoke exposure on telomere length in children. *Am. J. Public Health* **103**(Suppl. 1), S133–S135 (2013).
19. Ip, P. et al. Prenatal tobacco exposure shortens telomere length in children. *Nicotine Tob. Res.* **19**, 111–118 (2017).
20. Entringer, S., de Punder, K., Buss, C. & Wadhwa, P. D. The fetal programming of telomere biology hypothesis: an update. *Philos. Trans. R. Soc. Lond. Ser. B* **373**, 20170151 (2018).
21. Kawanishi, S. & Oikawa, S. Mechanism of telomere shortening by oxidative stress. *Ann. NY Acad. Sci.* **1019**, 278–284 (2004).
22. US Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General* (US Department of Health and Human Services, Atlanta, 2014).
23. Luck, W., Nau, H., Hansen, R. & Steldinger, R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev. Pharm. Ther.* **8**, 384–395 (1985).
24. Longo, L. D. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. *Am. J. Obstet. Gynecol.* **129**, 69–103 (1977).
25. Arnould, J. P., Verhoest, P., Bach, V., Libert, J. P. & Belegaud, J. Detection of benzo [*a*]pyrene-DNA adducts in human placenta and umbilical cord blood. *Hum. Exp. Toxicol.* **16**, 716–721 (1997).
26. Goyer, R. A. Transplacental transport of lead. *Environ. Health Perspect.* **89**, 101–105 (1990).
27. Piasek, M., Blanusa, M., Kostial, K. & Laskey, J. W. Placental cadmium and progesterone concentrations in cigarette smokers. *Reprod. Toxicol.* **15**, 673–681 (2001).
28. Celermajer, D. S. et al. Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. *N. Engl. J. Med.* **334**, 150–154 (1996).
29. Reyes, F. I., Boroditsky, R. S., Winter, J. S. & Faiman, C. Studies on human sexual development. II. Fetal and maternal serum gonadotropin and sex steroid concentrations. *J. Clin. Endocrinol. Metab.* **38**, 612–617 (1974).
30. Vina, J. et al. Females live longer than males: role of oxidative stress. *Curr. Pharm. Des.* **17**, 3959–3965 (2011).
31. Prochaska, J. J., Grossman, W., Young-Wolff, K. C. & Benowitz, N. L. Validity of self-reported adult secondhand smoke exposure. *Tob. Control* **24**, 48–53 (2015).
32. Entringer, S. et al. Maternal folate concentration in early pregnancy and newborn telomere length. *Ann. Nutr. Metab.* **66**, 202–208 (2015).
33. Entringer, S. et al. Maternal psychosocial stress during pregnancy is associated with newborn leukocyte telomere length. *Am. J. Obstet. Gynecol.* **208**, 134 e1–134 e7 (2013).
34. Unryn, B. M., Cook, L. S. & Riabowol, K. T. Paternal age is positively linked to telomere length of children. *Aging Cell* **4**, 97–101 (2005).