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Telomere length and early trauma in schizophrenia

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Abstract

Background: Childhood trauma is emerging as a risk factor for schizophrenia, but its mechanism with respect to etiology is unknown. One possible pathway is through leucocyte telomere length (LTL) shortening, a measure of cellular aging associated with trauma. This study examined early trauma and LTL shortening in schizophrenia and considered sex effects.

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Author contributions

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Eugene Ruby – writing, data analysis.
Raymond R. Goetz – data collection and analyses, data interpretation, writing, final review of manuscript.
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Conflicts of interests

None exist.

Methods: The early trauma inventory (ETI) was administered to 48 adults with DSM-5 schizophrenia and 18 comparison participants. LTL was measured using qPCR.

Outcomes: Cases had significantly more global trauma ($F = 4.10$, $p < 0.01$) and traumatic events ($F = 11.23$, $p < 0.001$), but case and control groups had similar LTL (1.91 ± 0.74 and 1.83 ± 0.62: $p = 0.68$). The association of early trauma and LTL differed by sex in cases and controls (Fisher's R: $Z < 0.05$). Significant negative associations were shown in male cases and, conversely, in female controls. For example, physical punishment was associated LTL shortening in males' cases ($r = -0.429$, $p < 01$). Only female controls showed significant telomere shortening in association with early trauma.

Interpretation: This data confirms the substantial excess of early trauma among schizophrenia cases. There were significant sex-differences in the relationship of the trauma to LTL, with only male cases showing the expected shortening. There were converse sex effects in the control group. Mean LTL was notably similar in cases and controls, despite the trauma-related shortening in male cases, cigarette smoking, older age and chronic illness of the cases. Factors may lengthen LTL in some schizophrenia cases. The converse sex differences in the cases are consistent with findings defective sexual differentiation in schizophrenia, consistent with other findings in the field.

Keywords

Early trauma; Schizophrenia; Childhood trauma; Leukocytes; Telomeres; Stress

1. Introduction

Early trauma exposure is a major risk factor for schizophrenia (Heins et al., 2011; Ruby et al., 2014; Varese et al., 2012), which is furthermore associated with clinical features in the disease, particularly with treatment refractory psychotic symptoms, including auditory hallucinations and command hallucinations (Carr et al., 2013; Heins et al., 2011; Rajkumar, 2015; Read et al., 2005; Ruby et al., 2017; Van Os et al., 2008; Varese et al., 2012). There are a number of possible pathways that could explain the relationship of early trauma to the development of schizophrenia (Read et al., 2001; Ruby et al., 2014; Veras et al., 2018) but none are yet shown to explain the association. One possible mechanism is the shortening telomere lengths by trauma. Shorter telomeres are a biological marker of cellular aging that has been linked to early trauma exposure in population studies (Epel et al., 2004; Kananen et al., 2010; Price et al., 2013; Shalev, 2012; Shalev et al., 2013).

Briefly, telomeres are tandem repeats of TTAGGG at both ends of mammalian chromosomes that form a protective cap to buffer genes against damage during replication. Telomere lengths decrease with each cell replication in somatic cells. Shorter telomeres predict fewer future cell divisions and more rapid cell senescence, ultimately triggering programmed cell death (apoptosis). Telomere length, usually measured as leukocyte telomere length (LTL) predicts lifespan as well as cellular aging (Armanios, 2013). Cortisol and dysregulated Hypothalamic Pituitary Axis (HPA) activity can reduce LTL, with shorter telomeres demonstrated in stressed women caring for partners with dementia and in numerous other comparable circumstances (Damjanovic et al., 2007; Oliveira et al., 2016). The enzyme telomerase, which normally lengthens telomeres in stem cells but is silenced in somatic

cells, undergoes reduced activity from cortisol exposure in cultured T lymphocyte (Choi et al., 2008). Stress and elevated cortisol levels are furthermore linked to inflammation and oxidative stress, which also produce telomere erosion (Shalev, 2012). Glucocorticoids augment the oxidative stress that can produce double-stranded telomeric breaks leading to LTL shortening (Epel et al., 2004).Together these findings support a role for the HPA stress axis in telomere length maintenance.

Demonstrating that early trauma contributes to telomere shortening in schizophrenia may shed light on the contradictory findings concerning LTL in schizophrenia. An initial study reported shortened LTL in schizophrenia cases compared to controls, which was in keeping with the earlier mortality, cigarette smoking, cardiovascular diseases and chronic poor health of most persons with schizophrenia (Kao et al., 2008). For example, cigarette smoking is associated with shortened LTL in large population studies and the vast majority of cases, upwards of 80%, smoke cigarettes (McGrath et al., 2007). Moreover, shortened telomeres were observed in several other psychiatric disorders (Darrow et al., 2016). However subsequent studies found no mean difference in LTL between cases and controls and yet other reports described longer LTL in groups of schizophrenia cases (Nieratschker et al., 2013; Rao et al., 2016).

This study tested the hypothesis that childhood trauma is related to shorter LTL in schizophrenia. If so, then childhood adversity may contribute to the disease through cellular aging. We used a reliable and valid structured interview to assess trauma exposure in a sample of exceptionally well-characterized schizophrenia cases and healthy controls.

2. Materials and method

The study was conducted at a large urban public hospital and was approved by the Institutional Review Boards of NYU Medical Center and Bellevue Hospital Center. All participants provided written informed consent. Cases with schizophrenia or schizoaffective disorder on stable medication doses were recruited from inpatient and outpatient treatment settings and healthy controls were recruited from local postings and internet- recruitment sites. Healthy control participants were excluded if they met criteria for an Axis I diagnosis in the last two years, had ever taken psychiatric medications, or had any personal or family history of psychosis in first-degree relatives on structured interviews.

To determine DSM diagnosis, Master's level clinicians conducted assessments with the Diagnostic Interview for Genetic Studies (DIGS) and utilized hospital records (Nurnberger et al., 1994). Childhood trauma exposure was assessed with the early trauma inventory (ETI) (Bremner et al., 2000), which includes measures of general traumatic events, physical abuse, emotional abuse, and sexual abuse before age 18, as well as general trauma after the age of 18. Analyses of inter-rater reliability, test-retest reliability, internal consistency, and convergent validity all indicate that the ETI is a reliable and valid assessment for the measurement of reported childhood trauma (Bremner et al., 2000). For all participants, cigarette smoking history was categorized as never, past, or current. Lifetime cumulative antipsychotic equivalents were not assessed, but cases were categorized based

on their current psychiatric medications: those taking any Lithium, clozapine, Risperdal, aripiprazole, haloperidol injection, other atypical agents, none and unknown.

For LTL, DNA was extracted from lymphocytes (EAG Laboratories; Hercules, CA, USA) by quantitative polymerase chain reaction (qPCR) with iCycler real-time PCR system and several modifications, as we have previously detailed (Cawthon, 2002; Malaspina et al., 2014). Each sample was assayed in triplicate with the Rotor-Gene SYBR Green PCR Master Mix from Qiagen. LTL was determined by calculating the telomere to single copy gene ratio (T/S ratio) using ΔCt. The T/S ratio of each sample (x) was normalized relative to the mean T/S ratio of the reference sample [2 − (Δctx − ΔCtr) = 2 − ΔΔCt], which was used to construct standard curves for a reference and a validation sample.

3. Data analysis

Data was entered and verified using the SIR Database Management Software (SIR 2002, SIR Pty Ltd) and IBM/SPSS Statistics 23 was used for the analyses. Descriptive statistics and distributions of all measures were examined, whether continuous or categorical, to identify key features (e.g. non-normal distribution, outliers, skewness) that impacted inferential methods. Age, education, and LTL were compared across diagnosis and sex using ANOVA. Age of illness onset was compared across the male and female cases using the *t*-test statistic. The ETI Domains were analyzed using MANCOVA with age as a covariate. Smoking status was analyzed using the Chi-squared statistic. Due to the small sample size, spearman correlations were performed between LTL and the ETI Domains and scatterplots were run to assess for outliers. Male and female cases with outlier (elongated) LTL were determined statistically using the SPSS “Examine procedure,” which identifies values that are not within the interquartile range of values; i.e. within 1.5 standard deviations from the median. Post-hoc analysis investigated paternal age of male outliers.

4. Results

Schizophrenia cases were older and less educated than controls, and only two controls were current or past smokers compared to 32 of 48 cases, demonstrating a substantial group effect for smoking status among the schizophrenia cases ($p < 0.001$). Schizophrenia cases had significantly greater exposure to trauma than controls, particularly for general trauma and emotional abuse, with no significant sex differences in their trauma exposures or LTL measurements. However, the mean LTL measurements were similar for the groups of cases and controls, respectively 1.91 (0.74) and 1.83 (0.62). There was no significant group level association between LTL and subjects age (Spearman’s non-parametric statistics) in either the cases (rho = −0.009) or controls (rho = −0.203). In cases, LTL was also not significantly related to current medication groups, with sample sizes and mean LTL as follows: Lithium (n = 4), mean 1.57 (SD 0.12); clozapine (n = 6), 2.14 (0.67); Risperdal (n = 12), 1.95 (0.55); aripiprazole (n = 5), 2.32 (0.99); haloperidol injection (n = 1), 2.15; other atypical agents (n = 10), 1.74 (0.16); none (4), 1.92 (0.56) and unknown medications (6), 2.05 (0.53).

There were no significant associations between LTL and trauma indices for general events, physical punishment, emotional abuse, sexual events and the grand total of events (r’s

= −0.20 to +0.22) for cases or controls. Sex-specific analyses showed significant sex differences in the correlations of LTL with early trauma exposure. LTL was shorter in association with trauma severity in male cases, but not in female cases (−0.320 vs. 0.447: Fisher's R to Z Transformation < 0.05). The effect of trauma to shorten LTL with particularly strong for male cases exposed to early physical punishment and LTL (r = −0.429, p < 01). Conversely, female controls showed greater correlations between LTL reductions and trauma severity than male controls (−0.275 vs. 0.688: Fisher's R to Z Transformation < 0.05).

5. Discussion

This study demonstrated significantly greater exposure to early trauma for schizophrenia cases than healthy control subjects, supporting a large prior literature. While the trauma severity was not significantly associated with the mean group-level LTL in cases or controls, there were significant sex differences regarding these associations in both groups. Only male schizophrenia cases demonstrated the hypothesized significant LTL shortening from early trauma. Conversely, only female controls showed this same effect.

The identification of sex specific findings in LTL shortening with respect to trauma in schizophrenia males is also novel. However, the female sex specific finding in control subjects matches a recent report of sex differences in depressed subjects in the associations between LTL shortening and stress exposures (Liu et al., 2017). Any protective mechanism against trauma-related LTL shortening in males with depression is absent in the schizophrenia cases. While longer LTL for our female schizophrenia cases and for our male controls in relationship with trauma severity could certainly be a spurious finding, the results highlight the importance of sex stratification in studies of LTL. If validated in larger studies, the sex differences may explain some of the inconsistency in the literature concerning measures of stress exposure and LTL.

Although this is the first study examining the relationship of LTL and childhood adversity in schizophrenia, a recent meta-analysis showed a small but significant association (−0.08) could be measured at a mean age of 42 years (Hanssen et al., 2017), similar to the age of our samples. LTL is reported from other samples with respect to stress measures, but the results remain convoluted (Mathur et al., 2016), perhaps because of sex and illness effects. Shorter LTL in healthy adults was associated with stress-related reductions in heart rate variability, a measure of vagal activity, and greater cortisol output, but these relationships did not withstand corrections for covariates (Woody et al., 2017). Similar LTL in un-medicated depressed patients and healthy controls is reported in another study, but stress activation only predicted shorter LTLs in the healthy group (Fair et al., 2017). Longitudinal perspectives of life course exposures are likewise conflicting. Recent stressors, but not childhood adversities, predicted shorter LTL in one study (Verhoeven et al., 2015). Psychosocial stress has also been reported to be unrelated to LTL in older adults, but LTL still demonstrated weak negative associations with early life adversity (Schaakxs et al., 2015).

Antipsychotic medication was not a predictor of LTL in this study, although we did not have the data to calculate cumulative life course exposures to medications, did not have longitudinal data, and the samples were relatively small. It is notable that our cases on lithium actually had the shortest LTL. Among bipolar cases, long-term lithium was reported to predict longer LTL (Martinsson et al., 2013), although this study did not account for psychosis and was cross-sectional, so it is difficult to interpret with respect to the current findings (Table 1).

In light of their early trauma, cigarette smoking, medications, chronic illness and older ages, our cases did not have shorter LTL than the controls, consistent with a telomere lengthening mechanism, in at least some cases. The conflicting LTL findings in schizophrenia are consistent with etiological heterogeneity and different environmental exposures. While shorter or similar LTL in schizophrenia cases and controls have been reported (Czepielewski et al., 2016; Fernandez-Egea et al., 2009; Galletly et al., 2017; Kao et al., 2008; Mansour et al., 2011; Maurya et al., 2017; Polho et al., 2015; Rao et al., 2016; Wolkowitz et al., 2017), significantly longer LTL were demonstrated in a sample of over 500 schizophrenia cases (Nieratschker et al., 2013). One large meta-analytic study of subjects with diverse psychiatric disorders found LTL was not reduced in psychotic cases, whereas significant reductions were demonstrated for depressive and anxiety conditions (Darrow et al., 2016). Another study of elderly hospitalized schizophrenia cases in the Helsinki Birth Cohort Study likewise demonstrated longer LTL (Savolainen et al., 2012). These authors could not exclude a selection bias related to the late life survival of these elderly cases, particularly given the shorter lifespan of persons with mentally illness, but the finding still supports the heterogeneity of LTL in the disorder that may be useful. Both a family history of psychosis and with older paternal age are predictors of longer LTL in schizophrenia and both of these relationships suggest genetic effects (Aviv and Susser, 2013; Malaspina et al., 2001). If so, genes involved in telomere homeostasis are reasonable candidates (Rivera et al., 2017). Polymorphisms in the XRCC3 gene, which trims telomeres, are associated with schizophrenia (Odemis et al., 2016). Future studies could examine polymorphisms in XRCC3 with respect to person-specific LTL and clinical features. Schizophrenia cases with longer LTL in our previous study attained a higher education than other cases and demonstrated a preserved verbal intelligence with a lower performance IQ (Vaez-Azizi et al., 2015). As a family history of psychosis might also be related to greater adversity (Malaspina et al., 2014) it is clear that larger studies are needed to account for the impact of different etiological factors on LTL.

Strengths of the current study include the use of the early trauma inventory, which accounts for a much wider range of occurrences than other instruments that assess early trauma and is reliable (Bremner et al., 2007; Bremner et al., 2000). Furthermore, we used a clinician-administered version of the inventory that allows clinicians to determine the patient's understanding of the questions being asked. Weaknesses included the small sample size, especially for the control group. As this was a cross-sectional study, another limitation is its reliance on recall and retrospective accounts of childhood trauma, which may be impaired by poor memory or biased in the cases. However, the reliability of psychotic patients' abuse reports is well been established (Lataster et al., 2006). While qPCR has been proven to be an effective method for estimating TL, our study included leukocytes and not neurons with the

understanding that LTL is strongly correlated with telomere length in other tissues. Studying medication free patients may be optimal, but is often impractical. Our few subjects taking no medications actually showed the same LTL as the group mean value. Ideally, longitudinal designs, such as epidemiological cohort studies with recordings of actual trauma, could be employed with actual trauma data.

While it remains to be determined how stress influences LTL, it is clear that stress exposure is a risk factor for psychosis, altering hypothalamic-pituitary-adrenal axis function, which may produce altered cognition and behaviors (Ruby et al., 2017). Further Illuminating the relationship between stress and telomere lengths is of great interest for psychiatric research and for understanding stress effects in the population.

This work highlights a novel male sex-specific association between severe early trauma exposure and LTL reduction. Furthermore, this association is converse of that in controls, wherein females showed the relationship between trauma and stress exposure. This converse sex-association in schizophrenia compared to the healthy controls is yet another measure suggesting that the pathobiology of schizophrenia may lie, in part, in the mechanisms related to sexual differentiation.

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References

Armanios M, 2013. Telomeres and age-related disease: how telomere biology informs clinical paradigms. J. Clin. Invest 123 (3), 996–1002. [PubMed: 23454763]

Aviv A, Susser E, 2013. Leukocyte telomere length and the father's age enigma: implications for population health and for life course. Int. J. Epidemiol 42 (2), 457–462. [PubMed: 23382366]

Bremner JD, Vermetten E, Mazure CM, 2000. Development and preliminary psycho-metric properties of an instrument for the measurement of childhood trauma: the Early Trauma Inventory. Depression and anxiety 12 (1), 1–12. [PubMed: 10999240]

Bremner JD, Bolus R, Mayer EA, 2007. Psychometric properties of the early trauma inventory–self report. J. Nerv. Ment. Dis 195 (3), 211. [PubMed: 17468680]

Carr CP, Martins CMS, Stingel AM, Lemgruber VB, Juruena MF, 2013. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. J. Nerv. Ment. Dis 201 (12), 1007–1020. [PubMed: 24284634]

Cawthon RM, 2002. Telomere measurement by quantitative PCR. Nucleic Acids Res. 30 (10), e47–e47. [PubMed: 12000852]

Choi J, Fauce SR, Effros RB, 2008. Reduced telomerase activity in human T lymphocytes exposed to cortisol. Brain Behav. Immun 22 (4), 600–605. [PubMed: 18222063]

Czepielewski LS, Massuda R, Panizzutti B, da Rosa ED, de Lucena D, Macêdo D, Grun LK, Barbé-Tuana FM, Gama CS, 2016. Telomere length in subjects with schizophrenia, their unaffected siblings and healthy controls: evidence of accelerated aging. Schizophr. Res 174 (1), 39–42. [PubMed: 27131910]

Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B, Zou Y, Beversdorf DQ, Weng N. p., 2007. Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. J. Immunol 179 (6), 4249–4254. [PubMed: 17785865]

Darrow SM, Verhoeven JE, Révész D, Lindqvist D, Penninx BW, Delucchi KL, Wolkowitz OM, Mathews CA, 2016. The association between psychiatric disorders and telomere length: a meta-analysis involving 14,827 persons. Psychosom. Med 78 (7), 776. [PubMed: 27359174]

Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM, 2004. Accelerated telomere shortening in response to life stress. Proc. Natl. Acad. Sci. U. S. A 101 (49), 17312–17315. [PubMed: 15574496]

Fair B, Mellon SH, Epel ES, Lin J, Révész D, Verhoeven JE, Penninx BW, Reus VI, Rosser R, Hough CM, 2017. Telomere length is inversely correlated with urinary stress hormone levels in healthy controls but not in un-medicated depressed individuals-preliminary findings. J. Psychosom. Res 99, 177–180. [PubMed: 28712425]

Fernandez-Egea E, Bernardo M, Heaphy CM, Griffith JK, Parellada E, Esmatjes E, Conget I, Nguyen L, George V, Stöppler H, 2009. Telomere length and pulse pressure in newly diagnosed, antipsychotic-naive patients with nonaffective psychosis. Schizophr. Bull 35 (2), 437–442. [PubMed: 19279086]

Galletly C, Dhillon VS, Liu D, Balzan RP, Hahn LA, Fenech MF, 2017. Shorter telomere length in people with schizophrenia: a preliminary study from Australia. Schizophr. Res 190, 46–51. [PubMed: 28285024]

Hanssen LM, Schutte NS, Malouff JM, Epel ES, 2017. The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis. Health psychology research 5 (1).

Heins M, Simons C, Lataster T, Pfeifer S, Versmissen D, Lardinois M, Marcelis M, Delespaul P, Krabbendam L, van Os J, 2011. Childhood trauma and psychosis: a case-control and case-sibling comparison across different levels of genetic liability, psychopathology, and type of trauma. Am. J. Psychiatr 168 (12), 1286–1294. [PubMed: 21955935]

Kananen L, Surakka I, Pirkola S, Suvisaari J, Lönnqvist J, Peltonen L, Ripatti S, Hovatta I, 2010. Childhood adversities are associated with shorter telomere length at adult age both in individuals with an anxiety disorder and controls. PLoS One 5 (5), e10826. [PubMed: 20520834]

Kao H, Cawthon R, Delisi L, Bertisch H, Ji F, Gordon D, Li P, Benedict M, Greenberg W, Porton B, 2008. Rapid telomere erosion in schizophrenia. Mol. Psychiatry 13 (2), 118. [PubMed: 18202693]

Lataster T, van Os J, Drukker M, Henquet C, Feron F, Gunther N, Myin-Germeys I, 2006. Childhood victimisation and developmental expression of non-clinical delusional ideation and hallucinatory experiences. Soc. Psychiatry Psychiatr. Epidemiol 41 (6), 423–428. [PubMed: 16572272]

Liu JJ, Wei YB, Forsell Y, Lavebratt C, 2017. Stress, depressive status and telomere length: does social interaction and coping strategy play a mediating role? J. Affect. Disord 222, 138–145. [PubMed: 28704801]

Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES, 2001. Advancing paternal age and the risk of schizophrenia. Arch. Gen. Psychiatry 58 (4), 361–367. [PubMed: 11296097]

Malaspina D, Dracxler R, Walsh-Messinger J, Harlap S, Goetz RR, Keefe D, Perrin MC, 2014. Telomere length, family history, and paternal age in schizophrenia. Molecular genetics & genomic medicine 2 (4), 326–331. [PubMed: 25077175]

Mansour H, Chowdari K, Fathi W, Elassy M, Ibrahim I, Wood J, Bamne M, Tobar S, Yassin A, Salah H, 2011. Does telomere length mediate associations between inbreeding and increased risk for bipolar I disorder and schizophrenia? Psychiatry Res. 188 (1), 129–132. [PubMed: 21300409]

Martinsson L, Wei Y, Xu D, Melas P, Mathé A, Schalling M, Lavebratt C, Backlund L, 2013. Long-term lithium treatment in bipolar disorder is associated with longer leukocyte telomeres. Transl. Psychiatry 3 (5), e261. [PubMed: 23695236]

Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, Khazeni N, 2016. Perceived stress and telomere length: a systematic review, meta-analysis, and methodologic considerations for advancing the field. Brain Behav. Immun 54, 158–169. [PubMed: 26853993]

Maurya PK, Rizzo LB, Xavier G, Tempaku PF, Zeni-Graiff M, Santoro ML, Mazzotti DR, Zugman A, Pan P, Noto C, 2017. Shorter leukocyte telomere length in patients at ultra high risk for psychosis. Eur. Neuropsychopharmacol 27 (5), 538–542. [PubMed: 28274506]

McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I, 2007. Telomere length, cigarette smoking, and bladder cancer risk in men and women. Cancer Epidemiology and Prevention Biomarkers 16 (4), 815–819.

Nieratschker V, Lahtinen J, Meier S, Strohmaier J, Frank J, Heinrich A, Breuer R, Witt SH, Nöthen MM, Rietschel M, 2013. Longer telomere length in patients with schizophrenia. Schizophr. Res 149 (1), 116–120. [PubMed: 23870621]

Nurnberger JI, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T, 1994. Diagnostic interview for genetic studies: rationale, unique features, and training. Arch. Gen. Psychiatry 51 (11), 849–859. [PubMed: 7944874]

Odemis S, Tuzun E, Gulec H, Semiz UB, Dasdemir S, Kucuk M, Yalcınkaya N, Bireller ES, Cakmakoglu B, Küçükali CI, 2016. Association between polymorphisms of DNA repair genes and risk of schizophrenia. Genetic testing and molecular biomarkers 20 (1), 11–17. [PubMed: 26554302]

Oliveira BS, Zunzunegui MV, Quinlan J, Fahmi H, Tu MT, Guerra RO, 2016. Systematic review of the association between chronic social stress and telomere length: a life course perspective. Ageing Res. Rev 26, 37–52. [PubMed: 26732034]

Polho G, De-Paula V, Cardillo G, Dos Santos B, Kerr D, 2015. Leukocyte telomere length in patients with schizophrenia: a meta-analysis. Schizophr. Res 165 (2), 195–200. [PubMed: 25975826]

Price LH, Kao H-T, Burgers DE, Carpenter LL, Tyrka AR, 2013. Telomeres and early-life stress: an overview. Biol. Psychiatry 73 (1), 15–23. [PubMed: 22831981]

Rajkumar RP, 2015. The impact of childhood adversity on the clinical features of schizophrenia. Schizophrenia research and treatment 2015.

Rao S, Kota LN, Li Z, Yao Y, Tang J, Mao C, Jain S, Xu Y, Xu Q, 2016. Accelerated leukocyte telomere erosion in schizophrenia: evidence from the present study and a meta-analysis. J. Psychiatr. Res 79, 50–56. [PubMed: 27174400]

Read J, Perry BD, Moskowitz A, Connolly J, 2001. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. Psychiatry: Interpersonal and Biological Processes 64 (4), 319–345.

Read J, Os J.v., Morrison AP, Ross CA, 2005. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatr. Scand 112 (5), 330–350. [PubMed: 16223421]

Rivera T, Haggblom C, Cosconati S, Karlseder J, 2017. A balance between elongation and trimming regulates telomere stability in stem cells. Nat. Struct. Mol. Biol 24 (1), 30. [PubMed: 27918544]

Ruby E, Polito S, McMahon K, Gorovitz M, Corcoran C, Malaspina D, 2014. Pathways associating childhood trauma to the neurobiology of schizophrenia. Frontiers in psychological and behavioral science 3 (1), 1–17. [PubMed: 25419548]

Ruby E, Rothman K, Corcoran C, Goetz RR, Malaspina D, 2017. Influence of early trauma on features of schizophrenia. Early Interv. Psychiatry 11 (4), 322–333. [PubMed: 25808607]

Savolainen K, Räikkönen K, Kananen L, Kajantie E, Hovatta I, Lahti M, Lahti J, Pesonen A-K, Heinonen K, Eriksson JG, 2012. History of mental disorders and leukocyte telomere length in late adulthood: the Helsinki Birth Cohort Study (HBCS). J. Psychiatr. Res 46 (10), 1346–1353. [PubMed: 22884422]

Schaakxs R, Verhoeven JE, Voshaar RCO, Comijs HC, Penninx BW, 2015. Leukocyte telomere length and late-life depression. Am. J. Geriatr. Psychiatry 23 (4), 423–432. [PubMed: 25028345]

Shalev I, 2012. Early life stress and telomere length: investigating the connection and possible mechanisms. BioEssays 34 (11), 943–952. [PubMed: 22991129]

Shalev I, Moffitt TE, Sugden K, Williams B, Houts RM, Danese A, Mill J, Arseneault L, Caspi A, 2013. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. Mol. Psychiatry 18 (5), 576. [PubMed: 22525489]

Vaez-Azizi LM, Ruby E, Dracxler R, Rothman K, Perrin M, Walsh-Messinger J, Antonius D, Goetz RR, Goetz DM, Keefe DL, 2015. Telomere length variability is related to symptoms and cognition in schizophrenia. Schizophr. Res 164 (1), 268–269. [PubMed: 25841297]

Van Os J, Rutten BP, Poulton R, 2008. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr. Bull 34 (6), 1066–1082. [PubMed: 18791076]

Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, Read J, van Os J, Bentall RP, 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. Schizophr. Bull 38 (4), 661–671. [PubMed: 22461484]

Veras AB, Peixoto C, Messinger JW, Getz M, Goetz R, Buckley P, Chao MV, Nardi AE, Malaspina D, Kranz TM, 2018. Early trauma and clinical features of schizophrenia cases influenced by the BDNF Val66Met allele. Schizophr Res. 193, 453–455. [PubMed: 28711474]

Verhoeven JE, van Oppen P, Puterman E, Elzinga B, Penninx BW, 2015. The association of early and recent psychosocial life stress with leukocyte telomere length. Psychosom. Med 77 (8), 882–891. [PubMed: 26374947]

Wolkowitz OM, Jeste DV, Martin AS, Lin J, Daly RE, Reuter C, Kraemer H, 2017. Leukocyte telomere length: effects of schizophrenia, age, and gender. J. Psychiatr. Res 85, 42–48. [PubMed: 27835738]

Woody A, Hamilton K, Livitz IE, Figueroa WS, Zoccola PM, 2017. Buccal telomere length and its associations with cortisol, heart rate variability, heart rate, and blood pressure responses to an acute social evaluative stressor in college students. Stress 20 (3), 249–257. [PubMed: 28482730]

Table 1

Demographics, leukocyte telomere length and early trauma in controls and cases, data presented by sex. Includes ANOVA for age, education and LTL; *t*-test for onset age; Chi-square for smoking; MANCOVA with age as covariate for early trauma domains.

	Healthy controls		**Schizophrenia cases**		**Statistics**		
	Males (N = 11)	**Females (N = 7)**	**Males (N = 28)**	**Females (N = 20)**	**Diag.**	**Sex**	**Diag./sex**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**F**	**F**	**F**
Age	36.5 (8.5)	37.3 (9.4)	41.9 (10.2)	43.3 (10.0)	4.21 *	0.16	0.01
Onset age	–	–	20.1 (6.8)	21.3 (7.1)	–	t = 0.54	–
Education	15.2 (1.9)	13.9 (2.5)	12.1 (2.6)	13.9 (2.5)	4.57 *	0.09	4.80 *
LTL	1.92 (0.76)	1.58 (0.54)	2.04 (0.84)	1.82 (0.68)	0.72	1.68	0.08
	Healthy controls		**Schizophrenia cases**		**Statistics**		
	Males (N = 11)	**Females (N = 6)**	**Males (N = 23)**	**Females (N = 18)**	**Diag.**	**Sex**	**Diag./sex**
					F	**F**	**F**
Smokers: N (%)	1 (9%)	1 (17%)	19 (83%)	13 (72%)	$Chi^2 = 21.77$ ***	$Chi^2 = 0.00$	
Early trauma inventory							
	Healthy controls		**Schizophrenia cases**		**Statistics**		
	Males (N = 11)	**Females (N = 7)**	**Males (N = 28)**	**Females (N = 20)**	**Diag.**	**Sex**	**Diag./sex**
					F	**F**	**F**
Multivariate Wilks' Lambda statistics→					4.10 **	1.88	0.51
General events	5.9 (5.4)	8.7 (6.2)	19.7 (14.3)	15.9 (10.0)	6.76 *	0.10	1.27
Punishment	4.1 (2.3)	3.0 (2.5)	6.5 (6.6)	5.5 (3.7)	2.08	0.68	0.00
Emotional	1.6 (2.3)	4.9 (9.6)	8.9 (7.9)	14.7 (10.8)	9.84 **	3.25 *t*	0.26
Sexual	0.55 (1.3)	1.0 (1.9)	6.7 (13.0)	6.0 (8.6)	3.29 t	0.01	0.05
ETI overall total	12.2 (9.0)	17.6 (13.3)	41.8 (30.0)	42.0 (24.1)	11.23 ***	0.09	0.18

t = trend.

* p < 0.050.

** p < 0.010.

*** p = 0.001.