

25 **Abstract**

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

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

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

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

47

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

49 **Introduction**

50 Telomeres are non-coding, nucleoprotein complexes at the ends of eukaryotic chromosomes
51 whose function is to preserve genomic integrity. Telomeres naturally shorten due to incomplete
52 DNA replication during cellular divisions, otherwise known as cellular aging (Blackburn, 2001;
53 McEachern, Krauskopf, & Blackburn, 2000). Telomeres eventually reach a critical point in
54 length where they lose their protective functions and the cells stop dividing and enter either
55 apoptosis or cellular senescence (Gisselsson et al., 2001; Murnane, 2006; Verdun & Karlseder,
56 2007). Therefore, telomere length can be considered to be a measure of our “biological” age as
57 opposed to our “chronological” age (Oeseburg, de Boer, van Gilst, & van der Harst, 2010). As a
58 marker for cellular aging, telomere length (TL) is seen as a possible predictor of various age-
59 related diseases, including cognitive decline. For example, telomere length has been associated
60 with Alzheimer’s disease, (Roberts et al., 2014; Zhan et al., 2015) as well as poor cognitive
61 function in adults (Kingma, de Jonge, van der Harst, Ormel, & Rosmalen, 2012; Valdes et al.,
62 2010; Yaffe et al., 2011). Similarly, TL at young ages may be associated with cognition and
63 neurodevelopment in early life or may be related to adult cognitive function in later life, likely as
64 an indirect marker of other biological processes that may influence neurodevelopment such as
65 oxidative stress (Epel et al., 2004; Houben, Moonen, van Schooten, & Hageman, 2008; Von
66 Zglinicki, 2000, 2002). TL may be considered a surrogate measure for underlying oxidative
67 stress and inflammation and potentially a good biomarker of neurotoxicity, as has been indicated
68 in previous literature (Epel et al., 2004; Houben et al., 2008; Von Zglinicki, 2000, 2002).

69

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

72 outcomes in children (Costa Dde et al., 2015; Henje Blom et al., 2015; Z. Li et al., 2014;
73 Wojcicki et al., 2015). Two of these studies have reported correlations between shorter TL and
74 measures of depression and inattention in later childhood and adolescence (Costa Dde et al.,
75 2015; Henje Blom et al., 2015). Other studies showed a shorter TL in young children with
76 autism and defiant behavior (Z. Li et al., 2014; Wojcicki et al., 2015). Adding to this limited
77 literature, our study examines the association between relative telomere length (rTL) and
78 cognitive development, including motor, language, memory and problem-solving skills. These
79 are more subtle aspects of development that have not been previously assessed in relation with
80 TL.

81

82 **Methods**

83 *Study population*

84 The Seychelles Child Development Study (SCDS) is a series of longitudinal
85 observational studies that evaluate the development of children in Seychelles, and examine if low
86 levels of mercury exposure during pregnancy (due to a high fish diet) is associated with child
87 development. The present analysis used data from the Nutrition Cohort 1 (NC1) (Davidson et al.,
88 2008), a cohort of 300 mothers that were enrolled in 2001 during their first trimester of
89 pregnancy. The inclusion criteria included mothers at least 16 years of age, native born of
90 Seychelles, and residing on Mahé. Exclusion criteria included infants with major congenital
91 anomalies and twins. Research protocols were reviewed and approved by the Institutional
92 Review Boards of the University of Rochester, the Ministry of Health in Republic of Seychelles
93 and the Regional Ethics Committee, Lund University. The procedures followed were in
94 accordance with the Helsinki Declaration, and all participants gave informed consent. The

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

98

99 *Blood collection*

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

105

106 *Telomere length assessment*

107 DNA was isolated from peripheral blood using the Qiagen DNA blood Midi kit (Qiagen,
108 Hilden, Germany). Relative telomere length (rTL) was measured using real-time PCR (7900HT,
109 Applied Biosystems, Foster City, CA, USA), as described previously (Ameer et al., 2016; H. Li,
110 Engstrom, Vahter, & Broberg, 2012). Briefly, master mixes were prepared, containing 0.5 U
111 *Taq* Platina (Invitrogen, Carlsbad, CA, USA), 1×PCR Buffer, 0.8 mM dNTPs, 1.75 mM MgCl₂,
112 0.3 mM SybrGreen (Invitrogen), 1×Rox (Invitrogen), and either telomere primers (0.45 μM of
113 each primer), or hemoglobin beta chain (*HBB*) primers (0.45 μM for each primer). Five
114 microliters of sample DNA (3 ng/μl) was added to each reaction resulting in a final volume of 20
115 μl. A standard curve, a reference DNA, and a negative control were also included in each run,
116 and all samples, standards, and controls were run in triplicate. The relative length of the
117 telomeres was obtained through calculating the ratio (T/S) of the telomere repeat product to a

118 single-copy gene product (S, here *HBB*) for each individual, by the formula $T/S = 2^{-\Delta Ct}$, where
119 $\Delta Ct = Ct_{telomere} - Ct_{HBB}$. This ratio was then compared with the ratio of a reference DNA. The
120 telomere length ratio is an arbitrary value. Relative telomere length was measured at birth from
121 cord blood and again in blood collected at five years of age.

122

123 *Neurodevelopmental assessment*

124 We analyzed data from the Bayley Scales of Infant Development-II (BSID-II), a well-
125 standardized measure of infant cognition and development that was administered at ages 9 and
126 30 months. The BSID-II yielded two endpoints: the mental developmental index (MDI) and
127 psychomotor developmental index (PDI) (Davidson et al., 2008). We also examined the
128 following developmental tests at five years of age: finger tapping (dominant and non-dominant
129 hand), the Preschool Language Scale (total language score, verbal ability, and auditory
130 comprehension), the Woodcock-Johnson Scholastic Achievement Test (letter-word recognition
131 and applied problems), the Kaufman Brief Intelligence Test (verbal knowledge, matrices), and
132 the Child Behavior Checklist (Strain et al., 2012).

133

134 *Covariates*

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

141

142 *Statistical analysis*

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

156 Covariate-adjusted linear regression analyses of cord blood rTL were performed
157 separately for 9-month, 30-month and 5-year developmental outcomes. Similarly, adjusted
158 regression analyses modeled 5-year rTL against the outcomes at age five. We considered
159 examining categories of shortened, maintained, and lengthened rTL using cut-points of 5% and
160 10% difference between five-year and cord blood rTL as proposed elsewhere (Wojcicki,
161 Shiboski, et al., 2016). However, only a few children maintained or increased rTL using a 5%
162 ($n=13$) or 10% ($n=15$) cut off; therefore, this was not further pursued.

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

169

170 **Results**

171 *Study population*

172 Demographic, maternal and child characteristics are shown in Table 1. The sample size for cord
173 blood rTL was n=184 and for the 5-year rTL was n=209. A similar number of males and females
174 were included in the analysis, children had an average birth weight (SD) of 3247g (480), and had
175 one parent or less residing in the household (53%). On average, mothers were 27 years of age,
176 and had mean SES, PROCESS, and K-bit scores of 34, 152, and 86, respectively. Mean rTL was
177 1.18 at birth and decreased to 0.71 at age five. There was no considerable difference between
178 males and females in mean TL in cord blood (1.18 and 1.19, respectively) or at age 5 (0.70 and
179 0.73, respectively). Other covariates were also not associated with either cord blood or 5-year
180 rTL (data not shown).

181

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

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

186 and neurodevelopmental outcomes in this study population. The majority of the outcomes show a
187 slight positive association, however; the results are statistically imprecise and associations were
188 not consistent across the different developmental outcomes and rTL measures. Cord blood rTL
189 was associated with improved scores on the psychomotor development index ($\beta = 4.01$; 0.17,
190 7.85) at age 30 months and on the Woodcock Johnson test of achievement letter-word ($\beta = 2.88$;
191 95% CI: 1.21, 4.56) at age five (Table 2). When removing two outliers the Woodcock Johnson
192 letter-word score remained statistically significant (Table 2), whereas the association with the
193 psychomotor development index remained positive but lost precision and statistical significance
194 (Table 2). Inference for the other outcomes was not affected after excluding the two outliers,
195 despite the change in point estimate for some outcomes (e.g. MDI). In categorical cord rTL
196 analysis we did not observe clear monotonic dose-response patterns for psychomotor
197 development index (quartile 1: reference; quartile 2: $\beta = 5.42$; 95% CI: 0.03, 10.81; quartile 3:
198 $\beta = 7.51$; 95% CI: 2.04, 12.98; quartile 4: $\beta = 4.71$; 95% CI: -0.75, 10.18) and the Woodcock
199 Johnson Achievement letter-word scores (quartile 1: reference; quartile 2: $\beta = -0.27$; 95% CI: -
200 2.69, 2.15; quartile 3: $\beta = 0.24$; 95% CI: -2.24, 2.72; quartile 4: ($\beta = 1.72$; 95% CI: -0.77, 4.20)).
201 Other neurodevelopmental outcomes were not statistically significantly associated with cord
202 blood (Table 2), and none of the outcomes were associated with five-year rTL (Table 3).

203

204 **Discussion**

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

209 found no consistent dose-response relationship with these outcomes in categorical analyses
210 however, and the psychomotor developmental index association was no longer significant after
211 excluding two outliers; thus we should interpret our results cautiously. There were no significant
212 differences in rTL between males and females, consistent with the lack of a sex difference in rTL
213 in a case-control study of autism (Z. Li et al., 2014). Nevertheless, studies investigating the
214 association with TL in children are limited (Costa Dde et al., 2015; Henje Blom et al., 2015; Z.
215 Li et al., 2014; Wojcicki et al., 2015). No previous studies have investigated this association in
216 infants and young children using the measures of neurodevelopment as we studied, but studies of
217 other adverse cognitive or behavioral outcomes in children suggest an increased risk with
218 decreases in TL (Costa Dde et al., 2015; Henje Blom et al., 2015; Z. Li et al., 2014; Wojcicki et
219 al., 2015). In a case-control study of autism (n=239), children 4-6 years old with an autism
220 diagnosis had a statistically significantly lower telomere length (0.88) compared with children
221 without autism (1.01) (Z. Li et al., 2014). An additional study (n=108) was conducted
222 investigating oppositional defiant behavior in 3-5 year olds and telomere length (Wojcicki et al.,
223 2015). Telomere length was measured using base pairs, and the results showed that oppositional
224 defiant behavior was a predictor of shorter telomere length ($\beta = -359.25$ (95% CI: -633.84, -
225 84.66), $p=0.01$) (Wojcicki et al., 2015). Lastly, a study of inattention and behavior assessed
226 ADHD and telomere length in children aged 6-16 years of age (n=61) (Costa Dde et al., 2015).
227 The hyperactive and impulsive dimensions of ADHD were found to be negatively correlated TL
228 in children ($r = -0.34$, $p=0.0008$), while the inattention dimension was not found to be associated
229 with TL ($p>0.05$) (Costa Dde et al., 2015). Sample sizes in these studies range from n=61 to
230 n=239, and so the present study falls on the higher end of the spectrum with n=209. The methods
231 for measuring telomere length varied across studies, and therefore results from previous studies

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

235

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

248

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

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

263

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

275

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

278 in young children during the most critical period of brain development. This is also one of few
279 studies to assess this association longitudinally rather than cross-sectionally (Costa Dde et al.,
280 2015; Henje Blom et al., 2015; Z. Li et al., 2014; Wojcicki et al., 2015) using multiple rTL
281 measurements and using a more comprehensive array of developmental outcomes than in
282 previous studies. We were also able to account for important covariates.

283

284 **Conclusion**

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

289

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296

297 **Abbreviations:**

298 rTL- Relative telomere length

299 TL- Telomere length

300 SCDS- Seychelles Child Development Study

301 NC1- Nutritional Cohort 1

- 302 BSID-II- Bayley Scales of Infant Development-II
- 303 MDI- Mental Development Index
- 304 PDI- Psychomotor Development Index
- 305 SES- Socioeconomic status
- 306 GATB- General Aptitude-Test Battery
- 307 CANTAB- Cambridge Neuropsychological Test Automated Battery
- 308 HBB- Hemoglobin beta chain
- 309

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