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Child Telomere Length at 11–12 Years of Age Is Not Associated with Pregnancy Complications

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Abstract: Children born from pregnancy complications are at higher risk of chronic diseases in adulthood. Identifying which children born from a complicated pregnancy are likely to suffer from later chronic disease is important in order to intervene to prevent or delay the onset of disease. This study examined the associations between the major pregnancy complications (gestational diabetes, high blood pressure, small- and large for gestational age, and preterm birth) and child telomere length, a biomarker of chronic disease risk. This was a population-based longitudinal analysis using data from the Longitudinal Study of Australian Children. The primary outcome is telomere length, measured in 11–12-year-old children. Multivariable linear regression was used to estimate the association between pregnancy complications and child telomere length, adjusting for a range of a priori confounders. Data from 841 families were used. One in four pregnancies (27.1%) featured a pregnancy complication. In the adjusted analysis, there was no association between pregnancy complications and child telomere length (high blood pressure: mean difference (95% CI): 0.00 (−0.12, 0.12); gestational diabetes (0.05 (−0.10, 0.19)); small for gestational age (0.07 (−0.04, 0.19)); large for gestational age (−0.06 (−0.15, 0.03)); and preterm birth (−0.10 (−0.21, 0.01)). Our results do not support the notion that telomere length is shorter in children born to mothers after a pregnancy complication. Methodological considerations should be rigorous to improve the reproducibility of findings.

Keywords: pregnancy; telomere length; longitudinal analysis; Australia; pregnancy complication

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1. Introduction

Worldwide, 140 million babies are born each year, with approximately 35 million born from a complicated pregnancy. Compared to non-exposed children, those born from a complicated pregnancy, such as preeclampsia, gestational diabetes mellitus (GDM), those who are delivered preterm or are born small or large for gestational age, have higher rates of obesity, elevated glucose and blood pressure [1–3], and they are at an increased risk of metabolic syndrome [2] and cardiac functional abnormalities [4]. Offspring born from a pregnancy complication also have up to a six-fold higher risk of chronic diseases in adulthood, including stroke, coronary heart disease, and chronic kidney disease [5–7].

Maternal exposures play a critical role in both the short- and long-term health of the offspring. Thus, identifying which children born from a complicated pregnancy are likely to suffer from later chronic disease is important to intervene to prevent or delay the onset of disease. One way to achieve this is to measure biomarkers in the offspring.

Telomere length is one such biomarker and is often used to measure accelerated aging. Telomeres are repeating stretches of DNA found at the ends of chromosomes that become

shorter over time. Shorter telomeres are associated with a 20–40% greater likelihood of developing diabetes and heart disease in adulthood [8,9]. To date, there is limited and inconsistent literature regarding the impact of pregnancy complications on offspring telomere length. Some studies demonstrate no associations with GDM or preeclampsia and telomere length measured in cord blood [10–13], whereas Xu et al. found shorter cord blood telomeres in children from pregnancies with GDM [13]. There are mixed reports for longer and shorter telomere lengths in babies born preterm [14,15], and no association with babies born small for gestational age [16].

The rate of telomere shortening is greatest at birth, is virtually maintained in adulthood, and slows in older age [17,18]; thus, capturing telomere length after birth may provide optimal information about the effect of intrauterine exposures on telomere length. Few studies, however, have investigated adverse pregnancy outcomes and child telomere length. In children aged 9–16 years, telomere length was shorter in girls but not in boys if their mothers had GDM [19]. McAninch et al recently showed that 10-year-old children of mothers with metabolic syndrome in pregnancy have 14% shorter telomeres than children of mothers without metabolic syndrome in pregnancy [20]. Given the relationship between pregnancy complications and offspring health, measurement of telomere length in children may be used as an early indicator of future risk of chronic disease among these children.

We hypothesise that children born from a pregnancy complication have shorter telomeres than children born from an uncomplicated pregnancy. The aim of this study is to examine the associations between the major pregnancy complications (GDM, high blood pressure, small- and large for gestational age, and preterm birth) and child telomere length.

2. Materials and Methods

2.1. Study Design and Sample

This study used data from the birth cohort of the Longitudinal Study of Australian Children (LSAC), a prospective cohort study that commenced in 2004 [21]. Detailed study design and sampling have been described elsewhere [22]. Briefly, the sampling framework used two-stage clustered sampling that first included Australian postcodes and the second sampled children within postcodes. The postcodes were randomly selected and stratified by state/territory and urban/rural status to ensure a nationally representative sample. Participating families in LSAC have been interviewed every two years from 2004, and between-wave mail-out questionnaires were sent to families in 2005 (Wave 1.5), 2007 (Wave 2.5) and 2009 (Wave 3.5). The B cohort ("Baby" cohort) of around 5000 children was aged 0–1 years in 2003–2004, and the K cohort ("Kinder" cohort) of around 5000 children was aged 4–5 years in 2003–2004. LSAC birth data includes weeks gestation, birthweight, and preterm birth, with data linkage possible to access further medical or hospital records. In subsequent years, biological measures, obesity, diet, and physical and sedentary behaviours are available.

In 2015, a comprehensive, Australia-wide, cross-sectional physical health and biomarker module, the Child Health CheckPoint, was conducted for the B cohort between LSAC Waves 6 and 7, when children were 11–12 years of age (2015–2016). The participants used in this study were the index children who participated in this one-off CheckPoint. Children and their attending parent rotated through a series of 15 min stations, in which different aspects of health were assessed and biological samples were collected, including venous blood (DNA material used for the measurement of telomere length). The inclusion criteria were children whose biological mother completed Wave 1 (85% of Wave 1 sample); if the mother did not use diabetes, blood pressure, or thyroid medications in pregnancy; and if they had a singleton, term birth (between 37 and 42 weeks gestation). Approximately half (53%, n = 1874 families) of the Wave 6 sample agreed to participate in the Child Health CheckPoint. Of the 1237 children who had blood collected, 841 children had a whole-blood sample available for telomere length (Figure 1).

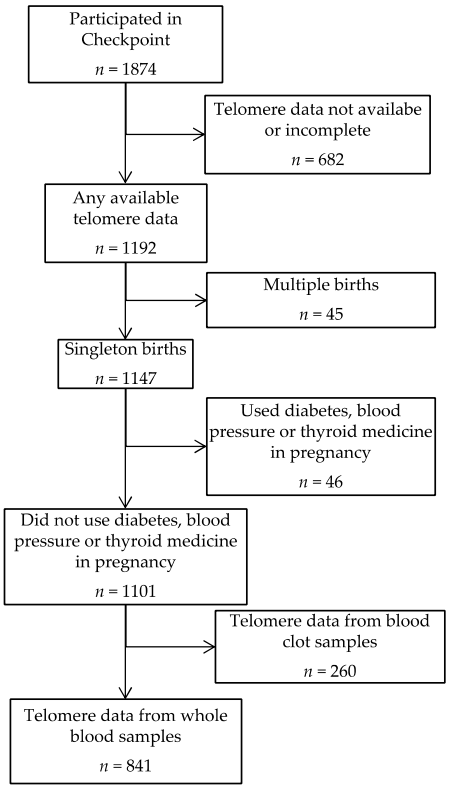

Figure 1. Participant inclusion and exclusion criteria.

2.2. Characteristics

Maternal data included sociodemographic status at birth and maternal factors during pregnancy, such as maternal age, ethnicity, number of children at home, socio-economic status of the family, diabetes, hypertension, and smoking during pregnancy [23]. The socio-economic status of the family was generated from the Socio-Economic Index for Areas released from national census data of 2006 and 2011. The index child parent identified at Wave 1 whether the study child was of Aboriginal and/or Torres Strait Islander background, which were categorised as Indigenous or Non-Indigenous. The independent variables were maternal pregnancy complications that were self-reported, including GDM, maternal high blood pressure during pregnancy, small for gestational age, and large for gestational age.

2.3. Assessment of Telomere Length

Data concerning the measurement and assessment of telomere length can be found in the Standard Operating Procedure on the Child Health CheckPoint website [21] and publication [24]. Briefly, genomic DNA was isolated from available blood using the QIAamp 96 DNA Blood Kit (Qiagen, Venlo, The Netherlands). Purity and integrity were confirmed using the NanoDrop 2000 Spectrophotometer (NanoDrop Technologies, Middleton, WI, USA), the Qubit 2.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA), and gel electrophoresis. Telomere length was measured via quantitative real-time PCR. This method measures the amount of telomeric genomic DNA (T)/b-globin single-copy gene (S) (T/S ratio) for each participant. The mean intra-assay variability between "T" and "S" quadruplicates used in the calculation of the T/S ratio was 1.7% (SD, 0.3%; range, 0.9–2.6%). The inter-assay variability between plates was 1.7% (SD, 1.4%; range, 0.3–6.2%).

Supplementary Figure S1 shows the differences in telomere length between measurements collected from whole blood compared to the blood clot samples. The telomere lengths from blood clot samples were significantly greater than the whole blood, indicating a systematic difference between the measurements of telomere length through these two methods, rendering them incomparable in the same analysis. The mean telomere length for blood clot samples was 1.528 ± 0.7241 compared to 0.9482 ± 0.3712 for the whole blood

samples (Mann–Whitney *t*-test $p < 0.0001$; Supplementary Figure S1). Therefore, telomere length data from the blood clot samples ($n = 260$; Figure 1) were excluded from the analyses.

2.4. Potential Confounding

Potential confounders of the relationship between maternal pregnancy complications and child telomere length were identified a priori using a directed acyclic graph. For model 1, confounders included maternal age, maternal smoking, maternal ethnicity, maternal folic acid during pregnancy, child sex, and indigenous status. For small and large for gestational age, confounders additionally included paternal ethnicity, and hypertensive disorders of pregnancy (for small for gestational age and preterm birth) and GDM (for large for gestational age) (Supplementary Figure S2).

2.5. Statistical Analysis

All of the analyses were conducted for a complete case sample. Descriptive analyses were performed, including the distribution of participants according to the exposure (GDM, hypertensive disorder in pregnancy, small and large for gestational age, and preterm birth), confounding factors, and outcome (child telomere length). Multivariable linear regressions were used to estimate the association between pregnancy complications and child telomere length using Beta coefficients and their 95% confidence intervals (CIs). The models were adjusted for the relevant confounding factors. Sensitivity analysis was conducted to identify if adjusting for different confounding factors impacted the results. The sensitivity analyses confirmed that patterns of associations remained for all approaches. Analyses were carried out using STATA 17.0.

3. Results

Of the 1874 families who participated in the Child Health CheckPoint study, data from 841 families (44.9%) were used. Table 1 describes the characteristics of the included families and their offspring. A majority of mothers were aged 25 to 39 years (88.4%), predominantly Australian or New Zealanders, and less than half were of low socio-economic status. During pregnancy, almost a third of mothers did not take folic acid supplements, and 12.5% smoked. A similar proportion of children were males and females.

Table 1. Characteristics of the study population.

Characteristics	Frequency (%)
Mother	
Age (years) ($n = 840$)	
<24	51 (6.1)
25–29	187 (22.3)
30–34	335 (39.9)
35–39	220 (26.2)
≥40	47 (5.6)
Ethnicity ($n = 840$)	
Australian or New Zealander	702 (83.6)
Asian	54 (6.4)
European	62 (7.4)
African	11 (1.3)
American	11 (1.3)
Highest education qualification at Wave 1 ($n = 829$)	
Certificate	354 (42.7)
Diploma (advanced/graduate)	158 (19.0)
Bachelor/Postgraduate	317 (38.2)

Table 1. *Cont.*

Characteristics	Frequency (%)
SEIFA index [1] (*n* = 841)	
<Q10	47 (5.6)
Q10–<Q25	68 (8.1)
Q25–<Q50	122 (14.5)
Q50–<Q75	232 (27.6)
Q75–<Q90	181 (21.5)
>Q90	191 (22.7)
Folic acid supplement during pregnancy (*n* = 841), Yes	587 (69.8)
Smoked during pregnancy (*n* = 767), Yes	96 (12.5)
Father	
Ethnicity (n = 807)	
Australian or New Zealander	650 (80.5)
Asian	54 (6.7)
European	73 (9.0)
African	21 (2.6)
American	9 (1.1)
Child (*n* = 841)	
Male	413 (49.1)
Female	428 (50.9)

[1] Index of relative socio-economic disadvantage.

The measurements of telomere length were obtained from children across different assessment areas within Australia. Brisbane (25.9%) and Sydney (25.4%) reported the most telomere measurements, while Melbourne City (1.5%), Darwin (1.7%), and Bundaberg (1.7%) contributed the lowest percentage (Supplementary Table S1). The mean (SD) relative telomere length of the children at 11-12 years of age was 0.97 (0.38). One in four pregnancies (27.1%) were reported to feature a complication of pregnancy such as GDM, high blood pressure, preterm birth, and being small or large for gestational age. The highest proportion of complicated pregnancies was babies born large for gestational age (11.1%), whereas the fewest was GDM (3.5%) (Table 2).

Table 2. Mean difference in children's relative telomere length according to pregnancy complication.

Pregnancy Complication	Yes, *n* (%)	No, *n* (%)	Mean Difference in Telomere Length (95% CI)
High blood pressure (*n* = 765)	39 (5.1)	726 (94.9)	0.00 (−0.12, 0.12) [1]
Gestational diabetes mellitus (*n* = 764)	27 (3.5)	737 (96.5)	0.05 (−0.10, 0.19) [1]
Small for gestational age (*n* = 832)	60 (7.2)	772 (92.8)	0.07 (−0.04, 0.19) [2]
Large for gestational age (*n* = 832)	92 (11.1)	740 (88.9)	−0.06 (−0.15, 0.03) [3]
Preterm birth (*n* = 839)	47 (5.6)	792 (94.4)	−0.10 (−0.21, 0.01) [4]

[1] Adjusted for maternal age, ethnicity, indigenous status, folic acid supplement intake, smoking in pregnancy, child sex; [2] Adjusted for model 1 plus high blood pressure induced by pregnancy and paternal ethnicity; [3] Adjusted for model 1 plus gestational diabetes and paternal ethnicity; [4] Adjusted for model 1 plus high blood pressure induced by pregnancy.

The mean (SD) telomere length of children born from an uncomplicated pregnancy (*n* = 613) was 0.98 (0.39), while children born from 1 (*n* = 196) or ≥2 (*n* = 32) pregnancy complications were 0.98 (0.34), and 0.85 (0.30). There was no difference in the mean telomere length of children born from mothers with vs. without a pregnancy complication: GDM (Δ 0.05, 95% CI −0.10, 0.19), high blood pressure in pregnancy (Δ 0.00, 95% CI −0.12, 0.12), small for gestational age (Δ 0.07, 95% CI −0.04, 0.19), large for gestational age (Δ −0.06, 95% CI −0.15, 0.03), and preterm birth (Δ −0.10, 95% CI −0.21, 0.01) (Table 2).

4. Discussion

In our sample of approximately 800 mother and child pairs, our results do not support our hypothesis of shorter telomeres in 11–12-year-old children born from a major pregnancy complication.

Adverse exposures are known to be associated with increased offspring chronic disease risk, such as heart disease and diabetes [1,3,5,25]. These chronic diseases are associated with shorter telomeres [8,9,26]. Studies have shown an association between shorter cord blood telomere length and adverse maternal exposure, including psychosocial stress [27] and alcohol [28], whereas positive factors have been associated with longer cord blood telomeres, for example, selenium [29], dietary vitamin D [30], and vitamin C intake [31]. A systematic review of maternal diet and offspring telomere length found higher circulating maternal folate and vitamin D3 concentrations, along with higher maternal dietary caffeine intakes, were associated with longer offspring telomere length [32]. Therefore, what happens in pregnancy can impact child telomere length and potentially future disease risk.

Despite the intergenerational effect of intrauterine exposure, there are fewer studies that have examined pregnancy complications and offspring telomere length, of which most assessed small numbers. In a study that included 40 growth-restricted babies and 40 babies born at an appropriate weight for gestational age, there was no significant difference in cord blood telomere length between the two groups [33], nor between a sample of 19 growth-restricted infants and 32 controls [34]. There are inconsistent results for preeclampsia; one study demonstrated shorter cord blood telomere length from 27 preeclamptic pregnancies compared to 53 healthy controls [35], one study found longer telomere lengths in preeclamptic pregnancies (n = 130) compared to controls (n = 341) [36], and another study reported no association between preeclampsia (n = 9) and uncomplicated (n = 14) pregnancies [37]. In a meta-analysis, shorter telomere length was associated with intrauterine growth restriction but only when measured in the placenta and not cord blood; and telomere length was longer in preterm birth, but only if measured by quantitative PCR [38]. As such, it is often difficult to compare across studies because telomere length can be impacted by tissue type and by the methodology used to measure it. Our study demonstrates this as there were large differences in telomere length when comparing DNA extracted from whole blood compared to blood clots. This is not surprising as telomere length varies depending on cell type [39,40].

In terms of associations between pregnancy complications and telomere length in children, there are even fewer studies. Hjort et al. found shorter telomeres in 9–16-year-old females born from GDM compared to non-GDM pregnancies [19], and McAninch et al. showed shorter telomeres in 10-year-old children from pregnancies with metabolic syndrome compared to healthy pregnancies [20]. Our findings build on the limited studies that have assessed telomere length in children born from an adverse pregnancy outcome. Further studies are still needed to elucidate the role of how adverse intrauterine exposures might impact potential accelerated aging in children.

A strength of this study is the large population-based cohort; 841 women and their child were included, of which 27% of the women had a complicated pregnancy. It is likely that the pregnancy complication rates may be higher if current diagnosis criteria, specifically for GDM, are used. This would result in some of the uncomplicated pregnancies potentially being reclassified as complicated. Furthermore, population-based samples were collected from clearly defined geographical regions. All measurements of maternal health were conducted at the same timepoint during the third trimester, with well-validated questionnaires [21].

Some of the limitations are that 13 centres were included that measured telomere length. Although this facilitated the large number of samples that form part of this study, it is likely to contribute to the large variation in telomere length, as this can be impacted by factors such as sample collection, site, and the time between sample storage and DNA extraction. Other limitations include the fact that a whole-blood sample is a mixture of cell types and telomere length varies across cell types [40]. Thus, different telomere

length measurements were obtained from whole-blood samples compared to the blood clot samples, which reduced our final sample size.

5. Conclusions

In 841 mother–child pairs, there was no difference in child telomere length if they were born after a pregnancy complication (GDM, high blood pressure, preterm birth, and being large or small for gestational age) or not. Although telomere length might serve as a marker for accelerated aging, methodological considerations should be rigorous to improve the reproducibility of findings. Further studies are still warranted to investigate the associations between pregnancy complications, child telomere length, and future disease risk. Telomere shortening is a marker of accelerated aging, which is known to be associated with an increased risk of chronic diseases. Future studies need to assess telomere length in combination with other markers of accelerated aging as well as in cohorts with longer-term follow-up. This would help determine whether markers of aging can be used to predict which individuals born from a complicated pregnancy are at an increased risk of chronic disease later in life.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/dna4020011/s1, Table S1: Mean (SD) telomere length by assessment city; Figure S1: Relative telomere length (mean and SD) for measurements obtained from DNA samples extracted from whole blood compared to the blood clot samples; Figure S2: Directed Acyclic Graphs for the association between maternal pregnancy complications and child telomere length.

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Institutional Review Board Statement: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (LSAC study) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Australian Institute of Family Studies Ethics Committee. Ethical approval for the Child Health CheckPoint module was granted by the Australian Institute of Family Studies Ethics Committee (14–26) in January–February 2014.

Informed Consent Statement: Parents provided written informed consent.

Data Availability Statement: Data are available from the Australian Institute of Family Studies who meet the criteria for access to confidential data. Data users are required to complete a dataset application and read and sign a completed deed of licence. The detailed information about accessing the LSAC data is available via the website: https://growingupinaustralia.gov.au/data-and-documentation/accessing-lsac-data (accessed on 12 August 2021).

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Conflicts of Interest: The authors declare no conflicts of interest.

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