Journal of Psychiatric Research 111 (2019) 169–185

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Psychometric liability to psychosis and childhood adversities are associated with shorter telomere length: A study on schizophrenia patients, unaffected siblings, and non-clinical controls

Burcu Çevik[a,b], Öykü Mançe-Çalışır[a], Eşref Cem Atbaşoğlu[c], Meram Can Saka[c], Köksal Alptekin[d], Alp Üçok[e], Burcu Sırmatel[f], Sinan Gülöksüz[g,h], Ajlan Tükün[i], Jim van Os[j,k,l], Güvem Gümüş-Akay[a,*]

[a] Brain Research Center, Ankara University, Ankara, Turkey
[b] Biotechnology Institute, Ankara University, Ankara, Turkey
[c] Department of Psychiatry, Ankara University Faculty of Medicine, Ankara, Turkey
[d] Department of Psychiatry, Dokuz Eylül University Faculty of Medicine, Izmir, Turkey
[e] Department of Psychiatry, Istanbul University Faculty of Medicine, Istanbul, Turkey
[f] Department of Physiology, Gazi University Faculty of Medicine, Ankara, Turkey
[g] Department of Psychiatry and Neuropsychology Maastricht University Medical Center, Maastricht, the Netherlands
[h] Department of Psychiatry, Yale School of Medicine, New Haven, USA
[i] Center of Genetic Diagnosis, Duzen Laboratories Group, Ankara, Turkey
[j] Maastricht University Medical Centre, Maastricht, the Netherlands
[k] Brain Centre Rudolf Magnus, Utrecht University Medical Centre, Utrecht, the Netherlands
[l] King's College London, Department of Psychosis Studies, Institute of Psychiatry, London, UK

ARTICLE INFO

Keywords:
Telomere length
Schizophrenia
Healthy siblings
Psychometric liability to psychosis
Childhood trauma
Resilience

ABSTRACT

Compared to the general population, individuals diagnosed with Schizophrenia (SCZ) experience a higher frequency and an earlier onset of chronic medical disorders, resulting in a reduction in life expectancy by an average of 15–25 years. Recently, it has been hypothesized that SCZ is a syndrome of accelerated aging. Childhood adversity was also associated with the pathogenesis and course of SCZ. Our hypothesis was that both SCZ patients and their unaffected siblings would have shorter telomere length (TL) compared to of non-clinical controls. Our additional goals were to determine (1) whether shorter TL correlates with intermediate phenotypes of SCZ (i.e. Psychosis-like symptoms and schizotypal traits); and (2) whether childhood adversities have a moderating role in TL shortening among SCZ and their unaffected siblings. To this end, SCZ patients (n = 100), their unaffected siblings (n = 100) and non-clinical controls (n = 100) were enrolled. The main variables were TL, measured by aTL-qPCR; psychotic-like and schizotypal symptoms, assessed by The Community Assessment of Psychic Experience (CAPE) and the Structured Interview for Schizotypy-Revised (SIS-R), respectively; and childhood adversities evaluated by the Childhood Experience of Care and Abuse (CECA)-*Interview*. Potentially relevant variables also included in the analyses were: Global Assessment of Functioning (GAF) scores, cognitive performance, and socio-demographic features. In contrast to our hypothesis patients had similar TL when compared to the non-clinical controls. Interestingly, unaffected siblings had longer TL compared to both patients and controls ($p < 0.001$). Independent from group status a negative correlation was observed between TL and psychotic-like symptoms as rated by the CAPE ($p < 0.01$). Childhood adversities, especially loneliness between ages 0 and 11 were also negatively associated with TL ($p < 0.05$). Our findings suggest that psychometric liability to psychosis and childhood adversities may be associated with shorter TL. Unaffected siblings had longer TL, suggesting the potential role of resilience on both the TL and the clinical presentation. These findings must be considered preliminary, calling for larger-scale replication efforts.

* Corresponding author. Ankara University Brain Research Center, Mamak Cad. No.33 06100 Demirlibahçe, Ankara, Turkey.
E-mail address: ggumusakay@ankara.edu.tr (G. Gümüş-Akay).

https://doi.org/10.1016/j.jpsychires.2019.01.022
Received 4 September 2018; Received in revised form 20 December 2018; Accepted 27 January 2019

1. Introduction

Schizophrenia (SCZ) is a complex disorder that affects perception, thoughts, and behaviour, and is characterized by alterations of intellectual abilities and emotional responses. Family, twin, and adoption studies have shown that multiple genetic and environmental factors play an important role in its etiology, but the molecular mechanisms underlying the disorder remain obscure (Keshavan et al., 2011; Perala et al., 2007). It has been recently hypothesized that SCZ is a syndrome of accelerated aging, which is defined as the earlier than normal onset or increased frequency of an age-related attribute or disease (Anthes, 2014; Kirkpatrick et al., 2008; Kirkpatrick and Kennedy, 2018; Nguyen et al., 2017). In support of this hypothesis, disorders that increase in incidence with age including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and cardiovascular diseases are more common and have an earlier onset in patients with SCZ compared to the general population (Weinberg et al., 2007). It is known that the life expectancy of patients is on average 15–25 years shorter than the general population, which is associated with high rates of smoking, substance use, metabolic side-effects of antipsychotic (AP) treatment, and unhealthy lifestyle ensuing from negative symptoms (Anthes, 2014; Kirkpatrick et al., 2008). On the other hand, it has been argued that external factors cannot fully explain the shortened life-span in SCZ and that the increased mortality rates may be related with somatic disorders inherent in the pathophysiology of SCZ (Dieset et al., 2016; Ringen et al., 2014).

The number of molecular biomarkers to test accelerated aging is still limited. However, telomere length (TL) and global DNA methylation changes are among the most promising estimators of biological age (Bacalini et al., 2017; Simm et al., 2008; Xia et al., 2017). Telomeres are specialized DNA-protein complexes composed of tandemly repeated DNA sequences, (TTAGGG)*n* in humans, and associated proteins at the end of all linear chromosomes (Blackburn et al., 2015). They protect chromosomes from nucleolytic degradation, end-to-end fusions, and from being recognized as damaged DNA. They also play a role in the regulation of gene expression by contributing to the functional organization of chromosomes within the nucleus. Telomeres shorten 50-300bp with each cell division because of the end-replication problem, causing cells to stop dividing and become senescent. Telomeres function as a biological time recorder that determines the replicative capacity of the cells (Blackburn et al., 2015; Gümüs and Tükün, 2012; Huffman et al., 2000; Lindqvist et al., 2015; Makarov et al., 1997; Olovnikov, 1973).

A growing body of evidence has been emerged linking mental disorders, psychological stress and TL (Oliveira et al., 2016; Shalev et al., 2012). Evaluation of the accelerated aging in SCZ patients based on TL has been attracted new attention. However, there are variation among the results of different groups, with studies reporting that TL in SCZ is shorter (Czepielewski et al., 2016; Fernandez-Egea et al., 2009; Kao et al., 2008; Kota et al., 2015; Yu et al., 2008), similar (Mansour et al., 2011; Vaez-Azizi et al., 2015) or even longer (Nieratschker et al., 2013) when compared to controls. On the other hand, recent meta-analyses support shorter TL in SCZ patients (Polho et al., 2015; Rao et al., 2016). One of the reasons for discrepancies between different studies might be the implementation of different methodologies to measure the TL by different laboratories. In addition, investigations into the associations of SCZ and TL have based primarily on clinical diagnosis itself, but knowledge of possible relationship between the intermediate phenotypes (a.k.a. endophenotypes) of SCZ and TL is still lacking.

First-degree relatives offer several advantages in studying the role of gene-environment interactions in the pathophysiology of SCZ. As SCZ is a heterogeneous syndrome, the inclusion of markers of genetic risk, or intermediate phenotypes, in siblings may represent a useful strategy, as they are not impacted by secondary and relatively nonspecific variables related to chronic stress, lifestyle alterations, and exposure to AP medication (Braff et al., 2007; Gottesman and Gould, 2003). Czepielewski et al. (2016) have investigated TL in a relatively small sample size containing subjects with SCZ (n = 36), their unaffected siblings (n = 36) and healthy controls (n = 47), but without any assessment of intermediate phenotypes.

The influence of early childhood adversity on the pathophysiology of SCZ has attracted attention in research (Varese et al., 2012). Studies suggest that SCZ is strongly associated with childhood adversity, with a 2- to 7-fold higher prevalence of childhood abuse than in non-psychiatric comparison group (Bendall et al., 2008; Morgan and Fisher, 2007). Lee et al. (2018) have recently shown that people with SCZ reported more severe childhood trauma, lower resilience, worse mental and physical health and had worse metabolic biomarker levels than non-clinical controls. Recent meta-analyses support the significant association between early childhood adversity and shorter TL (Hanssen et al., 2017; Ridout et al., 2017; Shalev et al., 2014, 2012). Association between childhood adversities and TL in SCZ has recently been reported in a study containing only 48 patients and 18 controls (Riley et al., 2018). However, the role of childhood adversities on TL has yet to be tackled in a large group of SCZ patients and also their first-degree relatives sharing similar genetic and/or environmental factors.

In this study, we made use of absolute telomere length – quantitative polymerase chain reaction (aTL-qPCR) method to test the hypothesis that both SCZ patients (*SCZ*) and their unaffected siblings (*Sibs*) would have shorter TL compared to non-clinical controls (*Cnt*). Our additional goals were to determine (1) whether shorter TL correlates with psychotic-like experiences and schizotypal traits of SCZ; (2) whether childhood adversities have moderating role in TL shortening among *SCZ* or *Sibs*. Demographics as well as certain factors associated with SCZ or TL, such as obesity, smoking, cognitive functions, education, and symptom severity were also explored.

2. Materials and methods

2.1. Study sample

The study population consisted of 100 patients diagnosed with SCZ (*SCZ*), 100 of their unaffected siblings (*Sibs*) and 100 control individuals from the general, non-clinical population (*Cnt*), all of whom were selected from among the participants of a large gene-environment interaction study: European Network of National SCZ Networks Studying Gene-Environment Interactions (EU-GEI). Details of EU-GEI project were provided elsewhere (Van Os et al., 2014). Diagnosis of SCZ was made using the Operational Criteria Checklist, based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) F20 criteria. Groups were frequency matched by age and gender. The exclusion criteria for the *SCZ* included any serious comorbid medical condition (i.e. chronic medical conditions of T2DM and cardiovascular disorders, as well as degenerative neuropsychiatric disorders, and history of head trauma with loss of consciousness), alcohol and substance abuse, illiteracy, presence of an Intellectual Developmental Disability (IDD) at clinical evaluation or by an estimated IQ score < 70 as measured by the brief WAIS-III R. *Sibs* group was stipulated to include all consenting unaffected siblings, without stratification for socioeconomic variables. Since the primary goal in the EU-GEI was on the genome-wide associations relevant to SCZ, the socioeconomic stratification was not deemed necessary for the *Sibs*, who were to be analyzed at a genomic level. The exclusion criteria for the *Sibs* were the same as the *SCZ* with the addition of a previous diagnosis of any psychotic disorder or previous use of AP medication for any reason. Siblings with an age difference of > 5 years with the patients were also excluded. *Cnt* group, who had no current or previous history, or a first-degree family history of major mental disorders, were randomly recruited from the local community via stratified sampling and assessed at home. Stratification was based on neighborhood of residence, as defined by the Turkish Statistical Institute (www.turkstat.gov.tr), in order to secure socioeconomic similarity with the patients.

The exclusion criteria were the same as with the *Sibs*. Non-clinical controls with any serious comorbid medical condition were also excluded.

Sociodemographic, clinical, and psychosocial information were obtained via face-to-face interviews at the research site for the sib-pairs, and at home for the *Cnt*. All interviews were conducted by a research team who received specific training for the use of standardized assessments. Blood samples were taken and transferred immediately to the Biobank Facility of Ankara University Brain Research Center (AUBRC) for DNA isolation. The complete details of the entire study and procedures were in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. This study was approved by the Medical Ethics Committee of Ankara University, Ankara, Turkey (approval #07-302-15).

2.2. Measures

All the measures were applied to all groups, except for the *Structured Interview for Schizotypy–Revised (SIS-R)* and Scale for the Assessment of Negative Symptoms (SANS)/the Scale for the Assessment of Positive Symptoms (SAPS). SIS-R was given only to *Sibs* and *Cnt*, SANS/SAPS were applied only to *SCZ*.

2.3. Symptoms and functioning

Self-reported subclinical psychotic experiences in the affective and non-affective domains were evaluated by the *Community Assessment of Psychic Experiences (CAPE)* (Konings et al., 2006) in all groups. Clinical assessment of subclinical SCZ symptoms was completed in the *Sibs* and *Cnt* with the *SIS-R,* a semi-structured interview originally developed by Kendler et al. (1989), and revised by Vollema and Ormel (1997). Psychosocial functioning was examined in all groups using the *Global Assessment of Functioning (GAF)* Scale, as described in the DSM-IV-TR Axis 4, yielding scores in the range of 0–100. SANS/SAPS were used to rate the severity of SCZ symptoms only in the patient group (Andreasen, 1984, 1981). Descriptions of the CAPE, SIS-R and SANS/SAPS are provided in the Supplemental Methods (available at journal's web site).

2.4. Cognitive assessment

The brief version of the Wechsler Adult Intelligence Scale-Third Edition (Brief WAIS-III R), including the subscales of Arithmetic, General Information, Digit-Symbol Coding, and Block Design was used for the estimation of global IQ (Wechsler, 1997). As the reliability and validity of WAIS-III R in Turkey are in progress, age-adjusted Z-scores - based on the present sample - were used in the statistical analyses, since normative data for WAIS-III R are not available from any other study.

2.5. Childhood adversity

Information about childhood adversity experiences of the study groups was obtained via the *Childhood Experience of Care and Abuse-Interview* (CECA-*Interview*), which was designed to assess a wide range of negative childhood experiences up to the age of 17 in adolescents or adults and covers four main type of childhood trauma: household discord, physical abuse, psychological abuse and sexual abuse (Bifulco et al., 1994). CECA-*Interview* was applied as semi-structured interview and all the items were asked twice retrospectively for the age periods of both 0–11 and 12–17 by dichotomous yes/no responses. These age ranges were defined according to EU-GEI protocol to see the effects of trauma exposure during early childhood and adolescence, separately. Scoring of each item was done where (0) was adversity “absent (no)“, and (1) was adversity “present (yes)“. Global adversity score for up to the age of 17 was calculated as a numerical variable and equals the sum of all item's scores. To this end, each item was scored as (1), if the individual responded “yes” to that item for at least one of the two age ranges.

2.6. Telomere length measurement: aTL-qPCR

Telomere length was measured by aTL-qPCR method developed by O'Callaghan and Fenech (2011). For details about the aTL-qPCR protocol, see Supplemental Methods and Supplementary Table 1 (available at journal's web site).

2.7. Statistical analyses

Statistical analyses were performed with the IBM SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Graphs were drawn by GraphPad Prism 8.0.1. Data were presented both as mean ± standard deviation (SD) and median (minimum-maximum). Three groups (*SCZ*, *Sibs* and *Cnt*) were compared in terms of TL, age, CAPE, SIS-R, GAF, and estimated IQ scores first by Kruskal Wallis test. Since our variables were not normally distributed, pair-wise comparisons were conducted by the Mann-Whitney *U* test (*SCZ* vs. *Sibs*, *SCZ* vs. *Cnt*, *Sibs* vs. *Cnt*). Pearson $\chi 2$ test was used to compare these three groups in terms of categorical variables including gender, obesity, education, smoking, and childhood adversity. Post hoc Bonferroni correction was applied to all multiple comparisons. Comparative analyses of TL of independent groups were conducted by Mann-Whitney *U* test both in subsamples of *SCZ*, *Sibs*, and *Cnt* and in the whole sample. Independent from group status association between TL and other continuous variables including age, CAPE scores, SIS-R scores, WAIS-III R sub-test scores, and SANS/SAPS scores were tested by non-parametric Spearman's rho test. The predictors of TL were analyzed by bivariate logistic regression where longer or shorter than median TL was the dependent variable. Statistical significance was set at $p < 0.05$, otherwise indicated.

3. Results

3.1. Demographic, (sub)clinical and cognitive characteristics of the study population

Demographic, subclinical, and cognitive characteristics of the study sample are summarized in Table 1. Because of an unidentified technical problem in the aTL-qPCR, TL could not be measured in one participant in the *Sibs* group, who was excluded from the analyses. The three groups were similar in terms of age, gender, and the frequency of obesity (i.e. body mass index [BMI] ≥ 30) distribution. There were significant differences across groups in terms of education level and smoking. *Sibs* were more educated ($p = 0.002$) compared to the *SCZ* and *Cnt* groups. The frequency of smoking was significantly higher in *SCZ* ($p < 0.001$).

The *SCZ* group showed the highest score of psychotic-like symptoms for all CAPE sub-scores and CAPE total score when compared to both *Sibs* ($p < 0.001$) and *Cnt* ($p < 0.001$) (Table 1, Fig. 1). *Sibs* displayed significantly more positive and negative schizotypal symptoms than the *Cnt* ($p < 0.001$) (Table 1, Fig. 2). Functionality as assessed by the GAF scale differed across groups ($p < 0.001$). The *SCZ* group displayed significantly decreased functioning compared to both *Sibs* ($p < 0.001$) and *Cnt* ($p < 0.001$). *Sibs* had significantly higher levels of subclinical psychotic symptoms compared to *Cnt* ($p < 0.001$), however, their level of functioning was found to be closer to that of *Cnt* (Table 1, Fig. 3).

Age-adjusted Z-scores of cognitive WAIS-III R subtests in each group are presented in Table 1. Cognitive performances significantly differed across groups with the exception of General Information. *SCZ* had the lowest scores for all subtests, whereas *Sibs* showed the best cognitive performance.

3.2. Childhood adversity experiences of the study population

The relationship between childhood adversity and group status was

Table 1
Demographic, (sub)clinical and cognitive characteristics of the study population.

	SCZ	*Sibs*	*Cnt*	Statistical Comparison	Effect size
Age (Years)					
Mean (SD)					
Median (Min-Max)					
Male	n = 68	n = 57	n = 67	n = 192	
	31.03 (7.51)	31.61 (8.01)	31 (7.56)	H(2) = 0.12, p = 0.941*	
	30 (18–51)	31 (18–47)	31 (18–52)		
Female	n = 32	n = 42	n = 33	n = 107	
	33.09 (8.95)	31.98 (8.18)	32.91 (8.79)	H(2) = 0.59, p = 0.746*	
	34.50 (17–49)	31 (18–50)	34 (18.48)		
General	n = 100	n = 99	n = 100	n = 299	
	31.69 (8.01)	31.77 (8.04)	31.63 (7.99)	H(2) = 0.003, p = 0.999*	
	31.50 (17–51)	31 (18–50)	32 (18–52)		
Gender					
n (%)					
Male	68 (68)	57 (57.6)	67 (67)	p = 0.24 ǂ	
Female	32 (32)	42 (42.4)	33 (33)	X^2 = 2.86, df = 2	
Obesity					
n (%)					
BMI < 30	73 (73)	84 (84.8)	88 (88)	p = 0.015 ǂ	
BMI ≥ 30	27 (27)	15 (15.2)	12 (12)	X^2 = 8.45, df = 2	Cramér's V = 0.2
Education					
n (%)					
≤ *High school*	85 (85)	63 (65.6)	82 (82.8)	**p = 0.002** ǂ	
≥ *University*	15 (15)	33 (34.4)	17 (17.2)	X^2 = 12.75, df = 2	Cramér's V = 0.2
Smoking					
n (%)					
Non-smoker	33 (33)	50 (50.5)	63 (66.3)	**p < 0.001** ǂ	
Smoker	19 (19)	28 (28.9)	3 (3.1)	X^2 = 40.30, df = 4	Cramér's V = 0.3
Heavy smoker	48 (48)	21 (21.2)	29 (30.5)		
CAPE score					
Mean (SD)					
Median (Min-Max)					
Depression	n = 78	n = 92	n = 96	**H(2) = 25.28, p < 0.001***	
	14.78 (4.96)	11.96 (2.92)	11.58(2.91)	**SCZ vs. Sibs: U = 2350.50, p < 0.001** ¥	r = 0.3
	13.5 (8–29)	11.5 (8–23)	11 (8–23)	**SCZ vs. Cnt: U = 2182.00, p < 0.001** ¥	r = 0.4
				Sibs vs. Cnt: U = 4041.00, p = 0.998 ¥	
Negative symptoms	n = 79	n = 91	n = 93	**H(2) = 35.94, p < 0.001***	
	25.99 (7.87)	20.93 (4.80)	19.81 (4.41)	**SCZ vs. Sibs: U = 2130.00, p < 0.001** ¥	r = 0.4
	24 (14–52)	20 (14–37)	20(14–32)	**SCZ vs. Cnt: U = 1833.50, p < 0.001** ¥	r = 0.4
				Sibs vs. Cnt: U = 3737.50, p = 0.592¥	
Positive symptoms	n = 74	n = 89	n = 94	**H(2) = 40.17, p < 0.001***	
	33.47(10.62)	26.09 (4.67)	26.07 (6.30)	**SCZ vs. Sibs: U = 1668.00, p < 0.001** ¥	r = 0.4
	31 (20–67)	25 (20–40)	24.50 (20–63)	**SCZ vs. Cnt: U = 1711.00, p < 0.001¥**	r = 0.4
				Sibs vs. Cnt: U = 3858.50, p = 1.000 ¥	
Total	n = 62	n = 84	n = 87	**H(2) = 35.71, p < 0.001***	
	72.82 (20.11)	58.71 (11.02)	56.10 (10.62)	**SCZ vs. Sibs: U = 1443.50, p < 0.001** ¥	r = 0.4
	69 (43–142)	56.50 (43–87)	54 (42–80)	**SCZ vs. Cnt: U = 1231.00, p < 0.001¥**	r = 0.5
				Sibs vs. Cnt: U = 3426.00, p = 0.385 ¥	
SIS-R score					
Mean (SD)					
Median (Min-Max)					
Positive	na	n = 83	n = 91		
		3.33 (2.60)	0.78 (1.42)	SCZ vs. Sibs: nc	
		3 (0–11)	0 (0–6)	SCZ vs. Cnt: nc	
				Sibs vs. Cnt: U = 1384.50, p < 0.001 ¥	r = 0.6
Negative	na	n = 95	n = 98		
		1.76 (1.71)	0.31 (0.61)	SCZ vs. Sibs: nc	
		1 (0–7)	0 (0–3)	SCZ vs. Cnt: nc	
				Sibs vs. Cnt: U = 2241.00, p < 0.001 ¥	r = 0.5

(*continued on next page*)

Table 1 (*continued*)

	SCZ	*Sibs*	*Cnt*	**Statistical Comparison**	**Effect size**
Total	na	n = 80 5.09 (3.58) 5 (0–13)	n = 89 1.09 (1.81) 0 (0–6)	SCZ vs. Sibs: nc SCZ vs. Cnt: nc **Sibs vs. Cnt: U = 1086.00, p < 0.001** ¥	 r = 0.6
SCZ symptom scores Mean (SD) Median (Min-Max)					
SANS-Negative symptoms *Affective flattening or blunting*	n = 71 14.54 (8.52) 16 (0–32)	na	na	nc	
Allogia	n = 71 7.44 (4.97) 8 (0–21)	na	na	nc	
Avolition-apathy	n = 71 10.34 (4.36) 11 (0–19)	na	na	nc	
Anhedonia	n = 71 12.92 (5.33) 14 (0–25)	na	na	nc	
Attention	n = 71 5.21 (3.27) 6 (0–15)	na	na	nc	
SANS total	n = 71 50.44 (21.60) 52 (2–108)	na	na	nc	
SAPS-Positive symptoms *Hallucinations*	n = 71 10.99 (7.08) 11 (0–29)	na	na	nc	
Delusions	n = 71 21.45 (10.32) 20 (1–48)	na	na	nc	
Bizzare behaviour	n = 71 7.49 (4.30) 7 (0–17)	na	na	nc	
Positive formal thought disorder	n = 71 8.87 (6.74) 9 (0–28)	na	na	nc	
SAPS total	n = 71 48.80 (19.49) 46 (7–95)	na	na	nc	
GAF score Mean (SD) Median (Min-Max)					
Symptom	n = 94 46.19 (15.38) 40.50 (25–87)	n = 97 78.99 (10.47) 80 (50–100)	n = 100 87.34 (1.51) 87 (82–92)	**H(2) = 189.62, p < 0.001*** **SCZ vs. Sibs: U = 449.00, p < 0.001** ¥ **SCZ vs. Cnt: U = 44.50, p < 0.001**¥ **Sibs vs. Cnt: U = 2517.00, p < 0.001** ¥	 r = 0.8 r = 0.9 r = 0.4
Functioning	n = 94 49.62 (16.21) 50 (15–87)	n = 96 81.33 (9.22) 81 (55–100)	n = 100 87.37 (1.50) 87 (82–91)	**H(2) = 182.27, p < 0.001*** **SCZ vs. Sibs: U = 501.50, p < 0.001** ¥ **SCZ vs. Cnt: U = 106.00, p < 0.001**¥ **Sibs vs. Cnt: U = 2659.50, p < 0.001** ¥	 r = 0.8 r = 0.8 r = 0.4
Age adjusted WAIS-III R Z scores Mean (SD) Median (Min-Max)					

(*continued on next page*)

Table 1 (*continued*)

	SCZ	*Sibs*	*Cnt*	Statistical Comparison	Effect size
General information	n = 89 −0.009 (0.99) −0.32 (−1.60–6.15)	n = 91 0.001 (1.24) −0.32 (−1.42–9.14)	n = 100 0.07 (0.71) −0.004 (−0.93–1.87)	H(2) = 5.99, p = 0.05* SCZ vs. Sibs: U = 3949.5 p = 1.000 ¥ **SCZ vs. Cnt: U = 3562.00, p = 0.069** ¥ Sibs vs. Cnt: U = 3873.00, p = 0.181 ¥	
Arithmetic	n = 88 −0.35 (1.03) −0.43 (−2.63–2.21)	n = 91 0.25 (1.13) 0.45 (−1.97–2.45)	n = 100 0.08 (0.71) 0.01 (−1.19–2.45)	**H(2) = 19.38, p < 0.001*** **SCZ vs. Sibs: U = 2797.50, p < 0.001** ¥ **SCZ vs. Cnt: U = 2888.50, p = 0.001**¥ Sibs vs. Cnt: U = 4078.50, p = 1.000 ¥	r = 0.3 r = 0.3
Block design	n = 89 −0.28 (1.03) −0.59 (−2.03–2.53)	n = 90 0.59 (1.03) 0.54 (−1.34–2.53)	n = 100 −0.28 (0.65) −0.20 (−1.31–1.82)	**H(2) = 43.18, p < 0.001*** **SCZ vs. Sibs: U = 2157.50, p < 0.001** ¥ SCZ vs. Cnt: U = 4065.00, p = 1.000 ¥ **Sibs vs. Cnt: U = 2224.00, p < 0.001** ¥	r = 0.4 r = 0.4
Digit-Symbol coding	n = 84 −0.39 (0.82) −0.40 (−2.13–1.48)	n = 93 0.66 (0.89) 0.77 (−1.07–2.30)	n = 100 −0.26 (0.92) −0.37 (−1.91–2.36)	**H(2) = 24.40, p < 0.001*** **SCZ vs. Sibs: U = 2298.00, p < 0.001** ¥ **SCZ vs. Cnt: U = 2982.00, p < 0.001**¥ Sibs vs. Cnt: U = 3916.50, p = 1.000 ¥	r = 0.5 r = 0.2

* Kruskal Wallis test. Significance values were adjusted by Bonferroni correction for multiple tests.
¥ Mann-Whitney *U* test.
ǂ Pearson's chi square test. Significance values were adjusted by Bonferroni correction. p values less than 0.008 were considered significant.
na: not applicable.
nc: not calculated.

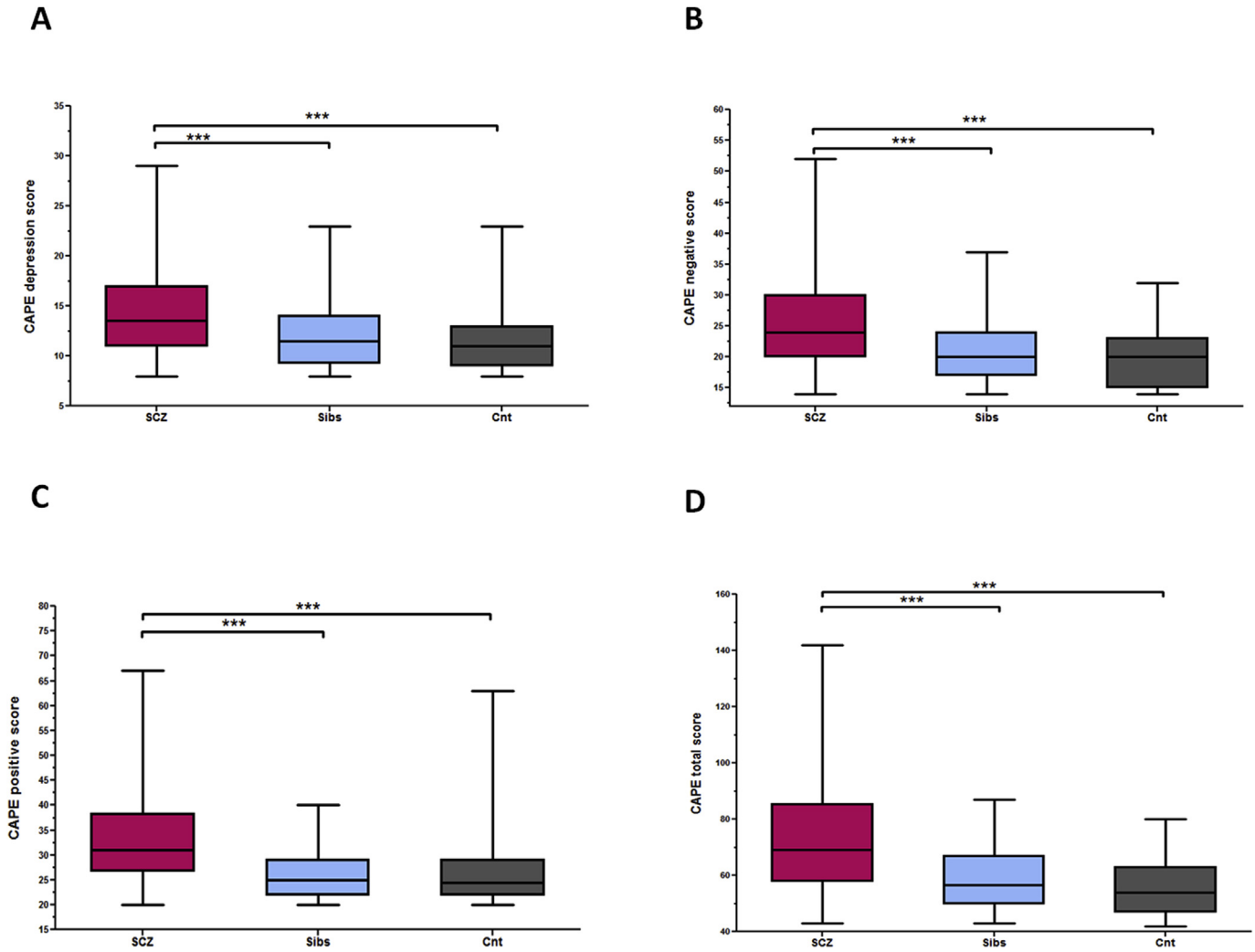

Fig. 1. Box plot representation of CAPE subscale comparisons of the *SCZ*, *Sibs* and *Cnt* groups. (**A**) Depression, (**B**) Negative symptoms, (**C**) Positive symptoms, and (**D**) Total symptom score. Data are presents as median (min-max). ***p < 0.001, Mann Whitney *U* test. CAPE: The Community Assessment of Psychic Experience; SCZ: Schizophenia patients; Sibs: Unaffected siblings; Cnt: Non-clinical controls.

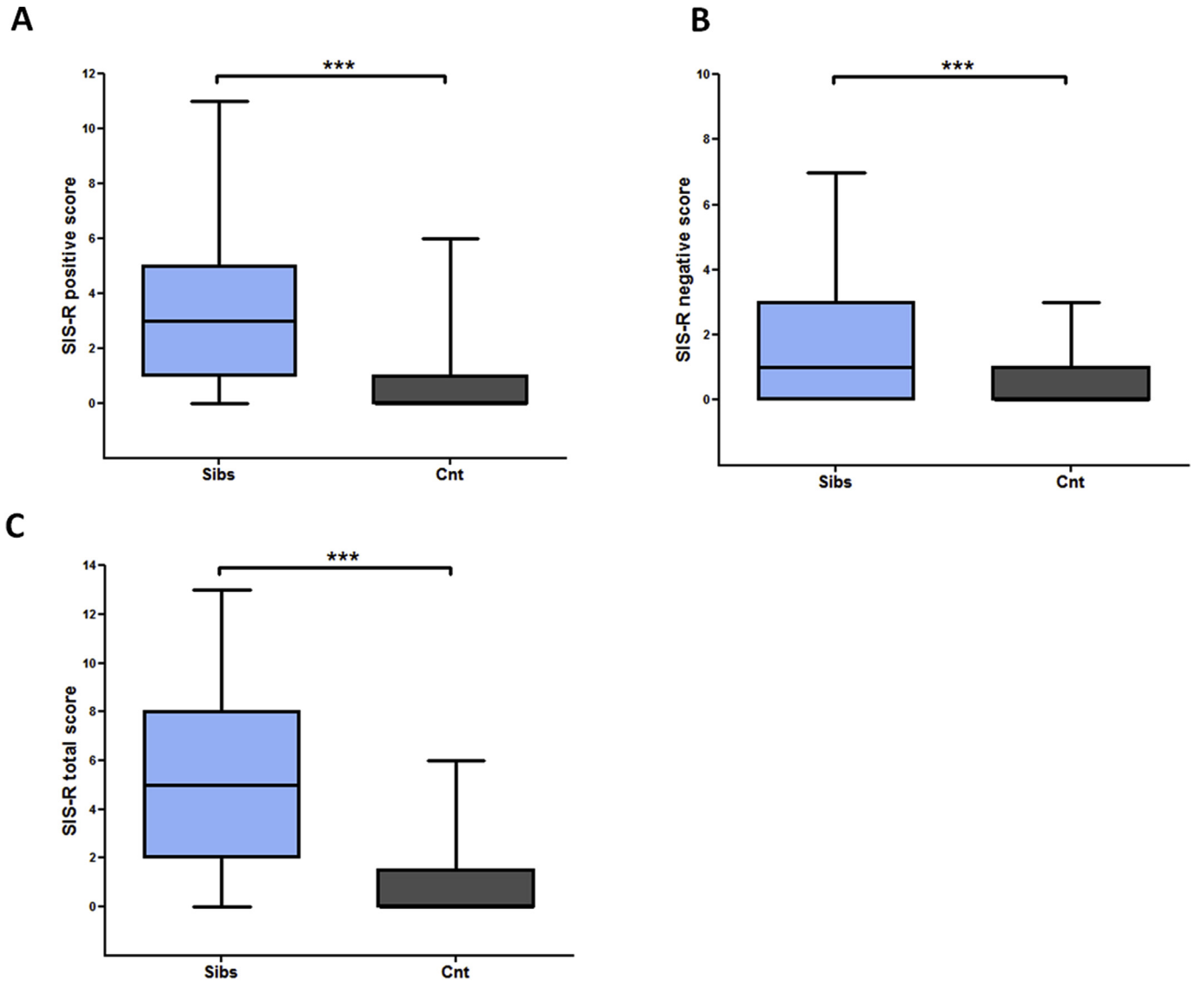

Fig. 2. Box plot representation of SIS-R subscale comparisons of the *SCZ*, *Sibs* and *Cnt* groups. (**A**) Positive (**B**) Negative (**C**) Total score. Data are presents as median (min-max). ***p < 0.001, Mann Whitney *U* test. SIS-R: Structured Interview for Schizotypy-Revised; Sibs: Unaffected siblings; Cnt: Non-clinical controls.

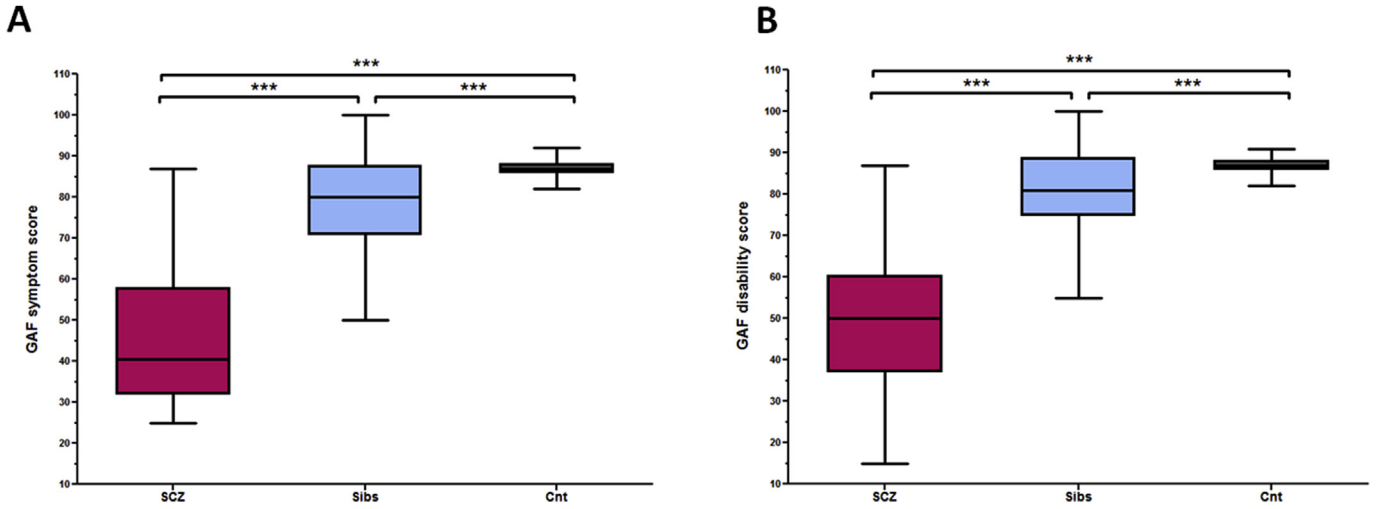

Fig. 3. Box plot representation of GAF symptom (**A**) and disability (**B**) score comparisons of the *SCZ*, *Sibs* and *Cnt* groups. Data are presents as median (min-max). *p < 0.05, **p < 0.01, ***p < 0.001, Mann Whitney *U* test. GAF: Global Assessment of Functioning; SCZ: Schizophenia patients; Sibs: Unaffected siblings; Cnt: Non-clinical controls.

Table 2
Childhood care and abuse experiences of the study population (%).

CECA item	*SCZ* n (%)	*Sibs* n (%)	*Cnt* n (%)	p ǂǂ	χ 2 (df)	Cramér's V
Death of mother before age 17						
No	93 (93)	92 (93.9)	96 (96)	0.643	0.884 (2)	
Yes	7 (7)	6 (6.1)	4 (4)			
Total	100 (100)	98 (100)	100 (100)			
Death of father before age 17						
No	90 (90)	90 (91.8)	96 (96)	0.251	2.263 (2)	
Yes	10 (10)	8 (8.2)	4 (4)			
Total	100 (100)	98 (100)	100 (100)			
Being separated from mother more than* 6 months *before age 17						
No	87 (87.9)	81 (83.5)	98 (98)	**0.002**	12.003 (2)	0.2
Yes	12 (12.1)	16 (16.5)	2 (2)			
Total	99 (100)	97 (100)	100 (100)			
Being separated from father more than* 6 months *before age 17						
No	80 (81.6)	76 (78.4)	98 (98)	< **0.001**	18.336 (2)	0.3
Yes	18 (18.4)	21 (21.6)	2 (2)			
Total	98 (100)	97 (100)	100 (100)			
Change of school						
0-11 years age						
No	74 (74.7)	68 (68.7)	99 (99)	< **0.001**	33.147 (2)	0.3
Yes	25 (25.3)	31 (31.3)	1 (1)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						
No	77 (78.6)	75 (77.3)	100 (100)	< **0.001**	25.875 (2)	0.3
Yes	21 (21.4)	22 (22.7)	0 (0)			
Total	98 (100)	97 (100)	100 (100)			
Being expeled from school						
0-11 years age						
No	98 (99)	96 (97)	100 (100)	0.168	3.573 (2)	
Yes	1 (1)	3 (3)	0 (0)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						
No	95 (96)	96 (98)	99 (99)	0.357	2.062 (2)	
Yes	4 (4)	2 (2)	1 (1)			
Total	99 (100)	98 (100)	100 (100)			
Being taken into care						
0-11 years age						
No	98 (99)	99 (100)	100 (100)	0.365	2.017 (2)	
Yes	1 (1)	0 (0)	0 (0)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						
No	98 (99)	98 (100)	100 (100)	0.367	2.007 (2)	
Yes	1 (1)	0 (0)	0 (0)			
Total	99 (100)	98 (100)	100 (100)			
Run away from home						
0-11 years age						
No	97 (98)	99 (100)	99 (99)	0.363	2.027 (2)	
Yes	2 (2)	0 (0)	1 (1)			
Total	100 (100)	100 (100)	100 (100)			
12-17 years age						
No	92 (92.9)	94 (94.9)	99 (99)	0.102	4.563 (2)	
Yes	7 (7.1)	5 (5.1)	1 (1)			
Total	99 (100)	99 (100)	100 (100)			
Significantly short of money						
0-11 years age						
No	69 (69.7)	69 (69.7)	99 (99)	< **0.001**	35.045 (2)	0.3
Yes	30 (30.3)	30 (30.3)	1 (1)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						
No	65 (65.7)	66 (66.7)	99 (99)	< **0.001**	40.711 (2)	0.4
Yes	34 (34.3)	33 (33.3)	1 (1)			
Total	99 (100)	99 (100)	100 (100)			
Neglect of basic needs						
0-11 years age						
No	88 (88.9)	87 (87.9)	100 (100)	**0.002**	12.659 (2)	0.2
Yes	11 (11.1)	12 (12.1)	0 (0)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						

(*continued on next page*)

Table 2 (*continued*)

CECA item	*SCZ* n (%)	*Sibs* n (%)	*Cnt* n (%)	p ǂǂ	χ 2 (df)	Cramér's V
No	86 (86.9)	90 (90.9)	100 (100)	**0.001**	13.179 (2)	0.2
Yes	13 (13.1)	9 (9.1)	0 (0)			
Total	99 (100)	99 (100)	100 (100)			
Frequent arguments in the family						
0-11 years age						
No	52 (53.6)	62 (62.6)	97 (98)	< **0.001**	53.157 (2)	0.4
Yes	45 (46.4)	37 (37.4)	2 (2)			
Total	99 (100)	98 (100)	99 (100)			
12-17 years age						
No	52 (53.1)	50 (50.5)	97 (97)	< **0.001**	61.503 (2)	0.5
Yes	46 (46.9)	49 (49.5)	3 (3)			
Total	98 (100)	99 (100)	100 (100)			
Treated cruelly						
0-11 years age						
No	91 (91.9)	89 (89.9)	99 (99)	0.022	7.625 (2)	
Yes	8 (9.1)	10 (10.1)	1 (1)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						
No	89 (89.9)	89 (89.9)	99 (99)	0.015	8.402 (2)	
Yes	10 (10.1)	10 (10.1)	1 (1)			
Total	99 (100)	99 (100)	100 (100)			
Experience of slap/hit						
0-11 years age						
No	64 (64.6)	69 (69.7)	98 (98)	< **0.001**	36.957 (2)	0.4
Yes	35 (35.4)	30 (30.3)	2 (2)			
Total	99 (100)	99 (100)	100 (100)			
12-17 years age						
No	59 (59.6)	68 (69.4)	97 (97)	< **0.001**	40.418 (2)	0.4
Yes	40 (40.4)	30 (30.6)	3 (3)			
Total	99 (100)	98 (100)	100 (100)			
Unwanted sexual experience						
0-11 years age						
No	95 (99)	97 (98)	100 (100)	0.365	2018 (2)	
Yes	1 (1)	2 (2)	0 (0)			
Total	96 (100)	99 (100)	100 (100)			
12-17 years age						
No	90 (94.7)	96 (97)	100 (100)	0.076	5.152 (2)	
Yes	5 (5.3)	3 (3)	0 (0)			
Total	95 (100)	99 (100)	100 (0)			
Having adults to go to with problems or to discuss feelings						
0-11 years age						
No	45 (45.9)	36 (36.4)	91 (91)	< **0.001**	69.561 (2)	0.5
Yes	53 (54.1)	63 (63.6)	9 (9)			
Total	98 (100)	99 (100)	100 (100)			
12-17 years age						
No	44 (44.9)	34 (34.7)	89 (89)	< **0.001**	62.274 (2)	0.5
Yes	54 (55.1)	64 (65.3)	11 (11)			
Total	98 (100)	98 (100)	100 (100)			
Having others your age to go to with problems or to discuss feelings						
0-11 years age						
No	41 (41.9)	22 (22.1)	92 (92)	< **0.001**	105.348 (2)	0.6
Yes	57 (57.1)	77 (77.9)	8 (8)			
Total	98 (100)	99 (100)	100 (100)			
12-17 years age						
No	35 (36.1)	20 (20.4)	90 (90)	< **0.001**	108.106 (2)	0.6
Yes	62 (63.9)	78 (79.6)	10 (10)			
Total	97 (100)	98 (100)	100 (100)			
Loneliness						
0-11 years age						
No	83 (85.6)	91 (92.9)	100 (100)	< **0.001**	15.513 (2)	0.2
Yes	14 (14.4)	7 (7.1)	0 (0)			
Total	97 (100)	98 (100)	100 (100)			
12-17 years age						
No	75 (77.3)	82 (84.5)	98 (100)	< **0.001**	23.685 (2)	0.3
Yes	22 (22.7)	15 (15.5)	0 (0)			
Total	97 (100)	97 (100)	98 (100)			

ǂǂ Pearson's Chi square test. Significance values were adjusted by Bonferroni correction. p values less than 0.008 were considered significant.

Table 3
Telomere length comparisons of the groups.

	SCZ	*Sibs*	*Cnt*	*All subjects*
Telomere Length (kbp/diploid genome)				
Mean (SD)	77.42 (31.09)	97.63 (29.19)	82.63 (50.75)	85.85 (39.12)
Median (Min-Max)	72.43 (25.99–93.45)	94.98 (16.29–214.48)	74.77 (21.90–260.99)	82.93 (16.29–260.99)
	n = 100	n = 99	n = 100	n = 299
Multiple comparison test	**H(2) = 28.265, p < 0.001***			
SCZ vs. Sibs	**U = 2573, p < 0.001¥**	**r = 0.4**		
SCZ vs. Cnt	U = 4928, p = 1.000 ¥			
Sibs vs. Cnt	**U = 3623, p = 0.001¥**	**r = 0.2**		
Gender				
Male	n = 68	n = 57	n = 67	n = 192
	77.15 (33.16)	96.05 (28.12)	88.10 (48.39)	86.68 (38.59)
	69.22 (25.99–193.45)	92.75 (16.29–171.93)	85.95 (21.90–220.57)	83.79 (16.29–220.57)
Female	n = 32	n = 42	n = 33	n = 107
	77.94 (27.08)	99.78 (30.80)	71.52 (54.30)	84.41 (40.17)
	73.69 (38.11–162.67)	99.42 (45.21–214.48)	49.13 (24.45–260.99)	78.03 (24.45–260.99)
Statistical comparison¥	U = 974, p = 0.400	U = 1101, p = 0.497	U = 841, p = 0.053	U = 9973, p = 0.677
Obesity				
	n = 73	n = 84	n = 88	n = 245
BMI < 30	75.09 (31.90)	98.50 (29.76)	84.45 (50.36)	86.48 (39.95)
	67.03 (25.99–193.45)	94.69 (16.29–214.48)	83.13 (21.90–260.99)	83.51 (16.29–260.99)
	n = 27	n = 15	n = 12	n = 54
BMI ≥ 30	83.70 (28.41)	92.78 (26.13)	69.23 (53.89)	83.00 (35.35)
	76.28 (45.51–162.67)	97.42 (52.42–141.34)	49.65 (24.45–220.57)	76.54 (24.45–220.57)
Statistical comparison¥	U = 743, p = 0.060	U = 586, p = 0.668	U = 419, p = 0.248	U = 6271, p = 0.550
Education				
≤ High school	n = 85	n = 63	n = 82	n = 230
	78.02 (33.11)	96.97 (31.17)	82.57 (21.90–260.99)	85.91 (41.22)
	73.16 (25.99–193.45)	92.50 (16.29–144.76)	82.57 (21.90–260.99)	81.06 (16.29–260.99)
≥ University	n = 15	n = 33	n = 17	n = 65
	75.59 (19.69)	97.14 (25.69)	72.58 (40.74)	85.74 (23.86)
	67.03 (50.25–128.06)	95.89 (25.99–146.42)	69.38 (23.86–152.72)	85.22 (23.86–152.72)
Statistical comparison¥	U = 597, p = 0.696	U = 991, p = 0.708	U = 619, p = 0.469	U = 7031, p = 0.465
Smoking				
Non-smoker	n = 33	n = 50	n = 63	n = 146
	81.22 (33.51)	96.70 (29.97)	81.90 (53.90)	86.81 (42.95)
	73.17 (38.11–193.45)	95.43 (16.29–214.48)	71.51 (23.86–260.99)	84.21 (16.29–261.00)
Smoker	n = 19	n = 28	n = 3	n = 50
	84.87 (31.69)	96.92 (26.61)	82.56 (4.57)	91.48 (28.26)
	76.80 (42.46–176.64)	95.54 (45.21–152.41)	83.52 (77.59–86.57)	88.31 (42.46–176.64)
Heavy-smoker	n = 48	n = 21	n = 29	n = 98
	71.85 (28.68)	100.84 (31.69)	90.51 (47.42	83.58 (37.44)
	66.23 (26.00–162.67)	94.41 (53.24–171.93)	96.43 (27.02–181.18)	76.12 (26.00–181.18)
Statistical comparison*	H(2) = 4.016, p = 0.476	H(2) = 0.011, p = 0.995	H(2) = 1.485, p = 0.476	H(2) = 3.274, p = 0.195

* Kruskal Wallis test. Significance values were adjusted by Bonferroni correction for multiple tests.
¥ Mann-Whitney *U* test.

assessed by multinomial logistic regression analysis in which the group status (i.e. *SCZ, Sibs, and Cnt*) was the dependent variable. We found the substantial excess of childhood adversities up to age of 17 among *SCZ* (OR: 5.528, 95%CI: 3.544–8.623, p < 0.001) and also their *Sibs* (OR:5.391, 95%CI: 3.460–8.400, p < 0.001) when compared to *Cnt* (Supplementary Table 2). As can be seen from Table 2, differences between the groups were observed for the CECA-*Interview* items: Being Separated from Mother more than six months (p < 0.001), Being Separated from Father more than six months (p < 0.001), Change of School (p < 0.001), Suffering from Significantly Short of Money (p < 0.001), Neglect of Basic Requirements (p < 0.01), Frequent Arguments in Family (p < 0.001), Experience of Being Hit or Slapped (p < 0.001) and Loneliness (p < 0.001) for both age ranges (i.e. 0–11 and 12–17).

3.3. Telomere length of the study population

Mean and median (min-max) TLs of the study groups are shown in Table 3. Although mean TL of the *SCZ* was shorter than the *Cnt*, this difference did not reach the statistical significance level (Fig. 4). On the other hand, *Sibs* had significantly longer TL compared to both *SCZ* (p < 0.001) and *Cnt* (p = 0.001).

Independent from group status no significant correlation was detected between age and TL (r = −0.06; p = 0.35, see Supplementary Fig. 1). Gender, obesity, and smoking had also no effect on TL in any of the groups. When the TLs of *SCZ*, *Sibs,* and *Cnt* were compared in terms of their education level, we couldn't find any significant difference (Table 3). Similarly, the duration of education had no effect on TL (data not shown).

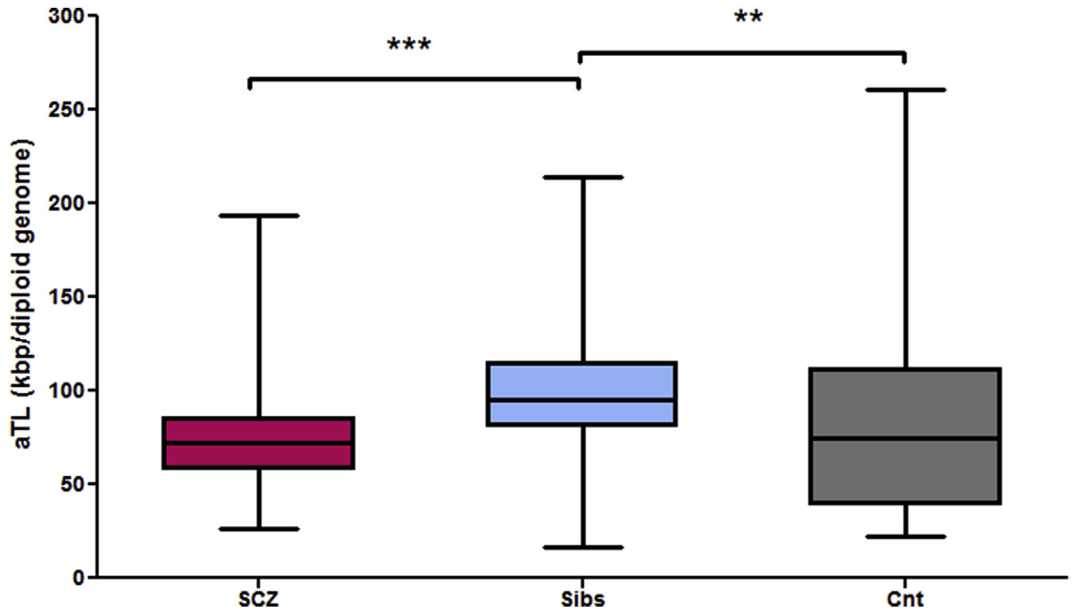

Fig. 4. Box plot representations of the TL in *SCZ*, *Sibs* and *Cnt* groups. Data are presents as median (min-max). **p < 0.01, ***p < 0.001, Mann Whitney *U* test. SCZ: Schizophenia patients; Sibs: Unaffected siblings; Cnt: Non-clinical controls.

3.4. (Sub)clinical and cognitive measurements and telomere length

Independent from group status and clinical diagnosis, we found a significant negative correlation between TL and the CAPE sub-scores of Depression ($r = -0.144$; $p = 0.019$), Positive symptoms ($r = -0.25$; $p < 0.001$), Negative symptoms ($r = -0.155$; $p = 0.012$), as well as the Total score ($r = -0.204$; $p = 0.002$), while with relatively small effect sizes (Fig. 5). However, there was no significant correlation between schizotypal symptoms and TL ($p > 0.05$). The correlation between TL and functioning as assessed by the GAF scale also was not significant ($p > 0.05$). The analysis of the relationship between cognitive performance and TL in the whole sample revealed significant positive correlations for Block-Design ($r = 0.22$; $p < 0.001$) and Arithmetic subscales ($r = 0.18$; $p = 0.003$). However, General Information and Digit-Symbol Coding subscales were not significantly correlated with the TL ($p > 0.05$) (Fig. 6). We also evaluated the possible relationship between symptom severity and TL in *SCZ*. We find no correlation between TL and total SANS/SAPS scores. Although not reaching statistical significance level, negative correlation between delusions and TL was noteworthy ($r = -0.229$; $p = 0.054$) (Supplementary Fig. 2).

3.5. Childhood adversities and telomere length

The relationship between each of the childhood adversity items and TL was tested both in the whole sample and in the subsamples of *SCZ*, *Sibs*, and *Cnt* (Table 4). Our results showed that Death of Mother before age of 17, Being Treated Cruelly and Loneliness before age of 11, and Loneliness between ages 12–17 were significantly associated with shorter TL. Independent from group status, people lost their mother before age of 17 had shorter TL compared to those who didn't ($p = 0.05$). Loss of mother before age of 17 had a more pronounced effect on TL in the *Sibs* ($p = 0.005$). Telomere length of the people who reported the experience of being treated cruelly before age of 11 was found significantly shorter in both *Sibs* ($p = 0.005$) and in the whole sample ($p = 0.04$). Loneliness longer than 6 months before age of 11 was found to be associated with shorter TL in the whole sample ($p = 0.043$). *SCZ* group reported loneliness most frequently and the effect of this adversity on TL shortening was more pronounced in this group ($p = 0.008$). Loneliness during age periods of 12–17 was also associated with shorter TL in *SCZ* ($p = 0.025$).

Since we found a negative association between some of the childhood adversity items and TL, we also wanted to test whether degree of exposure to childhood adversities would be associated with TL shortening in each group. To this end, we categorized each group into two sub-groups based on their global adversity scores: the lowest quartiles (Q1 + Q2 + Q3) and the highest quartile (Q4). In the *SCZ* group, TL was found to be significantly shorter in the highest quartile, when compared to the lowest quartiles ($p = 0.022$) (Table 5, Fig. 7). In addition, negative association between childhood adversity and TL was intriguing in the *SCZ* group ($r = -0.205$, $p = 0.051$), even though not statistically significant. On the contrary, TL did not differ between the two subgroups in *Sibs*.

3.6. Logistic regression

Table 6 shows the logistic regression model by which all the potentially related parameters, stood out as significantly associated with TL, were tested against one another. The predictors significantly contributed to the TL were being in the *Sibs* group, having positive psychotic-like symptoms, and having experience of loneliness during early childhood. Being in the *Sibs* group predicted longer TL (OR: 4.196; 95% CI [1.764-9.983]; $p = 0.001$), whereas positive psychotic-like symptoms (OR: 0.908; 95%CI [0.829–0.994]; $p = 0.036$) and loneliness before age of 11 (OR: 0.078; 95%CI [0.007–0.851]; $p = 0.036$) predicted shorter TL. Other potentially confounding factors including cognitive function, age, sex, obesity, and smoking had no effect on TL.

4. Discussion

In this study, we tested whether SCZ patients and their unaffected siblings have shorter TL compared to non-clinical controls. We aimed also to determine (1) whether shorter TL correlates with psychometric liability to psychosis; (2) whether childhood adversities have a moderating role in TL shortening. We found no significant difference between *SCZ* and *Cnt* with regard to their TL. Interestingly, *Sibs* had the longest TL among the other groups. Our results showed that shorter TL is negatively associated with psychotic-like symptoms. In addition, we found that childhood adversities are negatively associated with TL.

In contrast to our accelerated aging hypothesis in SCZ, we couldn't

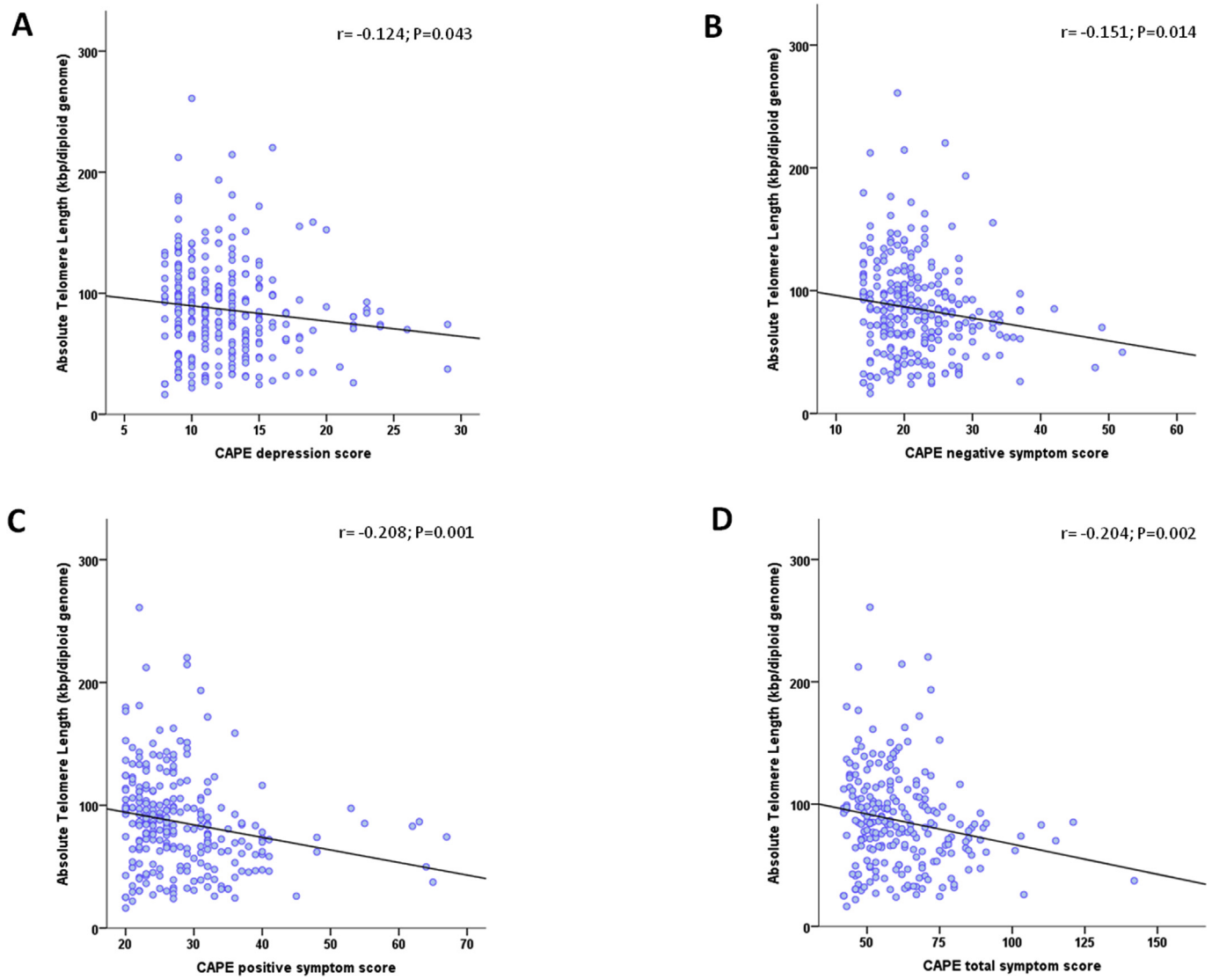

Fig. 5. Scatter plot representation of correlation between TL and subclinical psychotic symptoms measured by CAPE subscales. (**A**) Depression, (**B**) Negative symptoms, (**C**) Positive symptoms, and (**D**) Total symptom score. Sperman's Correlation test. CAPE: The Community Assessment of Psychic Experience; kbp: kilo base pairs.

detect any significant telomere shortening in the *SCZ* group when compared to the *Cnt*. Our finding is consistent with some of the previous reports indicating TL in SCZ was similar to controls (Li et al., 2015; Malaspina et al., 2014; Mansour et al., 2011). Apart from the TL measurement, McKinney et al. (2017) have used a different method which compares DNA methylation levels at 353 genomic sites to test the accelerated aging hypothesis of SCZ in the postmortem superior temporal gyrus and suggested no acceleration of brain aging in SCZ. In the patient group, we also explored the relationship between TL and symptom severity. Our results showed TL is not associated either with SANS or SAPS total scores. On the other hand, negative correlation between delusions and TL was noteworthy, although not reached statistically significance level. Pawelczyk et al. (2015) have reported that the severity of SCZ symptoms correlated significantly with telomere attrition. Maurya et al. (2018), on the other hand, have reported that the severity of psychopathology measured by PANSS scores was positively correlated with TL.

Reasons of controversial results about SCZ and TL are not clear, however, may include methodological variations for TL measurement, along with demographic and lifestyle factors such as age, smoking, BMI, education, as well as life stressors such as childhood adversities. In the current study, we have used aTL-qPCR method developed by O'Callaghan and Fenech (2011). This method utilizes telomeric repeat and single copy gene standards and allows measuring the absolute TL as kbp/diploid genome in contrast to the other methods that use T/S ratio to estimate the relative TL. In addition, we explored the confounding effects of other variables on TL including age, gender, smoking, obesity, and cognitive function. We found that these variables did not substantially contribute to our TL findings.

All studies have been reported so far based on clinical diagnosis of SCZ itself. Intermediate phenotypes that lie mid-distance between genetic risk and clinical end-point of interest have never been taken into consideration. An important strength of our study is that, for the first time, we investigated the association between TL and intermediate phenotypes of SCZ (i.e. psychometric liability to psychosis), independent of the clinical diagnosis. We showed that the psychotic-like experiences seem to be associated with shorter TL in all subscales including depression, positive symptoms, and negative symptoms, while with relatively small effect sizes. Both our correlation and regression analyses suggest that this association was particularly noticeable between TL and positive psychosis-like symptoms.

Recent studies have suggested that psychological stress is associated

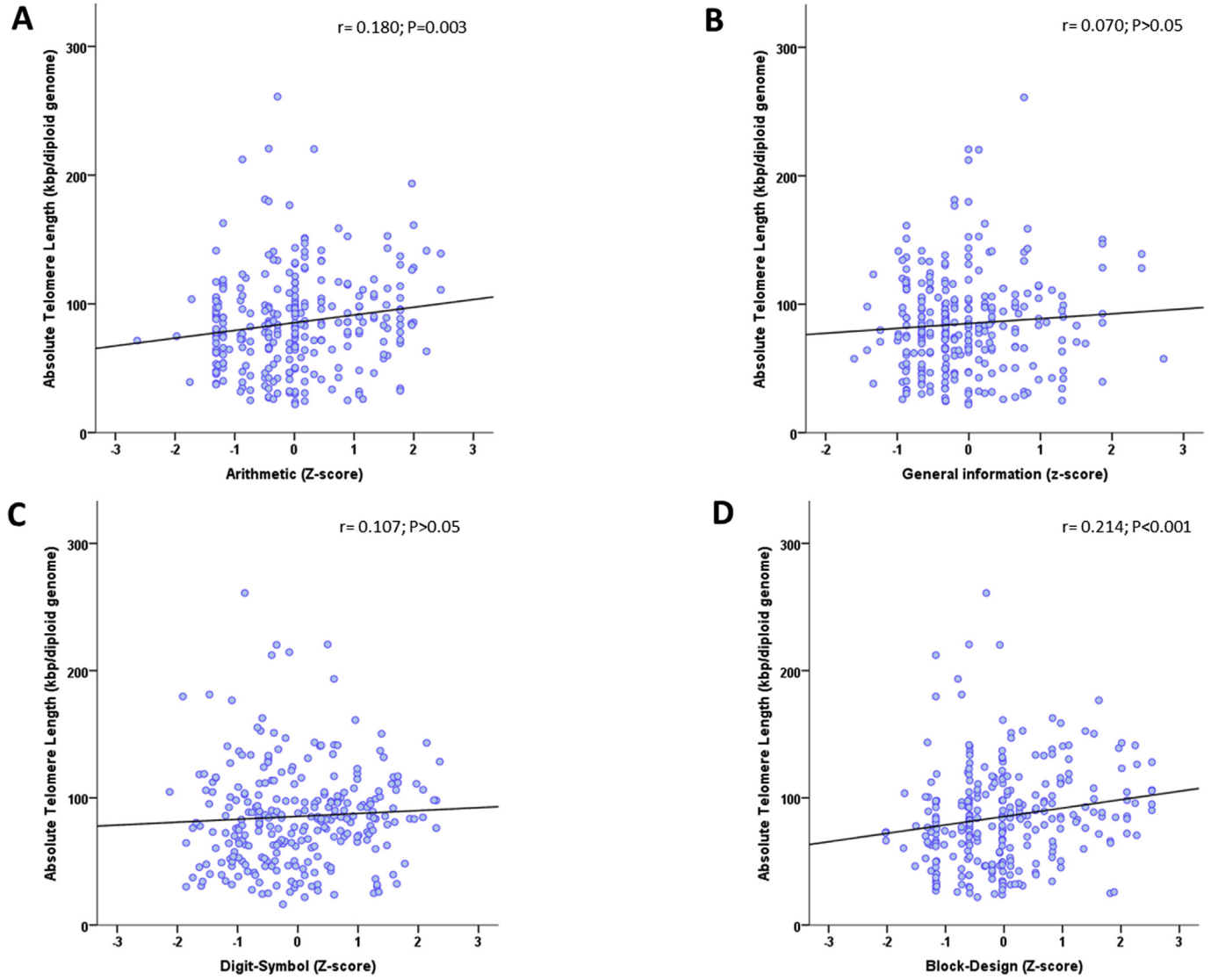

Fig. 6. Scatter plot representation of correlation between TL and cognitive performances measured by WAIS-III R subscales. (**A**) Arithmetic, (**B**) General information, (**C**) Digit-Symbol Coding, (**D**) Block-Design. Sperman's Rho Correlation test. kbp: kilo base pairs.

with shortening of TL. For example, it has been shown that young mothers who have to give primary care to their chronically ill children have significantly shorter TL when compared to age-matched mothers with a healthy child. In addition, the number of years of providing care significantly predicted shorter telomeres, lower telomerase activity and higher oxidative stress (Epel et al., 2004). Shorter TL has also been associated with depression and post-traumatic stress disorders (Kim et al., 2017; Verhoeven et al., 2018). As suggested by models of biological embedding in early life, although cumulative lifespan adversity should have bigger impacts than single events, it is also possible that adversity in childhood has larger effects on later life health than adult stressors (Puterman et al., 2016). Shalev et al. (2012) have reported that children exposed to two or more traumatic stressors at age 5, including maternal domestic violence, physical maltreatment by an adult, have significantly shorter telomeres at age 10 compared to children exposed to less or no violence. It has also been reported that the childhood adversities negatively associated with TL of adulthood. For example, Drury et al. (2014) have shown that cumulative exposure to interpersonal violence and family disruption was correlated with shorter TL. Riley et al. (2018) have recently investigated the effect of early trauma on TL in SCZ patients with a small sample size containing only 48 patients and 18 controls. They have reported SCZ patients had significantly more global trauma and traumatic events, but case and control groups had similar TL. They have reported significant negative associations in male cases and, conversely, in female controls. However, the association between childhood adversities and TL has yet to be investigated in a large group of SCZ patients and also their unaffected siblings who had shared similar environmental factors during their childhood. Our results showed that *SCZ* and *Sibs* groups reported significantly higher frequencies of abuse and neglect experiences during their childhood than *Cnt*. Death of Mother before age of 17, Being Treated Cruelly and Loneliness before age of 11 and Loneliness between ages 12–17 were associated with telomere shortening. Balzan et al. (2018) have investigated the effect of social isolation and loneliness on TL in a small number of male SCZ patients (n = 44). They reported a significant relationship between living alone and telomere attrition which is in accordance with our findings. Our results suggest that loneliness, especially during early childhood is associated with shorter TL in *SCZ*. As far as we know, this is the first study reporting the negative association of childhood adversities with TL in SCZ patients and their unaffected siblings in a relatively larger sample size.

Stressors over the lifetime (e.g. maternal stress, early life adversity, unemployment, caregiving, relationship conflict etc.) stimulate the hypothalamic-hypophyseal-adrenal axis and immunological and

Table 4
Childhood adversities and telomere length.

Mean (SD)	*SCZ*	*Sibs*	*Cnt*	*All subjects*
Median (Min-Max)				
Death of mother before age 17				
No	n = 93	n = 92	n = 96	n = 281
	78.18 (32.12)	99.84 (29.09)	83.39 (51.65)	87.09 (40.02)
	72.43 (25.99–193.45)	96.02 (16.29–214.48)	76.78 (21.90–260.99)	83.52 (16.29–260.99)
Yes	n = 7	n = 6	n = 4	n = 17
	68.40 (17.04)	72.94 (16.37)	67.13 (32.65)	69.50 (20.17)
	75.63 (37.31–85.72)	68.56 (52.42–97.20)	70.75 (24.45–102.58)	74.42 (24.45–102.58)
Statistical comparison[¥]	U = 300, p = 0.730	**U = 86, p = 0.005, r = 0.3**	U = 158, p = 0.550	U = 1713, p = 0.050
Treated cruelly between ages 0–11				
No	n = 91	n = 89	n = 99	n = 279
	79.07 (31.78)	100.25 (29.74)	83.00 (51.20)	87.18 (40.15)
	72.44 (25.99–193.45)	96.33 (16.29–214.48)	77.59 (21.90–260.99)	83.52 (16.29–260.99)
Yes	n = 8	n = 10		n = 19
	59.50 (18.95)	80.94 (14.06)	nc	7.07 (19.14)
	50.31 (39.20–92.64)	81.01 (52.42–107.51)	nc	69.32 (39.20–107.51)
Statistical comparison[¥]	U = 224, p = 0.072	**U = 205, p = 0.005, r = 0.3**	nc	**U = 1919, p = 0.044, r = 0.1**
Lonelinessbetween ages 0–11				
	n = 83	n = 91	n = 100	n = 274
No	80.34 (32.29)	97.58 (25.72)	82.73 (51.00)	86.89 (39.11)
	73.18 (25.99–193.45)	95.80 (16.29–152.41)	74.77 (21.90–260.99)	83.85 (16.29–260.99)
	n = 14	n = 7		n = 21
Yes	58.49 (15.80)	109.43 (59.92)	nc	75.47 (42.95)
	51.25 (37.31–90.18)	82.20 (53.89–214.48)	nc	66.11 (37.31–214.48)
Statistical comparison[¥]	**U = 323, p = 0.008, r = 0.3**	U = 281, p = 0.605	nc	**U = 2114, p = 0.043, r = 0.1**
Loneliness between ages 12–17				
No	n = 75	n = 82	n = 98	n = 255
	81.25 (33.55)	99.15 (28.24)	82.73 (51.00)	87.53 (40.53)
	73.79 (25.99–193.45)	96.02 (16.29–21.48)	74.77 (21.90–260.99)	83.52 (16.29–260.99)
	n = 22	n = 15		n = 37
Yes	63.34 (16.55)	94.59 (34.42)	nc	76.01 (29.37)
	61.94 (37.31–92.64)	89.14 (25.99-171-93)	nc	74.05 (25.99–171.93)
Statistical comparison¥	**U = 564, p = 0.025, r = 0.2**	U = 556, p = 0.556	nc	U = 3903, p = 0.090

Only the CECA items that reached the significance level were included in this Table.
[¥] Mann-Whitney *U* test.
nc: Not calculated because n = 0 in this group.

Table 5
Relationship between TL and global childhood adversity score.

Mean (SD)	*SCZ*	*Sibs*	*Cnt*
Median (Min-Max)			
Three lowest quartiles (Q1 + Q2 + Q3)	n = 71 81.426 (34.450) 74.218 (25.999–193.451)	n = 73 97.102 (25.368) 95.889 (16.290–152.407)	n = 98 82.730 (51.003) 74.771 (21.901–260.998)
Highest quartile (Q4)	n = 20 63.379 (15.990) 61.941 (39.200–97.476)	n = 17 104.578 (42.445) 93.747 (53.243–214.476)	n = 0 nc nc
Statistical comparison[¥]	**U = 471.000; p = 0.022**	U = 612.000; p = 0.930	nc

nc: Not calculated.
[¥] Mann-Whitney *U* test.

autonomic systems to create a response and adapt the organism to these conditions. Hormones and cytokines secreted by the excessive frequent response at the cellular level cause to increase in the allostatic load (Tsigos et al., 2016). However, not all individuals are under the risk of an equal cellular allostatic burden to the same stressor exposure. The net effect of the stressors depends on the presence of resilience factors. Recent studies have led to the idea that TL might be a biomarker reflecting differences between individuals in terms of their psychological stress resilience. Low resilience factors such as high vulnerability to stress reactivity, weak social interactions and unhealthy lifestyle are assumed to be related to increased cellular response, which in turn cause to increase in allostatic load and eventually accelerated telomere erosion (Mainous et al., 2011; O'Donovan et al., 2012). Studies have supported that multisystem resilience factors including psychological stress resilience, social connections, and healthy lifestyle factors are associated with longer telomeres, and all of these are supposed to protect people from stress-induced telomere erosion (Puterman and Epel, 2011). In the current study, contrary to our hypothesis, *Sibs* showed the longest TL. *Sibs* in this study are a subgroup of those who participated in a large EU-GEI study. They were the siblings who agreed to participate upon invitation with a phone call and accompanied the patients to the hospital. Despite having more psychotic and schizotypal symptoms than *Cnt*, the functionality of the *Sibs* was found as better as of *Cnt*. When compared to the *SCZ* and *Cnt* groups higher educational level, higher cognitive performance, higher work experiences (data not shown), and higher long-term relationship frequencies (data not shown) were remarkable in the *Sibs*. In our recent study, we have evaluated the liability to psychosis and liability to T2DM in discordant siblings and non-clinical controls in a larger cohort involving study population of the current study. We have reported that the *Sibs* had a more favorable metabolic profile on several measures, including lower frequencies of metabolic syndrome and abnormal triglyceride and high-density lipoprotein cholesterol (HDL-C) levels (Atbasoglu et al., 2018). We could hypothesize that even though sibs have psychometric liability to psychosis, genetic and/or environmental resilience factors that are

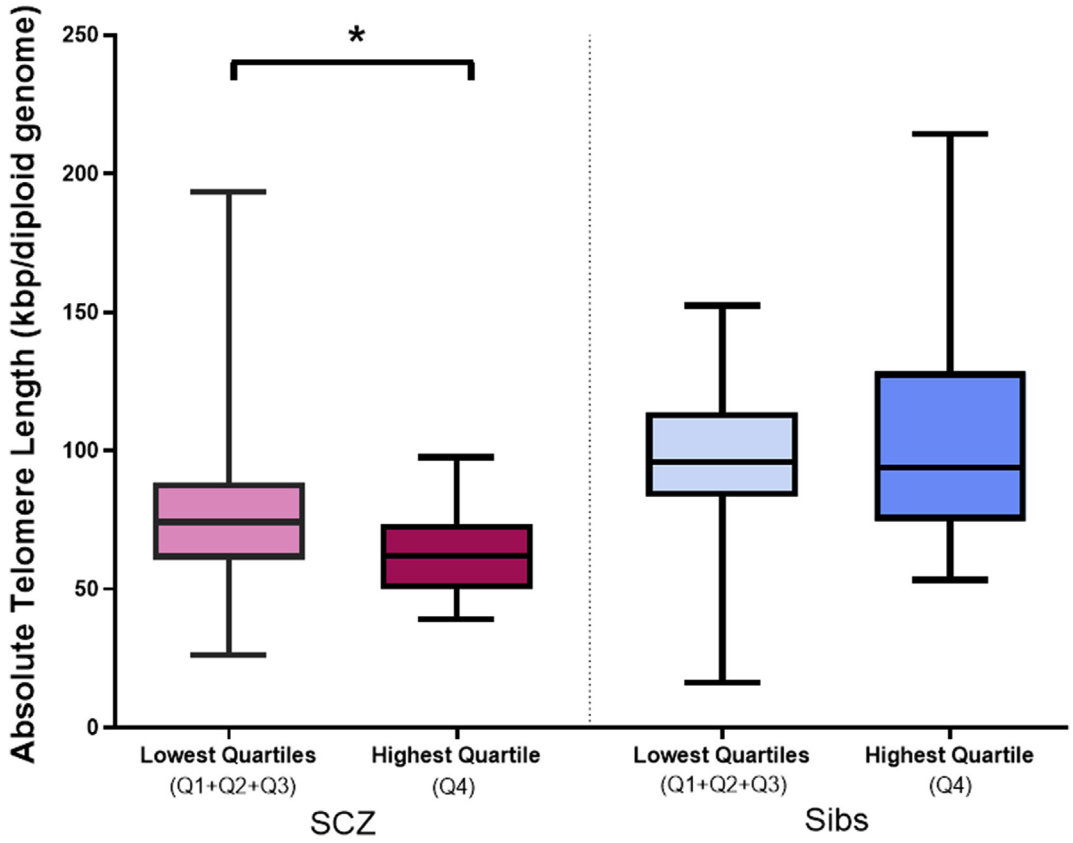

Fig. 7. Box plot representations of the TLs in the group with no/less exposure to childhood trauma (lowest quartiles) and in the group with the over-exposure (highest quartile). Data are presents as median (min-max). *p < 0.05, Mann Whitney *U* test. SCZ: Schizophenia patients; Sibs: Unaffected siblings; kbp: kilo base pairs.

not shared by the affected sibling might have protected *Sibs* from stress-induced telomere erosion and also from the onset of psychosis. One of the resilience factors might be higher emotional intelligence (EI) in the *Sibs*. It has been reported that people with high EI cope better with the stressful encounters since they are able to effectively regulate their mood states. EI is thought to buffer the effects of aversive events through emotional self-awareness, expression, and management (Armstrong et al., 2011; Salovey et al., 2002). Indeed, our data showed

Table 6
Bivariate logistic regression.

Dependent variable: Longer Telomere Length[a]	β	S.E.	Wald	P	OR (95% CI)
Independent variables					
Group					
SCZ	0.013	0.462	0.001	0.978	1.103 (0.409–2.506)
Sibs	1.434	0.442	10,516	**0.001**	**4.196 (1.764–9.983)**
Cnt (Reference)					
Psychotic-like symptoms					
CAPE despression	0.055	0.086	0.406	0.524	1.057 (0.892–1.251)
CAPE negative	−0.017	0.056	0.088	0.766	0.983 (0.0881–1.098)
CAPE positive	−0.097	0.046	4400	**0.036**	**0.908 (0.829–0.994)**
Childhood adversities					
Death of mother before age 17	−0.126	0.754	0.028	0.867	0.882 (0.201–3.864)
Treated cruelly between ages 0-11	−1.017	0.838	1472	0.225	0.362 (0.070–1.870)
Loneliness between ages 0-11	−2.552	1220	4377	**0.036**	**0.078 (0.007–0.851)**
Loneliness between ages 12-17	0.265	0.630	0.177	0.674	1.304 (0.379–4.486)
Cognitive performance					
Block design	0.215	0.218	0.968	0.325	1.240 (0.808–1.902)
Arithmetic	0.054	0.211	0.065	0.799	1.055 (0.698–1.594)
Age	0.031	0.022	2053	0.152	1.301 (0.989–1.076)
Gender	−0.570	0.367	2407	0.121	0.566 (0.276–1.162)
Obesity	−0.231	0.458	0.254	0.614	0.794 (0.324–1.947)
Smoking	0.073	0.326	0.051	0.822	1.076 (0.568–2.308)

[a] Above median.

that similar to *SCZ* group, *Sibs* were more exposed to childhood adversity experiences compared to *Cnt*. In the SCZ group TL was found to be even further shortened in people more exposed to childhood adversities; however, this is not the case for the *Sibs*. This also might support the idea that Sibs in this study have resilient profile. However, resilience status of the study group including EI and need to be addressed by future studies.

4.1. Limitations

The results found in the present study should be interpreted considering the following limitations. First limitation is that there is a problem inherent to the application of self-report measures such as CAPE, SIS-R, and CECA-Interview. Although they allow gathering qualitative and quantitative data quickly, self-reported measures possess several limitations like social desirability bias, a lack of flexibility, and low response rates especially to the childhood adversity experiences. Second limitation of this study is that our SCZ group was not drug-naïve and first episode patients. To date, a limited number of studies have investigated the association between TL and AP treatment in SCZ. Yu et al. (2008) have evaluated clinical response to APs in a group of 68 patients with SCZ and reported that poorer treatment response was associated with shorter TL. Li et al. (2015) have assessed TL in first-episode, AP-naïve patients with SCZ (n = 89) prior to 8 weeks of risperidone treatment and found that patients with poorer treatment response had shorter TL. Our SCZ group was selected from among the participants of a large gene-environment interaction study: EU-GEI. As for the most genome-wide association studies (GWAS), it was difficult to find a homogeneous group of patients receiving the same treatment regimen in terms of a type of the APs, dosage level, and duration. Therefore, effects of AP treatment which might be one of the potential cofounding factors of TL could not be analyzed. Indeed, our patient group had significantly higher prevalence of obesity and smoking that might affect TL, however, those variables that were likely to confound the results were included in the statistical analyses and showed no effect on TL. Our results do not support the premature aging hypothesis in SCZ, but do not preclude *vice versa*. Another limitation of this study was the lack of a random sampling procedure in the recruitment of the *Sibs*. This was unavoidable, given that the study sample was a subgroup of individuals participating in the EU-GEI Project, stipulating the recruitment of unaffected siblings without randomization. In order to control for potential bias, however, several variables that were likely to confound our TL results were included in the statistical analyses.

In conclusion, our data suggest that psychometric liability to psychosis and childhood adversities are associated with shorter TL, although these findings must be considered preliminary, pending larger-scale replication. Further longitudinal studies evaluating the effects of lifestyle factors (physical activity, diet, and sleep), blood stress hormone levels (norepinephrine, epinephrine, etc), pro-inflammatory cytokines, oxidant/antioxidant status and telomerase activity are warranted in order to identify the physiological mechanisms underlying the relationship between telomere shortening, psychometric liability to psychosis and childhood adversities. In addition, further investigations are needed to identify which biological/environmental factors have protected *Sibs* from telomere attrition and onset of psychosis.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK, Project No: 215S151), and partially funded by the 7th Frame Work Programme of the European Union (grant agreement no. HEALTH-F2-2009-241909, Project EU-GEI). All the DNA samples were provided by the Biobank facility of the Ankara University Brain Research Center funded by Ankara University Scientific Research Projects (AUBAPRO) (grant number: 10A6055003).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.022.

References

Andreasen, N.C., 1981. The Scale for the Assessment of Negative Symptoms (SANS). Univ. Iowa. Iowa City, , IA.
Andreasen, N.C., 1984. The Scale for the Assessment of 134 Positive Symptoms (SAPS). Univ. Iowa. Iowa City, , IA.
Anthes, E., 2014. Live faster, die younger. Nature 508, 16–17.
Armstrong, A.R., Galligan, R.F., Critchley, C.R., 2011. Emotional intelligence and psychological resilience to negative life events. Pers. Indiv. Differ. 51, 331–336. https://doi.org/10.1016/j.paid.2011.03.025.
Atbasoglu, E.C., Gumus-akay, G., Guloksuz, S., Saka, M.C., Ucok, A., Alptekin, K., 2018. Higher schizotypy predicts better metabolic profile in unaffected siblings of patients with schizophrenia. Psychopharmacology (Berlin) 235, 1029–1039.
Bacalini, M.G., D'Aquila, P., Marasco, E., Nardini, C., Montesanto, A., Franceschi, C., Passarino, G., Garagnani, P., Bellizzi, D., 2017. The methylation of nuclear and mitochondrial DNA in ageing phenotypes and longevity. Mech. Ageing Dev. 165, 156–161. https://doi.org/10.1016/j.mad.2017.01.006.
Balzan, R.P., Dhillon, V.S., Liu, D., Hahn, L., Fenech, M.F., Galletly, C., 2018. Shorter telomere length in people with schizophrenia who live alone? Schizophr. Res. 199, 422–423. https://doi.org/10.1016/j.schres.2018.02.039.
Bendall, S., Jackson, H.J., Hulbert, C.A., McGorry, P.D., 2008. Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. Schizophr. Bull. 34, 568–579. https://doi.org/10.1093/schbul/sbm121.
Bifulco, A., Brown, G.W., Harris, T.O., 1994. Childhood experience of care and abuse (CECA): a retrospective interview measure. Child Psychol. Psychiatry Allied Discip. 35, 1419–1435. https://doi.org/10.1007/s00127-002-0589-9.
Blackburn, E.H., Epel, E.S., Lin, J., 2015. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. Science 69 (80), 1193–1198.
Braff, D.L., Freedman, R., Schork, N.J., Gottesman, I.I., 2007. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. Schizophr. Bull. 33, 21–32.
Czepielewski, L.S., Massuda, R., Panizzutti, B., da Rosa, E.D., de Lucena, D., Macedo, D., Grun, L.K., Barbe-Tuana, F.M., Gama, C.S., 2016. Telomere length in subjects with schizophrenia, their unaffected siblings and healthy controls: evidence of accelerated aging. Schizophr. Res. 174, 39–42.
Dieset, I., Andreassen, O.A., Haukvik, U.K., 2016. Somatic comorbidity in schizophrenia: some possible biological mechanisms across the life span. Schizophr. Bull. 42, 1316–1319. https://doi.org/10.1093/schbul/sbw028.
Drury, S.S., Mabile, E., Brett, Z.H., Esteves, K., Jones, E., Shirtcliff, E.A., Theall, K.P., 2014. The association of telomere length with family violence and disruption. Pediatrics 134, e128–e137.
Epel, E.S., Blackburn, E.H., Lin, J., Dhabhar, F.S., Adler, N.E., Morrow, J.D., Cawthon, R.M., 2004. Accelerated telomere shortening in response to life stress. Proc. Natl. Acad. Sci. U.S.A. 101, 17312–17315.
Fernandez-Egea, E., Bernardo, M., Heaphy, C.M., Griffith, J.K., Parellada, E., Esmatjes, E., Conget, I., Nguyen, L., George, V., Stöppler, H., Kirkpatrick, B., 2009. Telomere length and pulse pressure in newly diagnosed, antipsychotic-naive patients with nonaffective psychosis. Schizophr. Bull. 35, 437–442.
Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 636–645.
Gümüs, G., Tükün, A., 2012. Telomere and telomerase in Cancer : recent progress. In: Li, B. (Ed.), Reviews on Selected Topics of Telomere Biology. InTech, pp. 95–122.
Hanssen, L.M., Schutte, N.S., Malouff, J.M., Epel, E.S., 2017. The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis. Heal. Psychol. Res. 5, 14–22. https://doi.org/10.4081/hpr.2017.6378.
Huffman, K.E., Levene, S.D., Tesmer, V.M., Shay, J.W., Wright, W.E., 2000. Telomere shortening is proportional to the size of the G-rich telomeric 3'-overhang. J. Biol. Chem. 275, 19719–19722.
Kao, H.-T., Cawthon, R.M., Delisi, L.E., Bertisch, H.C., Ji, F., Gordon, D., Li, P., Benedict, M.M., Greenberg, W.M., Porton, B., 2008. Rapid telomere erosion in schizophrenia. Mol. Psychiatr. 13, 118–119.
Kendler, K.S., Lieberman, J.A., Walsh, D., 1989. The structured interview for schizotypy (SIS): a preliminary report. Schizophr. Bull. 15, 559–571.
Keshavan, M.S., Nasrallah, H.A., Tandon, R., 2011. Schizophrenia, "Just the Facts" 6. Moving ahead with the schizophrenia concept: from the elephant to the mouse. Schizophr. Res. 127, 3–13.
Kim, T.Y., Kim, S.J., Choi, J.R., Lee, S.T., Kim, J., Hwang, I.S., Chung, H.G., Choi, J.H., Kim, H.W., Kim, S.H., Kang, J.I., 2017. The effect of trauma and PTSD on telomere length: an exploratory study in people exposed to combat trauma. Sci. Rep. 7, 1–7. https://doi.org/10.1038/s41598-017-04682-w.
Kirkpatrick, B., Kennedy, B.K., 2018. Accelerated aging in schizophrenia and related disorders: future research. Schizophr. Res. 196, 4–8. https://doi.org/10.1016/j.schres.2017.06.034.

Kirkpatrick, B., Messias, E., Harvey, P.D., Fernandez-Egea, E., Bowie, C.R., 2008. Is schizophrenia a syndrome of accelerated aging? Schizophr. Bull. 34, 1024–1032.
Konings, M., Bak, M., Hanssen, M., Van Os, J., Krabbendam, L., 2006. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr. Scand. 114, 55–61.
Kota, L.N., Purushottam, M., Moily, N.S., Jain, S., 2015. Shortened telomere in unremitted schizophrenia. Psychiatr. Clin. Neurosci. 69, 292–297.
Lee, E.E., Martin, A.S., Tu, X., Palmer, B.W., Jeste, D.V., 2018. Childhood adversity and schizophrenia. J. Clin. Psychiatr. 79. https://doi.org/10.4088/JCP.17m11776.
Li, Z., Hu, M., Zong, X., He, Y., Wang, D., Dai, L., Dong, M., Zhou, J., Cao, H., Lv, L., Chen, X., Tang, J., 2015. Association of telomere length and mitochondrial DNA copy number with risperidone treatment response in first-episode antipsychotic-naïve schizophrenia. Sci. Rep. 5.
Lindqvist, D., Epel, E.S., Mellon, S.H., Penninx, B.W., Révész, D., Verhoeven, J.E., Reus, V.I., Lin, J., Mahan, L., Hough, C.M., Rosser, R., Bersani, F.S., Blackburn, E.H., Wolkowitz, O.M., 2015. Psychiatric disorders and leukocyte telomere length : underlying mechanisms linking mental illness with cellular aging. Neurosci. Biobehav. Rev. 55, 333–364.
Mainous, A.G., Everett, C.J., Diaz, V.A., Baker, R., Mangino, M., Codd, V., Samani, N.J., 2011. Leukocyte telomere length and marital status among middle-aged adults. Age Ageing 40, 73–78.
Makarov, V.L., Hirose, Y., Langmore, J.P., 1997. Long G tails at both ends of human chromosomes suggest a C strand degradation mechanism for telomere shortening. Cell 88, 657–666.
Malaspina, D., Dracxler, R., Walsh-Messinger, J., Harlap, S., Goetz, R.R., Keefe, D., Perrin, M.C., 2014. Telomere length, family history, and paternal age in schizophrenia. Mol. Genet. genomic Med. 2, 326–331. https://doi.org/10.1002/mgg3.71.
Mansour, H., Chowdari, K., Fathi, W., Elassy, M., Ibrahim, I., Wood, J., Bamne, M., Tobar, S., Yassin, A., Salah, H., Elsayed, H., Eissa, A., El-Boraie, H., Ibrahim, N.E., Elsayed, M., El-Bahaei, W., Gomaa, Z., El-Chennawi, F., Nimgaonkar, V.L., 2011. Does telomere length mediate associations between inbreeding and increased risk for bipolar I disorder and schizophrenia? Psychiatr. Res. 188, 129–132. https://doi.org/10.1016/j.psychres.2011.01.010.
Maurya, P.K., Rizzo, L.B., Xavier, G., Tempaku, P.F., Ota, V.K., Santoro, M.L., Spíndola, L.M., Moretti, P.S., Mazzotti, D.R., Gadelha, A., Gouvea, E.S., Noto, C., Maes, M., Cordeiro, Q., Bressan, R.A., Brietzke, E., Belangero, S.I., 2018. Leukocyte telomere length variation in different stages of schizophrenia. J. Psychiatr. Res. 96, 218–223. https://doi.org/10.1016/j.jpsychires.2017.10.016.
McKinney, B.C., Lin, H., Ding, Y., Lewis, D.A., Sweet, R.A., 2017. DNA methylation evidence against the accelerated aging hypothesis of schizophrenia. npj Schizophr 3, 1–3. https://doi.org/10.1038/s41537-017-0017-5.
Morgan, C., Fisher, H., 2007. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma - a critical review. Schizophr. Bull. 33, 3–10. https://doi.org/10.1093/schbul/sbl053.
Nguyen, T.T., Eyler, L.T., Jeste, D.V., 2017. Systemic biomarkers of accelerated aging in schizophrenia: a critical review and future directions. Schizophr. Bull. 44, 398–408. https://doi.org/10.1093/schbul/sbx069.
Nieratschker, V., Lahtinen, J., Meier, S., Strohmaier, J., Frank, J., Heinrich, A., Breuer, R., Witt, S.H., Nöthen, M.M., Rietschel, M., Hovatta, I., 2013. Longer telomere length in patients with schizophrenia. Schizophr. Res. 149, 116–120.
Oliveira, B.S., Zunzunegui, M.V., Quinlan, J., Fahmi, H., Tu, M.T., Guerra, R.O., 2016. Systematic review of the association between chronic social stress and telomere length: a life course perspective. Ageing Res. Rev. 26, 37–52.
Olovnikov, A.M., 1973. A theory of marginotomy. J. Theor. Biol. 41, 181–190.
O'Callaghan, N.J., Fenech, M., 2011. A quantitative PCR method for measuring absolute telomere length. Biol. Proced. Online 13, 3.
O'Donovan, A., Tomiyama, A.J., Lin, J., Puterman, E., Adler, N.E., Kemeny, M., Wolkowitz, O.M., Blackburn, E.H., Epel, E.S., 2012. Stress appraisals and cellular aging: a key role for anticipatory threat in the relationship between psychological stress and telomere length. Brain Behav. Immun. 26, 573–579.
Pawelczyk, T., Szymanska, B., Grancow-Grabka, M., 2015. Telomere length in blood cells is related to the chronicity , severity , and recurrence rate of schizophrenia. Neuropsychiatric Dis. Treat. 1493–1503.
Perala, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppa, T., Harkanen, T., Koskinen, S., Lonnqvist, J., 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch. Gen. Psychiatr. 64, 19–28.
Polho, G.B., De-Paula, V.J., Cardillo, G., dos Santos, B., Kerr, D.S., 2015. Leukocyte telomere length in patients with schizophrenia: a meta-analysis. Schizophr. Res. 165, 195–200.
Puterman, E., Epel, E., 2011. An intricate dance: life experience, multisystem resiliency, and rate of telomere decline throughout the lifespan. Soc Pers. Psychol Compass. 4, 807–825.
Puterman, E., Gemmill, A., Karasek, D., Weir, D., Adler, N.E., Prather, A.A., Epel, E.S., 2016. Lifespan adversity and later adulthood telomere length in the nationally representative US Health and Retirement Study. Proc. Natl. Acad. Sci. Unit. States Am. 113, E6335–E6342.
Rao, S., Kota, L.N., 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.
Ridout, K.K., Levandowski, M., Ridout, S.J., Gantz, L., Goonan, K., Palermo, D., Price, L.H., Tyrka, A.R., 2017. Early life adversity and telomere length: a meta-analysis. Mol. Psychiatr. 1–14.
Riley, G., Perrin, M., Vaez-Azizi, L.M., Ruby, E., Goetz, R.R., Dracxler, R., Walsh-Messinger, J., Keefe, D.L., Buckley, P.F., Szeszko, P.R., Malaspina, D., 2018. Telomere length and early trauma in schizophrenia. Schizophr. Res. 199, 426–430. https://doi.org/10.1016/j.schres.2018.02.059.
Ringen, P.A., Engh, J.A., Birkenaes, A.B., Dieset, I., Andreassen, O.A., 2014. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes and interventions. Front. Psychiatry 5, 1–11. https://doi.org/10.3389/fpsyt.2014.00137.
Salovey, P., Stroud, L.R., Woolery, A., Epel, E.S., 2002. Perceived emotional intelligence, stress reactivity, and symptom reports: further explorations using the trait meta-mood scale. Psychol. Health 17, 611–627. https://doi.org/10.1080/08870440290025812.
Shalev, I., Moffitt, T.E., Sugden, K., Williams, B., Houts, R.M., Danese, A., Mill, J., Arseneault, L., Caspi, A., 2012. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. Mol. Psychiatr. 18, 576–581.
Shalev, I., Entringer, S., Wadhwa, P.D., Wolkowitz, O.M., Puterman, E., 2014. Stress and telomere biology: a lifespan perspective. Psychoneuroendocrinology 38, 1835–1842. https://doi.org/10.1016/j.psyneuen.2013.03.010.Stress.
Simm, A., Nass, N., Bartling, B., Hofmann, B., Silber, R.E., Navarrete Santos, A., 2008. Potential biomarkers of ageing. Biol. Chem. 389, 257–265. https://doi.org/10.1515/BC.2008.034.
Tsigos, C., Kyrou, I., Kassi, E., Chrousos, G.P., 2016. Stress, Endocrine Physiology and Pathophysiology. MDText.com, Inc.
Vaez-Azizi, L.M., Ruby, E., Dracxler, R., Rothman, K., Perrin, M., Walsh-Messinger, J., Antonius, D., Goetz, R.R., Goetz, D.M., Keefe, D.L., Malaspina, D., 2015. Telomere length variability is related to symptoms and cognition in schizophrenia. Schizophr. Res. 164, 268–269. https://doi.org/10.1016/j.schres.2015.03.011.
Van Os, J., Rutten, B.P., Myin-Germeys, I., Delespaul, P., Viechtbauer, W., Van Zelst, C., Bruggeman, R., Reininghaus, U., Morgan, C., Murray, R.M., Di Forti, M., McGuire, P., Valmaggia, L.R., Kempton, M.J., Gayer-Anderson, C., Hubbard, K., Beards, S., Stilo, S.A., Onyejiaka, A., Bourque, F., Modinos, G., Tognin, S., Calem, M., O'Donovan, M.C., Owen, M.J., Holmans, P., Williams, N., Craddock, N., Richards, A., Humphreys, I., Meyer-Lindenberg, A., Leweke, F.M., Tost, H., Akdeniz, C., Rohleder, C., Bumb, J.M., Schwarz, E., Alptekin, K., Ucok, A., Saka, M.C., Atbasoglu, E.C., Guloksuz, S., Gumus-Akay, G., Cihan, B., Karadag, H., Soygur, H., Cankurtaran, E.S., Ulusoy, S., Akdede, B., Binbay, T., Ayer, A., Noyan, H., Karadayi, G., Akturan, E., Ulas, H., Arango, C., Parellada, M., Bernardo, M., Sanjuan, J., Bobes, J., Arrojo, M., Santos, J.L., Cuadrado, P., Solano, J.J.R., Carracedo, A., Bernardo, E.G., Roldan, L., L0pez, G., Cabrera, B., Cruz, S., Mesa, E.M.D., Pouso, M., Jimenez, E., Sanchez, T., Rapado, M., Gonzalez, E., Martinez, C., Sanchez, E., Olmeda, M.S., De Haan, L., Velthorst, E., Van Der Gaag, M., Selten, J.P., Van Dam, D., Van Der Ven, E., Van Der Meer, F., Messchaert, E., Kraan, T., Burger, N., Leboyer, M., Szoke, A., Schurhoff, F., Llorca, P.M., Jamain, S., Tortelli, A., Frijda, F., Vilain, J., Galliot, A.M., Baudin, G., Ferchiou, A., Richard, J.R., Bulzacka, E., Charpeaud, T., Tronche, A.M., De Hert, M., Van Winkel, R., Decoster, J., Derom, C., Thiery, E., Stefanis, N.C., Sachs, G., Aschauer, H., Lasser, I., Winklbaur, B., Schlogelhofer, M., Riecher-Rossler, A., Borgwardt, S., Walter, A., Harrisberger, F., Smieskova, R., Rapp, C., Ittig, S., Soguel-Dit-Piquard, F., Studerus, E., Klosterkotter, J., Ruhrmann, S., Paruch, J., Julkowski, D., Hilboll, D., Sham, P.C., Cherny, S.S., Chen, E.Y.H., Campbell, D.D., Li, M., Romeo-Casabona, C.M., Cirion, A.E., Mora, A.U., Jones, P., Kirkbride, J., Cannon, M., Rujescu, D., Tarricone, I., Berardi, D., Bonora, E., Seri, M., Marcacci, T., Chiri, L., Chierzi, F., Storbini, V., Braca, M., Minenna, M.G., Donegani, I., Fioritti, A., La Barbera, D., La Cascia, C.E., Mul??, A., Sideli, L., Sartorio, R., Ferraro, L., Tripoli, G., Seminerio, F., Marinaro, A.M., McGorry, P., Nelson, B., Amminger, G.P., Pantelis, C., Menezes, P.R., Del-Ben, C.M., Tenan, S.H.G., Shuhama, R., Ruggeri, M., Tosato, S., Lasalvia, A., Bonetto, C., Ira, E., Nordentoft, M., Krebs, M.O., Barrantes-Vidal, N., Cristobal, P., Kwapil, T.R., Brietzke, E., Bressan, R.A., Gadelha, A., Maric, N.P., Andric, S., Mihaljevic, M., Mirjanic, T., 2014. Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr. Bull. 40, 729–736. https://doi.org/10.1093/schbul/sbu069.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., Van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. Schizophr. Bull. 38, 661–671. https://doi.org/10.1093/schbul/sbs050.
Verhoeven, J.E., Révész, D., Picard, M., Epel, E.E., Wolkowitz, O.M., Matthews, K.A., Penninx, B.W.J.H., Puterman, E., 2018. Depression, telomeres and mitochondrial DNA: between- and within-person associations from a 10-year longitudinal study. Mol. Psychiatr. 23, 850–857. https://doi.org/10.1038/mp.2017.48.
Vollema, M.G., Ormel, J., 1997. Reliability of the structured interview for schizotypy-revised (SIS-R). Schizophr. Res. 24, 8.
Wechsler, D., 1997. Wechsler adult intelligence scale, 3rd edn. Administration and Scoring Manual. In: WAIS-III. Psychological Corporation, San Antonio, TX, USA.
Weinberg, S.M., Jenkins, E.A., Marazita, M.L., Maher, B.S., 2007. Minor physical anomalies in schizophrenia: a meta-analysis. Schizophr. Res. 4, 72–85.
Xia, X., Chen, W., McDermott, J., Han, J.-D.J., 2017. Molecular and phenotypic biomarkers of aging. F1000Research 6, 860. https://doi.org/10.12688/f1000research.10692.1.
Yu, W.-Y., Chang, H.-W., Lin, C.-H., Cho, C.-L., 2008. Short telomeres in patients with chronic schizophrenia who show a poor response to treatment. J. Psychiatry Neurosci. 33, 244–247.