The Association between Early-life Relative Telomere Length and Childhood Neurodevelopment

Marina Oktapodas Feiler, MS[a], Deven Patel, PhD[b], Huiqi Li, PhD[c], Philip J. Meacham, MS[a], Gene E. Watson, DDS, PhD[a], Conrad Shamlaye, MBChB[d], Alison Yeates, PhD[e], Karin Broberg, PhD[f], Edwin van Wijngaarden, PhD*[a]

[a] University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

[b] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD

[c] Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden

[d] Ministry of Health, Republic of Seychelles, Seychelles

[e] Ulster University, Coleraine, UK

[f] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

***Please address correspondence to:**

Edwin van Wijngaarden, PhD

Department of Public Health Sciences

University of Rochester Medical Center

265 Crittenden Blvd, CU 420644

Rochester, NY 14642

edwin_van_wijngaarden@urmc.rochester.edu

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Abstract

Purpose: To examine the association between telomere length and neurodevelopment in children.

Methods: We examined the relationship between relative telomere length (rTL) and neurodevelopmental outcomes at 9 and 30 months, and 5 years of age in children enrolled in the Seychelles Child Development Study Nutrition Cohort 1 (NC1). Relative telomere length was measured in cord blood and in child blood at age five. Multivariable linear regression examined associations between neurodevelopmental outcomes and rTL adjusting for relevant covariates.

Results: Mean rTL was 1.18 at birth and 0.71 at age five. Increased cord blood rTL was associated with better scores on two neurodevelopmental tests, the psychomotor developmental index (β =4.01; 95% confidence interval (CI)=0.17, 7.85) at age 30 months, and the Woodcock Johnson test of achievement letter-word score (β=2.88; CI=1.21-4.56) at age five. The Woodcock Johnson test of achievement letter-word score remained statistically significant after two outliers were excluded (β=2.83; CI=0.69, 4.97); the psychomotor developmental index did not (β =3.62; CI=-1.28, 8.52). None of the neurodevelopmental outcomes at age five were associated with five-year rTL.

Conclusion: Although increased cord blood rTL was associated with better test scores for a few neurodevelopmental outcomes, this study found little consistent evidence of an association between rTL and neurodevelopment. Future studies with a larger sample size, longer follow-up, and other relevant biological markers (e.g. oxidative stress) are needed to clarify the role of rTL in neurodevelopment and its relevance as a potential surrogate measure for oxidative stress in the field of developmental neurotoxicity.

Keywords: children, epidemiology, cognition, language**.**

Introduction

Telomeres are non-coding, nucleoprotein complexes at the ends of eukaryotic chromosomes whose function is to preserve genomic integrity. Telomeres naturally shorten due to incomplete DNA replication during cellular divisions, otherwise known as cellular aging (Blackburn, 2001; McEachern, Krauskopf, & Blackburn, 2000). Telomeres eventually reach a critical point in length where they lose their protective functions and the cells stop dividing and enter either apoptosis or cellular senescence (Gisselsson et al., 2001; Murnane, 2006; Verdun & Karlseder, 2007). Therefore, telomere length can be considered to be a measure of our "biological" age as opposed to our "chronological" age (Oeseburg, de Boer, van Gilst, & van der Harst, 2010). As a marker for cellular aging, telomere length (TL) is seen as a possible predictor of various age-related diseases, including cognitive decline. For example, telomere length has been associated with Alzheimer's disease, (Roberts et al., 2014; Zhan et al., 2015) as well as poor cognitive function in adults (Kingma, de Jonge, van der Harst, Ormel, & Rosmalen, 2012; Valdes et al., 2010; Yaffe et al., 2011). Similarly, TL at young ages may be associated with cognition and neurodevelopment in early life or may be related to adult cognitive function in later life, likely as an indirect marker of other biological processes that may influence neurodevelopment such as oxidative stress (Epel et al., 2004; Houben, Moonen, van Schooten, & Hageman, 2008; Von Zglinicki, 2000, 2002). TL may be considered a surrogate measure for underlying oxidative stress and inflammation and potentially a good biomarker of neurotoxicity, as has been indicated in previous literature (Epel et al., 2004; Houben et al., 2008; Von Zglinicki, 2000, 2002).

The relationship between TL and neurodevelopmental outcomes in children has received little attention. Only four studies to date have examined the association with neurobehavioral

outcomes in children (Costa Dde et al., 2015; Henje Blom et al., 2015; Z. Li et al., 2014; Wojcicki et al., 2015). Two of these studies have reported correlations between shorter TL and measures of depression and inattention in later childhood and adolescence (Costa Dde et al., 2015; Henje Blom et al., 2015). Other studies showed a shorter TL in young children with autism and defiant behavior (Z. Li et al., 2014; Wojcicki et al., 2015). Adding to this limited literature, our study examines the association between relative telomere length (rTL) and cognitive development, including motor, language, memory and problem-solving skills. These are more subtle aspects of development that have not been previously assessed in relation with TL.

Methods

Study population

The Seychelles Child Development Study (SCDS) is a series of longitudinal observational studies that evaluate the development of children in Seychelles, and examine if low levels of mercury exposure during pregnancy (due to a high fish diet) is associated with child development. The present analysis used data from the Nutrition Cohort 1 (NC1) (Davidson et al., 2008), a cohort of 300 mothers that were enrolled in 2001 during their first trimester of pregnancy. The inclusion criteria included mothers at least 16 years of age, native born of Seychelles, and residing on Mahé. Exclusion criteria included infants with major congenital anomalies and twins. Research protocols were reviewed and approved by the Institutional Review Boards of the University of Rochester, the Ministry of Health in Republic of Seychelles and the Regional Ethics Committee, Lund University. The procedures followed were in accordance with the Helsinki Declaration, and all participants gave informed consent. The

present study examined child telomere length at birth and at the time of examination at approximately age 5 years in relation to developmental outcomes assessed in the children at 9 months, 30 months, and 5 years of age.

Blood collection

Cord blood samples were collected immediately after delivery into EDTA-containing tubes, from which whole blood was obtained and stored at -80°C until analysis. Similarly, children's venous non-fasting blood samples were collected in EDTA-containing tubes after completion of the 5-year developmental assessment, from which whole blood samples were obtained and stored at -80°C.

Telomere length assessment

DNA was isolated from peripheral blood using the Qiagen DNA blood Midi kit (Qiagen, Hilden, Germany). Relative telomere length (rTL) was measured using real-time PCR (7900HT, Applied Biosystems, Foster City, CA, USA), as described previously (Ameer et al., 2016; H. Li, Engstrom, Vahter, & Broberg, 2012). Briefly, master mixes were prepared, containing 0.5 U *Taq* Platina (Invitrogen, Carlsbad, CA, USA), 1×PCR Buffer, 0.8 mM dNTPs, 1.75 mM $MgCl_2$, 0.3 mM SybrGreen (Invitrogen), 1×Rox (Invitrogen), and either telomere primers (0.45 μM of each primer), or hemoglobin beta chain (*HBB*) primers (0.45 μM for each primer). Five microliters of sample DNA (3 ng/μl) was added to each reaction resulting in a final volume of 20 μl. A standard curve, a reference DNA, and a negative control were also included in each run, and all samples, standards, and controls were run in triplicate. The relative length of the telomeres was obtained through calculating the ratio (T/S) of the telomere repeat product to a

single-copy gene product (S, here *HBB*) for each individual, by the formula $T/S = 2^{-\Delta Ct}$, where $\Delta Ct = Ct_{telomere} - Ct_{HBB}$. This ratio was then compared with the ratio of a reference DNA. The telomere length ratio is an arbitrary value. Relative telomere length was measured at birth from cord blood and again in blood collected at five years of age.

Neurodevelopmental assessment

We analyzed data from the Bayley Scales of Infant Development-II (BSID-II), a well-standardized measure of infant cognition and development that was administered at ages 9 and 30 months. The BSID-II yielded two endpoints: the mental developmental index (MDI) and psychomotor developmental index (PDI) (Davidson et al., 2008). We also examined the following developmental tests at five years of age: finger tapping (dominant and non-dominant hand), the Preschool Language Scale (total language score, verbal ability, and auditory comprehension), the Woodcock-Johnson Scholastic Achievement Test (letter-word recognition and applied problems), the Kaufman Brief Intelligence Test (verbal knowledge, matrices), and the Child Behavior Checklist (Strain et al., 2012).

Covariates

As in previous studies of this cohort, covariates were selected *a priori* based on their known association with developmental outcomes (Strain et al., 2008; Strain et al., 2012). Covariates included: child sex, birth weight, age of child at testing, Hollingshead socioeconomic status (SES) at birth, maternal IQ, maternal age at birth of child, family status (i.e. whether or not both parents resided with the child) at 9 months, and home environment at birth. Smoking was not included as a covariate because only eight mothers reported smoking during pregnancy.

Statistical analysis

Descriptive statistics for relevant sample characteristics were calculated, including the mean, median, and standard deviation for all continuous variables, the proportions for categorical variables, and the distribution of cord blood rTL, 5-year rTL, and all neurodevelopment outcomes. We examined correlation coefficients for the association between cord rTL, 5-year r-TL, and change in rTL from birth to 5-years of age. Cord rTL and five-year rTL were poorly correlated (spearman $r=0.26$, $p=0.0007$; pearson $r=0.14$, $p=0.067$), whereas cord rTL and change in rTL were highly correlated (spearman $r= -0.90$, $p<0.0001$; pearson $r=-0.98$, $p<0.0001$). Therefore, the change in rTL was not further investigated as it did not contribute additional statistical information to cord blood rTL. Two outliers were identified in the cord blood rTL, defined as being at least three interquartile lengths above the third quartile (Tukey, 1977). Analyses of cord rTL were conducted with and without these observations. Appropriate assumptions were tested confirming regression models were appropriate for this analysis (Rosner, 2011).

Covariate-adjusted linear regression analyses of cord blood rTL were performed separately for 9-month, 30-month and 5-year developmental outcomes. Similarly, adjusted regression analyses modeled 5-year rTL against the outcomes at age five. We considered examining categories of shortened, maintained, and lengthened rTL using cut-points of 5% and 10% difference between five-year and cord blood rTL as proposed elsewhere (Wojcicki, Shiboski, et al., 2016). However, only a few children maintained or increased rTL using a 5% ($n=13$) or 10% ($n=15$) cut off; therefore, this was not further pursued.

In secondary analyses, we examined cord rTL in quartiles to assess the nature dose-response relationship between cord rTL and developmental outcomes that were statistically significantly associated in continuous cord rTL analyses, in order to check consistency in our findings. P values <0.05 were considered statistically significant. All data management and analyses were performed using the SAS software system (SAS Institute Inc., Cary, NC, USA; version 9.4).

Results

Study population

Demographic, maternal and child characteristics are shown in Table 1. The sample size for cord blood rTL was n=184 and for the 5-year rTL was n=209. A similar number of males and females were included in the analysis, children had an average birth weight (SD) of 3247g (480), and had one parent or less residing in the household (53%). On average, mothers were 27 years of age, and had mean SES, PROCESS, and K-bit scores of 34, 152, and 86, respectively. Mean rTL was 1.18 at birth and decreased to 0.71 at age five. There was no considerable difference between males and females in mean TL in cord blood (1.18 and 1.19, respectively) or at age 5 (0.70 and 0.73, respectively). Other covariates were also not associated with either cord blood or 5-year rTL (data not shown).

Relative telomere length and neurodevelopmental outcomes at age 9 and 30 months, and age 5

Table 2 shows the adjusted results for the associations of cord blood and 5-year rTL with the various neurodevelopmental outcomes at the three different time points, including the full sample and after removing outliers (n=2). Overall, there was no clear association between rTL

and neurodevelopmental outcomes in this study population. The majority of the outcomes show a slight positive association, however; the results are statistically imprecise and associations were not consistent across the different developmental outcomes and rTL measures. Cord blood rTL was associated with improved scores on the psychomotor development index (β =4.01; 0.17, 7.85) at age 30 months and on the Woodcock Johnson test of achievement letter-word (β=2.88; 95% CI: 1.21, 4.56) at age five (Table 2). When removing two outliers the Woodcock Johnson letter-word score remained statistically significant (Table 2), whereas the association with the psychomotor development index remained positive but lost precision and statistical significance (Table 2). Inference for the other outcomes was not affected after excluding the two outliers, despite the change in point estimate for some outcomes (e.g. MDI). In categorical cord rTL analysis we did not observe clear monotonic dose-response patterns for psychomotor development index (quartile 1: reference; quartile 2: β=5.42; 95% CI: 0.03, 10.81; quartile 3: β=7.51; 95% CI: 2.04, 12.98; quartile 4: β=4.71; 95% CI: -0.75, 10.18) and the Woodcock Johnson Achievement letter-word scores (quartile 1: reference; quartile 2: β=-0.27; 95% CI: -2.69, 2.15; quartile 3: β=0.24; 95% CI: -2.24, 2.72; quartile 4: (β=1.72; 95% CI: -0.77, 4.20). Other neurodevelopmental outcomes were not statistically significantly associated with cord blood (Table 2), and none of the outcomes were associated with five-year rTL (Table 3).

Discussion

Our study examined rTL with an array of neurodevelopmental tests in young children. We did not find consistent associations between rTL and neurodevelopmental outcomes. Only a few of the neurodevelopmental outcomes showed positive associations with cord blood rTL, including the Woodcock Johnson Achievement letter-word test and psychomotor development index. We

found no consistent dose-response relationship with these outcomes in categorical analyses however, and the psychomotor developmental index association was no longer significant after excluding two outliers; thus we should interpret our results cautiously. There were no significant differences in rTL between males and females, consistent with the lack of a sex difference in rTL in a case-control study of autism (Z. Li et al., 2014). Nevertheless, studies investigating the association with TL in children are limited (Costa Dde et al., 2015; Henje Blom et al., 2015; Z. Li et al., 2014; Wojcicki et al., 2015). No previous studies have investigated this association in infants and young children using the measures of neurodevelopment as we studied, but studies of other adverse cognitive or behavioral outcomes in children suggest an increased risk with decreases in TL (Costa Dde et al., 2015; Henje Blom et al., 2015; Z. Li et al., 2014; Wojcicki et al., 2015). In a case-control study of autism (n=239), children 4-6 years old with an autism diagnosis had a statistically significantly lower telomere length (0.88) compared with children without autism (1.01) (Z. Li et al., 2014). An additional study (n=108) was conducted investigating oppositional defiant behavior in 3-5 year olds and telomere length (Wojcicki et al., 2015). Telomere length was measured using base pairs, and the results showed that oppositional defiant behavior was a predictor of shorter telomere length (β= -359.25 (95% CI: -633.84, -84.66), p=0.01) (Wojcicki et al., 2015). Lastly, a study of inattention and behavior assessed ADHD and telomere length in children aged 6-16 years of age (n=61) (Costa Dde et al., 2015). The hyperactive and impulsive dimensions of ADHD were found to be negatively correlated TL in children (r= -0.34, p=0.0008), while the inattention dimension was not found to be associated with TL (p>0.05) (Costa Dde et al., 2015). Sample sizes in these studies range from n=61 to n=239, and so the present study falls on the higher end of the spectrum with n=209. The methods for measuring telomere length varied across studies, and therefore results from previous studies

cannot be directly compared to ours. Nevertheless, these studies still provide information on the consistency of evidence that telomere length plays some role on neurodevelopment and neurobehavioral outcomes in childhood and adolescence.

An important potential pathway to consider is that through oxidative stress and inflammation. Telomere length can be considered a biomarker of oxidative stress (Epel et al., 2004; Houben et al., 2008; Von Zglinicki, 2000, 2002). Life stress has also shown to accelerate telomere length shortening in healthy premenopausal women, suggesting that higher levels of life stress are associated with higher levels of oxidative stress (Epel et al., 2004). Chronic inflammation has shown to lead to persistent damage to telomeres and in return increase the rate of biological aging (Houben et al., 2008), and may influence neurodevelopment, (Andrews et al., 2008; Stolp & Dziegielewska, 2009; van der Burg et al., 2016). Thus, TL may be a surrogate marker for underlying oxidative stress and inflammation, which more directly impact neurodevelopmental outcomes, and as such, be a useful marker in longitudinal studies to reflect these processes. The use of TL as an imperfect surrogate measure of underlying biological processes may have resulted in null findings in the present study.

More research has been done in adults to evaluate telomere length, aging and neuropsychological and cognitive outcomes (Kingma et al., 2012; Roberts et al., 2014; Valdes et al., 2010; Yaffe et al., 2011; Zhan et al., 2015). The PREVEND study in the Netherlands investigated intelligence and telomere length in adults (Kingma et al., 2012). Findings suggested increased general intelligence, measured by the General Aptitude-Test Battery (GATB), was associated with longer telomere length ($\beta = 0.163$, $p < .001$), after adjustment for additional covariates (Kingma et

al., 2012). A study of healthy women used the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess neuropsychological aptitude and examined the association with telomere length (Valdes et al., 2010). Three dimensions of the CANTAB (delayed matching to sample, pattern recognition and space span) were all found to be positively correlated with longer TL ($p<.05$) (Valdes et al., 2010). The other three dimensions (paired associations learning, reaction time, spatial working memory) were found to be negatively correlated with TL (Valdes et al., 2010). Further analyses in children using sensitive cognitive test batteries such as CANTAB may shed further light on this association.

Several studies have assessed predictors of telomere length in children (Gilfillan et al., 2016; Wojcicki, Olveda, et al., 2016). One study in particular examining Latino children found female sex, higher maternal education, and child head circumference to be associated with longer cord blood telomere length (Wojcicki, Olveda, et al., 2016). Furthermore, shorter cord blood telomere length was associated with some level of oxidative stress in utero (preeclampsia, maternal hypertension, gestational diabetes), as well as low birth weight and preterm birth (Wojcicki, Olveda, et al., 2016). Additionally, a study assessing fetal telomere length with maternal and fetal glucose levels found inverse associations, $\beta= -0.563$, $p<0.05$ and $\beta = -0.297$, $p<0.05$, respectively (Gilfillan et al., 2016). These associations suggest possibly mechanisms by which prenatal factors may influence child telomere length and neurodevelopment. We did not find clear associations with our covariates other than family status.

While the sample size was relatively small resulting in imprecise estimates of association, the present study is the first to directly assess rTL and an array of tests assessing neurodevelopment

in young children during the most critical period of brain development. This is also one of few studies to assess this association longitudinally rather than cross-sectionally (Costa Dde et al., 2015; Henje Blom et al., 2015; Z. Li et al., 2014; Wojcicki et al., 2015) using multiple rTL measurements and using a more comprehensive array of developmental outcomes than in previous studies. We were also able to account for important covariates.

Conclusion

In conclusion, our results do not strongly support an association between telomere length and child developmental outcomes at 5 years of age. Future studies with a larger sample size, longer follow-up, and other relevant biological markers (e.g. oxidative stress) are needed to clarify the role of rTL in neurodevelopment.

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Abbreviations:

rTL- Relative telomere length

TL- Telomere length

SCDS- Seychelles Child Development Study

NC1- Nutritional Cohort 1

BSID-II- Bayley Scales of Infant Development-II

MDI- Mental Development Index

PDI- Psychomotor Development Index

SES- Socioeconomic status

GATB- General Aptitude-Test Battery

CANTAB- Cambridge Neuropsychological Test Automated Battery

HBB- Hemoglobin beta chain

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