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Adverse pregnancy outcomes are associated with shorter telomere length in the 17-year-old child

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Original Article

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Abstract

This study examined associations between pregnancy and infant birth outcomes with child telomere length at age 17 years; and investigated if there are sex differences between pregnancy complications and telomere length. We utilised the population-based prospective Raine cohort study in Western Australia, Australia. 2900 pregnant women were recruited at 16–20 weeks' gestation (Gen 1), and their children (Gen 2) were followed up over several years. Generalised linear models were used to examine relationships between pregnancy or birth outcomes (gestational diabetes, pre-eclampsia, preterm birth, low birth weight, macrosomia), and as a composite, with telomere length, measured via a DNA sample from blood at 17 years of age. Analyses were adjusted for a range of confounders. Among the 1202 included children, there were no differences in child telomere length for any of the individual maternal or birth weight pregnancy outcomes nor were there any significant interactions between each of the complications (individual or composite) and the sex of the child. However, females born from any of the 5 adverse outcomes had shorter telomeres (estimated mean (SE) = -0.159 (0.061), $p = 0.010$) than females born in the absence of these complications. Specifically, females born from a pre-eclamptic pregnancy had shorter telomeres than females not born from a pre-eclamptic pregnancy (estimated mean (SE) = -0.166 (0.072), $p = 0.022$). No relationships were observed in males. Further longitudinal studies are needed to understand mediating factors that are important in predicting offspring telomere length and the necessity to investigate females and males independently.

Introduction

Increasing evidence shows that what occurs early in life impacts future health. In Australia, around 315,000 babies are born each year, of which 16.3% are born from a mother who had gestational diabetes (GDM), 3%–4% from gestational hypertension and 8.2% are born preterm.[1] Children born from a pregnancy complication have a 6-fold increased risk of developing chronic diseases like type 2 diabetes and heart disease, later in life.[2–4]

In addition to heightened risk for chronic disease, risk factors are already elevated in children if they were born after a pregnancy complication. Compared to non-exposed children, those born to mothers who had GDM have a 2-fold increased risk of metabolic syndrome in childhood[5], increased risk of cardiac functional abnormalities in infancy[6], and increased risk of obesity, elevated glucose and blood pressure in adolescence and early adulthood.[7] Offspring born from a pre-eclamptic pregnancy are at an increased risk of higher blood pressure and obesity[8], and those born preterm are at an increased risk of higher blood pressure in adolescence and in adulthood.[9] Critically, few studies have confirmed these results prospectively, due to the need for large longitudinal studies with appropriate and relevant data collection. The fact that these offspring are at an increased risk means it is imperative to identify which children born from a complicated pregnancy are likely to suffer from later chronic disease.

Screening to identify children born after a complicated pregnancy may be possible by using markers of accelerated ageing, such as telomere length. Shorter telomeres are associated with a 20%–40% greater likelihood of developing diabetes, cancer and heart disease in adulthood.[10,11] Risk factors for heart disease, such as elevated plasma glucose and blood pressure also associate with shorter telomeres.[12] We have demonstrated that 10-year-old children whose mothers had metabolic syndrome in pregnancy had shorter telomeres, than children of mothers without these risk factors.[13], however, among 841 children from the Longitudinal Study of Australian

Children cohort, there was no association between pregnancy complications and child telomere length at 11–12 years of age.[14] Therefore, given the relationship between pregnancy complications and future chronic disease risk, child telomere length may be an indicator of this risk. The objective of this study is to examine associations between maternal and infant pregnancy outcomes (GDM, pre-eclampsia, preterm birth, low birth weight, macrosomia), with offspring telomere length at 17 years of age. We also investigated the relationship between pregnancy complications and sex in offspring telomere length given the known sex differences in the prevalence of chronic diseases such as heart disease, cancer and kidney disease,[15–17].

Methods

Study population

Participants were enrolled in the Raine Study, a population-based prospective pregnancy cohort study in Perth, Western Australia, between May 1989 and November 1991. Initially, 2900 pregnant women were recruited between 16–20 weeks' gestation at King Edward Memorial Hospital into a randomised controlled trial to evaluate the effects of repeated ultrasound in pregnancy.[18] Women (Gen 1) and their children (Gen 2) have been followed up over multiple waves of data collection.[19] Complete information is available including anthropometry (body mass index, BMI) and blood pressure, intrauterine, and perinatal data. The cohort has been demonstrated to be representative of the population presenting to the antenatal tertiary referral centre in Western Australia.[18–20] The ethics committees of King Edward Memorial Hospital and Princess Margaret Hospital granted approval for the study protocols. The primary caregiver, who was the mother in most cases, provided written and informed consent. The parents of 2868 live born children consented for follow-up at the ages of 1, 2, 3, 5, 8, 10, 14 and 17 years. At regular intervals since birth, Gen 2 have had anthropometry (BMI, waist circumference) and blood pressure measured, with physical activity and cardiometabolic data recorded from adolescence. Most questionnaires were self-completed by the participants, fasted blood samples were collected by a trained phlebotomist and clinical measurements were taken by a trained research assistant.

Exposure variables

Women completed questionnaires regarding a range of exposures at 18 and 34 weeks', with detailed obstetric, pregnancy, birth and neonatal information also collected.[18] The major pregnancy complications in the current study analysis include GDM and pre-eclampsia (diagnoses based on clinical records) and preterm birth defined as birth < 37 weeks' gestation. Birth weight was also obtained from the medical records. Birth outcomes included low birth weight, defined as birth weight ≤2500 g, and macrosomia, defined as birth weight ≥4000 g. Uncomplicated pregnancies were defined as not having any of the diagnosed condition described above.

Outcome

The primary outcome was offspring telomere length, measured via a DNA sample from blood, at 17 y of age. Telomere length was provided as part of the data available from the Raine Study. Briefly, DNA was extracted from peripheral blood mononuclear cells using a commercially available kit (Qiagen). All DNA samples had a 260/280 nm and 260/230 nm between 1.8–1.95 and DNA integrity was assessed by agarose gel electrophoresis. Only high quality, high molecular DNA was used for subsequent analyses. The following primers were used in qPCR for Tel F 5'-CGGTTTG(TTTGGG)$_5$TT-3' and R 5'-GGCTTGCC(TTACC)$_5$T-3'[21] and single copy gene TBP F 5'-CCACAGCTCTTCCACTCACA-3' and R 5'-CTGCGGTACAATCCCAGAAC-3'. All qPCR reactions were performed at the King Edward Memorial Hospital, Perth, Western Australia. qPCR was performed using a Rotorgene 3000 in 10 µl reactions with a total of 30 ng DNA, 1 µl 10X ImmoBuffer, 0.05 µl IMMOLASE DNA Polymerase, 2 mM $MgCl_2$, 0.2 µl 10 mM dNTP, 0.3 µM each primer, 0.1 µl 10x EvaGreen dye and nuclease free water. The following PCR cycling conditions were used: 10 min at 95°C followed by 28 cycles of 15 s at 95°C, 10 s at 56°C and 5 s at 72°C. A standard curve using 1:3 dilutions of pooled DNA was included in each qPCR run. qPCR reactions were carried out in triplicate with a no template control and reference DNA positive control. Relative telomere length was calculated as per Cawthorn et al.[21] The ratio of telomere repeat copy number to a single copy gene (T/S ratio or ΔCq) was calculated. Relative T/S ratio (ΔΔCq) was calculated by subtracting ΔCq ratio of the reference gene from ΔCq of each unknown sample. Normalised relative T/S ratio was calculated using $2^{-\Delta\Delta Cq}$. Data on telomere length was screened to include eligible participants (Figure S1) but due to the large variation in telomere length (0.0180 – 24.50), we excluded telomere length data that was outside the interquartile range (Figure S2).[22–24]

Covariates

Covariates were determined a priori using a directed acyclic graph. Model 0 was the unadjusted model. Socioeconomic status can be described using the publicly available Index of Relative Socioeconomic Disadvantage of the Socioeconomic Indexes for Areas by the Australian Bureau of Statistics.[25] These data were available either during pregnancy, at birth, or at age 1 year for approximately half of the Raine Study participants who participated in the 14-year follow-up assessment. Thus, as a surrogate assessment of socioeconomic status, family income and schooling level were used as confounding variables. Model 1 included the following covariates: maternal age, population/race (Caucasian, other), schooling level (none, further/vocational training, tertiary studies, other), total family income before tax (1989–1991), per year (unknown/< $36,000AUD, $36,000AUD), smoking status, collected at 16–18 weeks' gestation (none, 1 to 10/day, 11/day), and alcohol intake, collected at 16–18 weeks' gestation (none, any drinking during pregnancy). The GDM model was additionally corrected for diabetes or GDM treatment. We could not adjust for family history of hypertension in the pre-eclampsia model because responses to the question were inconsistent between the data dictionary and survey question. For the GDM, pre-eclampsia and preterm birth models, Model 2 was: Model 1 plus infant sex and birth weight. When data were analysed by infant sex, Model 2 was Model 1 plus birth weight. For the macrosomia and low birth weight models, Model 2 was Model 1 plus infant sex.

Statistical analyses

Descriptive and frequency data were reported as percentages, mean and standard deviation (SD). This was a complete case analysis. The relationships between each exposure of interest (GDM, pre-eclampsia, preterm birth, low birth weight, macrosomia) and telomere length at 17 years of age were analysed using the generalised linear model (GLM) function of the stats package in

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Table 1. Participant characteristics in the mothers and infants (n = 1202)

Mother's characteristics	Mean (SD) or *n* (%)
Age (years)	28.97 (5.77)
Population/race	
Caucasian (European descent)	1088 (90.5%)
Other	111 (9.2%)
Highest level of education	
None	551 (45.8%)
Further/vocational training	238 (19.8%)
Tertiary studies	341 (28.4%)
Other	69 (5.7%)
Smoking status (16–18 weeks' gestation)	
None	928 (77.2%)
1–10 per day	271 (22.5%)
≥1 per day	3 (0.2%)
Alcohol status (16–18 weeks' gestation)	
None	615 (51.3%)
Any drinking during pregnancy	584 (48.7%)
Family income (1989–1991) (AUD)	
<$36,000	735 (61.1%)
≥$36,000	417 (34.7%)
Treated for diabetes or gestational diabetes	
No	1169 (97.3%)
Yes	33 (2.7%)
Gestational diabetes	
No	1175 (97.8%)
Yes	24 (2%)
Preterm birth (<37 weeks' gestation)	
No	1114 (92.7%)
Yes	85 (7.1%)
Pre-eclampsia	
No	929 (77.3%)
Yes	269 (22.4%)
Any maternal complication	
No	861 (71.6%)
Yes	341 (28.4%)
Any maternal and/or birth complication	
No	755 (62.8%)
Yes	447 (37.2%)
Infant characteristics	
Birth weight	3328.79 (592)
Male/female	621 (51.7%) / 581 (48.3%)
Macrosomia (≥4000 g)	
No/yes	1089 (90.6%) / 113 (9.4%)
Low birth weight (≤2500 g)	
No/yes	1110 (92.3%) / 92 (7.7%)

Three participants (0.2%) had no data for GDM, preterm birth, race, or highest level of education; four participants (0.3%) had no data for pre-eclampsia; 50 women (4.2%) did not report on their family income.

the R environment. GLMs were also used to explore the relationships between having any of maternal (GDM, pre-eclampsia, preterm birth) or maternal and birth (GDM, pre-eclampsia, preterm birth, low birth weight, macrosomia) pregnancy outcome, with telomere length, or having an uncomplicated pregnancy (i.e., pregnancies that were not complicated by GDM, pre-eclampsia, preterm birth, or babies born of low birth weight or with macrosomia). Within group comparisons were also made for males and females at 17 years of age. All models were corrected for the mother's age, population/race, schooling level, smoking status, alcohol status and family income. The confint function from the stats package in the R environment was used to generate confidence intervals for the estimated effects of the outcomes of interest. To test for sex-specific effects of each exposure on telomere length, AIC values were compared between *glm* models with and without an interaction term for infant sex and each exposure. Models with smaller AIC values were selected.

Results

Participant demographics

From the possible 2868 Raine Study participants, 1533 did not have telomere data, 133 were excluded due to telomere length out of IQR-based thresholds, leaving 1202 participants analysed (Figure S1). The mothers had a mean (SD) maternal age of 28.97 (SD 5.77) years at 16–18 weeks' gestation (Table 1). Most mothers were Caucasian (90.5%) and approximately 23% smoked one or more cigarettes per day during pregnancy. At the time of pregnancy, 61% reported a median salary < $36,000 AUD which would be equivalent to approximately $85,000 AUD in 2022. There were a similar number of female (48%) and male (52%) offspring. Maternal complications defined as GDM, pre-eclampsia or premature birth affected 28% of pregnancies. Low birth weight (≤2500 g) occurred in approximately 7.7% of births and macrosomia (4000 g) in 9.4% of the cohort. When combining maternal and birth complications, 447 (37%) of the cohort was affected (Table 1).

The mean (IQR) telomere length of the 17-year-old children was 1.41 (range 0.018–3.313). Differences between those who did and did not have assessment of telomere length is reported in Table S1. Of the 1202 children with telomere length data, 877 had systolic and diastolic blood pressure measurements recorded. The respective mean (SD) values for systolic blood pressure and diastolic blood pressure were 113.46 (10.28) mmHg and 58.74 (6.39) mmHg. BMI was recorded in 882 children, with a mean (SD) of 23.12 (4.45) kg/m^2.

Complicated versus uncomplicated pregnancies and offspring telomere length

There was no difference in child telomere length between children born from any of the 3 maternal complications versus children who were born from an uncomplicated pregnancy (Table 2, Test 1). However, children born from any of the 5 maternal and/or birth weight complications had shorter telomeres than children who were born from an uncomplicated pregnancy (Figure 1, Table 2, Test 3; coefficient = –0.099, p = 0.019). There was no significant interaction between any of the pregnancy complications and sex of the offspring. However among the females (Table 3; Table S2; Figure S3B), those born from any of the 3 maternal

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Table 2. Estimated effect of each predictor variable on relative telomere length in 17-year-old children and the interaction by sex

		Model 0			Model 1			Model 2		
Test	Relative telomere length	Coefficient	SE	$P>\|t\|$	Coefficient	SE	$P>\|t\|$	Coefficient	SE	$P>\|t\|$
1	**Any 3 maternal complications, all children**	−0.085	0.044	0.051	−0.086	0.0450	0.056	−0.087	0.046	0.061
2	Maternal complications *x* sex	−0.162	0.087	0.064	−0.143	0.090	0.111	−1.431	9.00	0.110
3	**Any 5 maternal and/or birth complications, all children**	**−0.094**	**0.041**	**0.021**	**−0.099**	**0.042**	**0.019**	**−0.099**	**0.042**	**0.019**
4	Maternal and/or birth complications *x* sex	0.110	0.081	0.176	−0.098	0.084	0.242	−9.715	8.380	0.247
5	**GDM, all children**	−0.073	0.141	0.603	−0.049	0.146	0.738	−0.053	0.146	0.716
6	GDM *x* sex	−0.105	0.285	0.713	−0.101	0.293	0.732	−1.056	2.939	0.720
7	**Pre-eclampsia, all children**	−0.084	0.047	0.074	−0.083	0.049	0.087	−0.083	0.049	0.091
8	Pre-eclampsia *x* sex	0.177	0.0945	0.062	−0.155	0.097	0.109	−1.570	9.698	0.106
9	**Preterm birth, all children**	−0.026	0.077	0.737	−0.025	0.082	0.759	−0.010	0.096	0.916
10	Preterm birth *x* sex	−0.211	0.154	0.173	−0.221	0.166	0.182	−2.224	1.661	0.181
11	**Low birth weight, all children**	−0.119	0.074	0.107	−0.120	0.077	0.118	−0.169	0.100	0.090
12	Low birth weight *x* sex	0.139	0.149	0.350	0.180	0.155	0.245	1.850	1.549	0.232
13	**Macrosomia, all children**	−0.018	0.067	0.790	−0.033	0.070	0.640	−0.064	0.081	0.432
14	Macrosomia *x* sex	−0.075	0.136	0.581	−0.061	0.141	0.665	−6.174	1.411	0.662
15	**Uncomplicated pregnancy, all children**	0.017	0.050	0.729	0.015	0.052	0.772	0.016	0.052	0.765

complications (Model 2, Estimated means and 95% CI: $mean_{yes}$ 1.20; 95% CI 1.06, 1.34 vs. $mean_{no}$ 1.37; 95% CI: 1.26, 1.48) or 5 maternal/birth complications (Model 2, Estimated means; 95% CI: $mean_{yes}$ 1.22; 95% CI: 1.09, 1.35 vs. $mean_{no}$ 1.38; 95% CI: 1.27, 1.49) had shorter telomeres than females not born from any of these complications. These relationships were not observed in males (Table 3; Table S3; Figure S3C).

When considering only the cohort of children who were not exposed to any pregnancy complications (i.e., an uncomplicated pregnancy), male and female offspring had the same telomere lengths (Table 2, Test 15; Figure S4A).

Individual pregnancy complications and offspring telomere length

In the 1202 children there was no association between offspring telomere length and individual pregnancy complications, that is, GDM, pre-eclampsia (Figure 2A), preterm birth, macrosomia, or low birth weight (Table 2). There was also no significant interaction between males and females for any individual pregnancy outcome and telomere length (Table 2). However, telomere length was shorter among female offspring exposed to pre-eclampsia compared to unexposed females (Figure 2B; Table S2; Model 2 Estimated means; 95% CI: $mean_{yes}$ 1.19; 95% CI: 1.03, 1.34 vs. $mean_{no}$ 1.35; 95% CI: 1.25, 1.46). This was not observed in females for any other individual pregnancy complication, and it was not observed in the group of males (Figure 2C, Table S3).

Discussion

Main findings

Children born from any of the 5 maternal and/or birth weight complications had shorter telomeres than children who were born from an uncomplicated pregnancy, but there was no interaction between pregnancy complications and sex of the offspring. Among the female offspring only, telomere length was shorter among those exposed to pre-eclampsia compared to unexposed females.

Strengths and limitations

The Raine Study in Australia is the largest prospective multigenerational observational study across pregnancy, childhood and adolescence that has been carried out anywhere in the world. It is one of the few studies where information is available on the mother during pregnancy with follow-up data from the child. Strengths include objectively collected clinical assessments at nearly every follow-up plus a range of subjective questionnaire assessments. The cohort is typically representative of the Western Australian population. Limitations include the sample of 17-year-old children who did not provide a sample for assessment of telomere length. This might have biased the sample as mothers of participants with missing data were not typically similar in demographics or outcome data to those with complete data; estimates will be less precise than if data were available for all participants. However, the participants with missing data were a random sample of those who were intended to be observed. A further limitation is the predominant Caucasian ethnicity; thus our findings may not be generalisable across different races. Further, we observed large variation in telomere length, however this is common in other studies that have measured telomere length[23,24], and we utilised informed processes to remove the potential outliers using interquartile ranges.[22–24]

Interpretation (in light of other evidence)

To our knowledge, this is the first study to assess the impact of major pregnancy complications on telomere length measured during adolescence in the offspring. The importance of telomere length in adults and the relationship to cardiovascular and other chronic diseases is evidenced in longitudinal and cross-sectional

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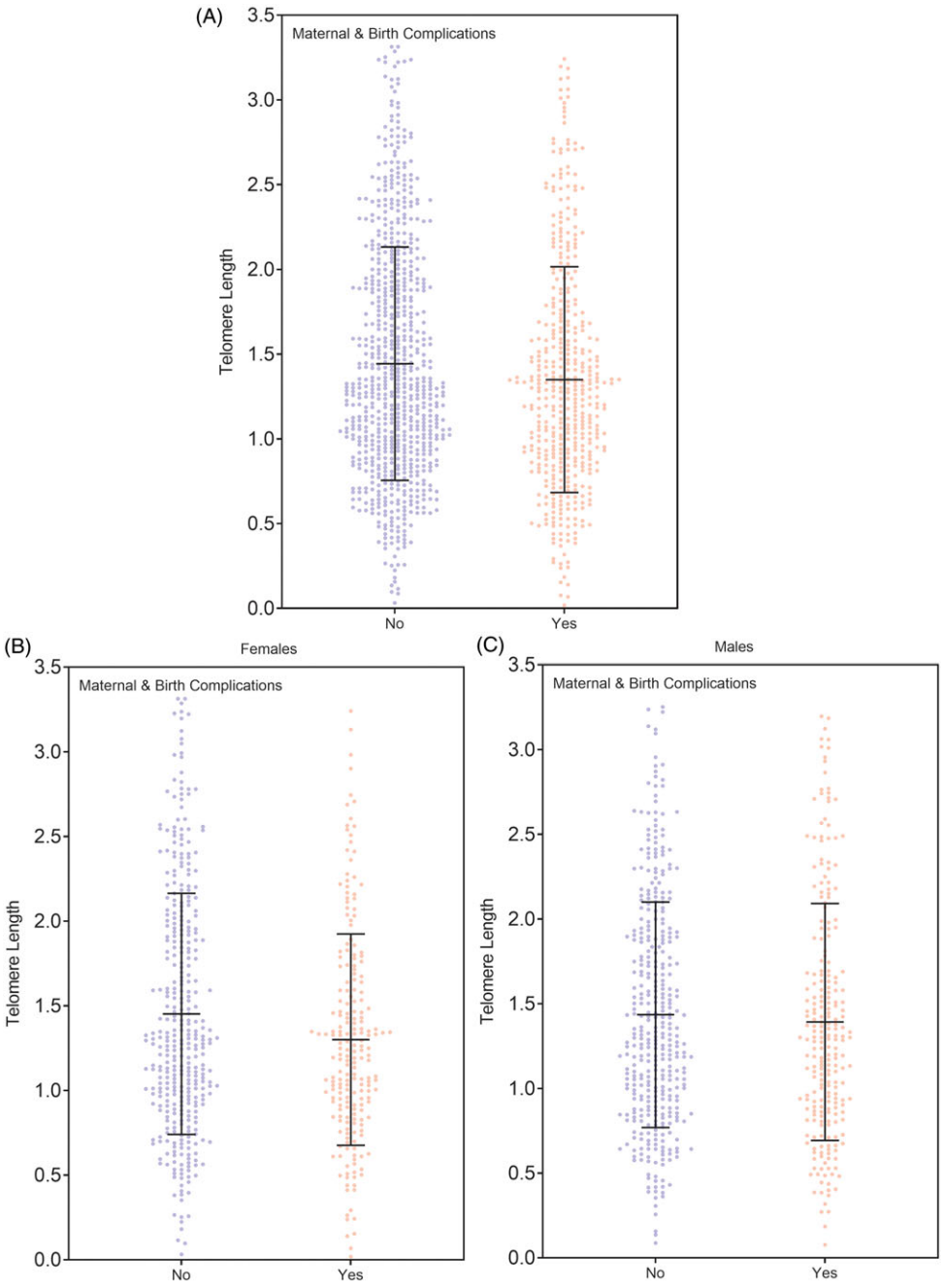

Figure 1. Mean (± SD) telomere lengths of the 17-year olds whose mothers did or did not have any of the maternal (gestational diabetes, preeclampsia and preterm birth) or infant (macrosomia >4000 g and low birthweight <2500 g) complications in (A) the entire cohort (A); in (B) females only and (C) males only.

studies.[26,27] Yet, although pregnancy complications are a predictor for later disease, and so too is telomere length, few studies have assessed the impact of pregnancy complications on telomere length of the offspring.[13,14,28] Our findings that males and females born from a healthy/uncomplicated pregnancy have the same relative telomere length, but that females born from a mother with pre-eclampsia had shorter telomeres than non-exposed females, are important.

Few studies have assessed the effect of pre-eclampsia and offspring telomere length, demonstrating inconsistent results. A small study of 9 women with pre-eclampsia showed no difference in cord blood telomere length compared to uncomplicated pregnancies ($n = 14$).[29] Comparatively, telomere length in placenta was shorter in pre-eclampsia ($n = 14$), intrauterine growth restriction ($n = 14$), or pre-eclampsia plus intrauterine growth restriction placentas ($n = 9$) compared to controls ($n = 20$)[30], and was shorter in cord blood from pre-eclamptic pregnancies ($n = 27$) compared to controls ($n = 54$).[31] These studies assessed cord blood or placental telomere length, but the impact of telomere length on future cardiovascular diseases has not been longitudinally assessed. We found that within the group of females, telomeres were shorter than females not exposed to pre-eclampsia. Our findings are valuable and support the impact of *in utero* programming. The 17-year-old females in this cohort will inevitably have their own pregnancies. Although shorter telomeres in women has been associated with recurrent miscarriage and ovarian insufficiency[32], it has also been theorised that despite the reduction of telomeres with ageing and during oocyte

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Table 3. Within sex comparisons and the estimated effect of each predictor variable on relative telomere length in 17-year-old children

	Model 0			Model 1			Model 2		
Relative Telomere Length	Coefficient	SE	$P>\|t\|$	Coefficient	SE	$P>\|t\|$	Coefficient	SE	$P>\|t\|$
Any 3 maternal complications									
Males	−0.009	0.060	0.884	−0.014	0.062	0.822	−0.004	0.064	0.956
Females	**−0.170**	**0.063**	**0.007**	**−0.159**	**0.0650**	**0.015**	**−0.170**	**0.067**	**0.012**
Any 5 maternal and/or birth complications									
Males	−0.042	0.056	0.451	−0.041	0.058	0.479	−0.040	0.058	0.490
Females	**−0.152**	**0.059**	**0.010**	**−0.157**	**0.061**	**0.010**	**−0.159**	**0.061**	**0.010**
GDM									
Males	−0.030	0.184	0.868	0.019	0.193	0.920	0.016	0.193	0.934
Females	−0.136	0.219	0.536	−0.122	0.225	0.560	−0.123	0.227	0.588
Pre-eclampsia									
Males	−0.005	0.064	0.943	−0.011	0.066	0.865	−0.004	0.067	0.953
Females	**−0.181**	**0.070**	**0.010**	**−0.166**	**0.072**	**0.021**	**−0.166**	**0.072**	**0.022**
Preterm birth									
Males	0.094	0.115	0.416	0.099	0.127	0.433	0.188	0.145	0.195
Females	−0.117	0.103	0.256	−0.121	0.108	0.261	−0.179	0.131	0.172
Low birth weight									
Males	−0.195	0.111	0.078	−0.224	0.116	0.055	−0.275	0.147	0.063
Females	−0.056	0.100	0.574	−0.049	0.103	0.635	−0.087	0.137	0.526
Macrosomia									
Males	0.013	0.089	0.884	0.010	0.092	0.912	−0.036	0.109	0.739
Females	−0.062	0.103	0.548	−0.078	0.107	0.471	−0.103	0.124	0.407

development, telomere length resets across generation.[33] Therefore, further research is required to determine if telomere length continues to shorten in females in subsequent generations.

The indication that telomere length was not shorter following the other individual major pregnancy complications or between sexes following any of the pregnancy complications is intriguing. Some studies demonstrate no associations with GDM and fetal telomere length measured in cord blood[34–37], there are mixed reports for longer and shorter telomere lengths in babies born preterm[38,39], and no association was reported for babies born small for gestational age.[40] However, Xu et al showed shorter telomere lengths in cord blood leucocytes following a GDM pregnancy compared with control offspring[37]; Hjort et al found shorter blood telomeres in children aged 9–16 years if their mother had GDM[28], and McAninch et al reported shorter telomere lengths in 10-year-old children born from women who had metabolic syndrome in pregnancy.[13] Interestingly, the study by Hjort found that the relationship with shorter telomeres from GDM was primarily driven by shortened telomeres in female offspring.[28] The inconsistent results between our study and others may be explained by a lack of power, the age of the offspring assessed and confounding variables. As telomere length is most variable at the time of birth[41,42] telomere length may be less variable in later childhood and adolescence. Further studies are needed to improve our understanding on pregnancy complications and telomere length across a range of ages after birth and after a pregnancy complication.

Conclusion

Males and females born from a healthy, uncomplicated pregnancy have the same relative telomere length, but females born after a pre-eclamptic pregnancy had shorter telomeres than females who were not born from a pre-eclamptic pregnancy. Further longitudinal assessment is warranted to understand mediating factors that are important in predicting offspring telomere length and the necessity to investigate females and males independently.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174424000291.

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Author contribution. Conceptualisation: T.BM. and J.A.G.; Data curation: L.J.B., T.A.M., C.E.P. and R.K.M; Formal analysis: A.L.P. and D.R.H; Funding acquisition: T.BM. and J.A.G.; Methodology: T.BM., L.J.B., T.A.M. and J.A.G; Supervision: T.BM. and J.A.G; Writing – original draft: T.BM. and J.A.G; Writing – review and editing: T.BM., A.L.P., D.R.H., C.E.P., R.K.M., L.J.B., T.A.M. and J.A.G. All authors have read and agreed to the published version of the manuscript.

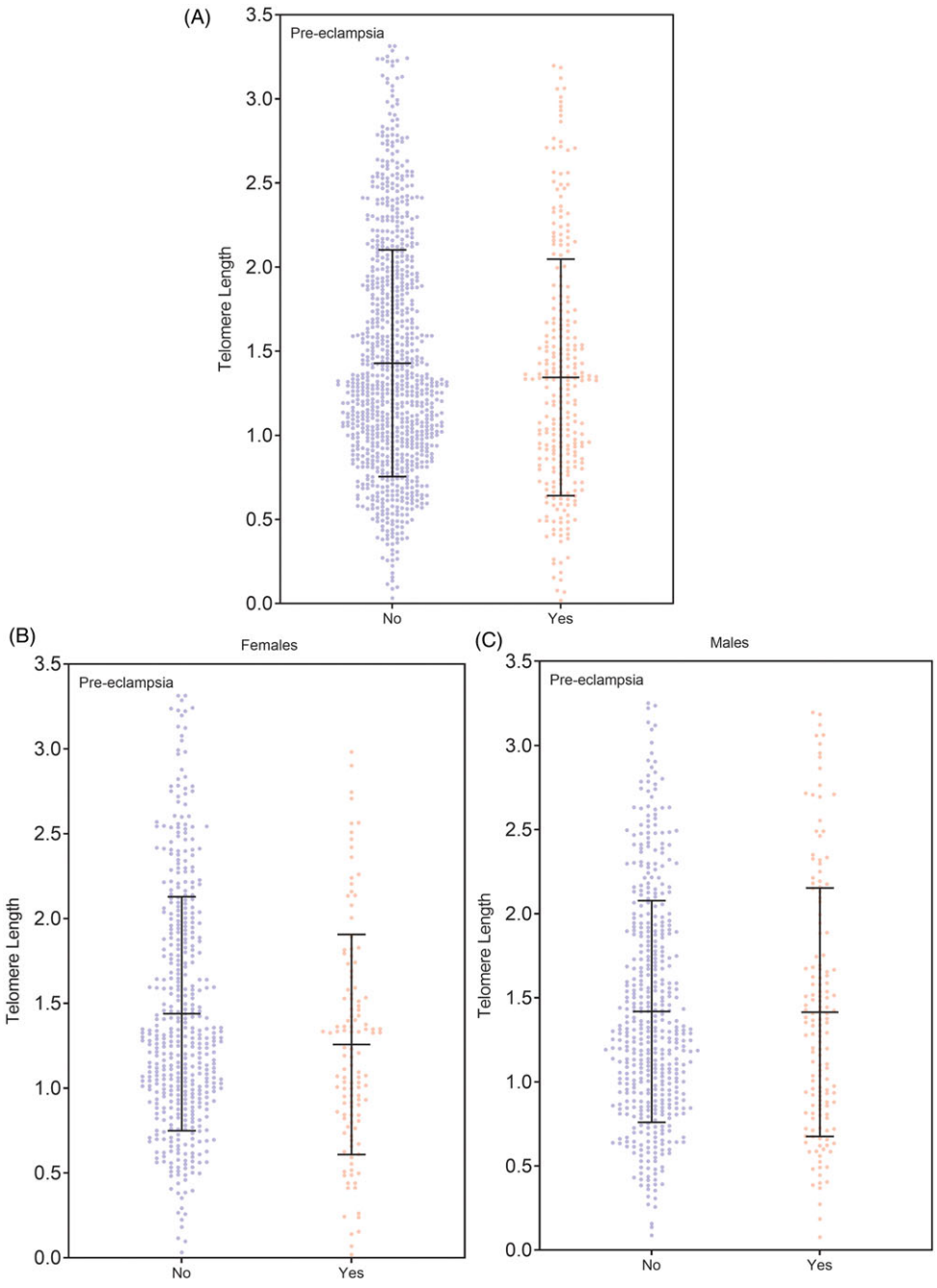

Figure 2. Mean (± SD) telomere lengths of the 17-year olds whose mothers did or did not have pre-eclampsia in (A) the entire cohort (A); in (B) females only and (C) males only.

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