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Leukocyte telomere length: Effects of schizophrenia, age, and gender

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ABSTRACT

Background: Schizophrenia is linked with early medical comorbidity and mortality. These observations indicate possible "accelerated biological aging" in schizophrenia, although prior findings are mixed, and few such studies have examined the role of gender. One putative marker of biological aging is leukocyte telomere length (LTL), which typically shortens with age.

Methods: We assessed LTL in phenotypically well characterized 134 individuals with schizophrenia (60 women and 74 men) and 123 healthy comparison subjects (HCs) (66 women and 57 men), aged 26 to 65 years.

Results: Overall, LTL was inversely associated with age ($t(249) = -6.2$, $p < 0.001$), and a gender effect on the rate of LTL decrease with age was found ($t(249) = 2.20$, $p = 0.029$), with men declining more rapidly than women. No significant overall effect of diagnosis on the rate of decline was detected. However, at the average sample age (48 years), there was a significant gender effect in both schizophrenia and HC groups ($t(249) = 2.48$, $p = 0.014$), with women having longer LTL than men, and a significant gender X diagnosis effect ($t(249) = 2.43$, $p = 0.016$) - at the average sample age, women with schizophrenia had shorter LTL than HC women.

Discussion: Gender, not the diagnosis of schizophrenia, was the major factor involved with LTL shortening across the age range studied. We discuss the constraints of a cross-sectional design and other methodological issues, and indicate future directions. Understanding the impact of schizophrenia on biological aging will require separate evaluations in men and women.

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1. Introduction

Schizophrenia is associated with major medical co-morbidity, a 3- to 5-fold increase in premature death, and an estimated 15–20 years of shortened life span (Dickerson et al., 2014; Kilbourne et al., 2009; Kirkpatrick et al., 2008; Olfson et al., 2015). This has led to a suggestion that schizophrenia is associated with accelerated biological aging (Anthes, 2014; Dawes et al., 2011; Kirkpatrick et al., 2008; Kochunov et al., 2013; Koutsouleris et al., 2014; Lindqvist et al., 2015; Okusaga, 2014; Schnack et al., 2016; Shivakumar et al., 2014). Whereas men have overall higher death rates than women, mortality ratios in schizophrenia (standardized to the general population with respect to age, race/ethnicity and geographic region) are higher in women than in men with schizophrenia, with cardiovascular disease being a leading cause of premature death in both genders (Olfson et al., 2015). The causes of medical co-morbidity and premature mortality in schizophrenia are not fully understood but are likely multifactorial, including lifestyle factors (Chwastiak et al., 2011; Robson and Gray, 2007), antipsychotic drugs, and poor access to health care (McCabe and Leas, 2008) as well as intrinsic biological differences (Ringen et al., 2014). Reasons for possible gender-related differences in mortality ratios in schizophrenia remain obscure.

Whereas chronological age is measured in calendar years, biological age is defined physiologically and is often more closely associated with disease processes (Cawthon et al., 2003; Epel,

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2009; Lindqvist et al., 2015). Accelerated biological aging occurs when biological age outpaces chronological age (Lindqvist et al., 2015). One marker of biological age is telomere length (TL), often measured in leukocytes (LTL), since it progressively declines with age and may be inversely related to diseases of aging and mortality (Bojesen, 2013; Cawthon et al., 2003; Mather et al., 2011; Muezzinler et al., 2013; Svensson et al., 2014). However, peak LTL (shortly after birth), the age at which a decline begins, the rate of decline, and when death interrupts the process, vary among individuals (Svensson et al., 2014), suggesting important inter-individual differences in the rates of biological aging (Epel, 2012; Lindqvist et al., 2015; Muezzinler et al., 2013). Variability in telomere length among people of the same chronological age raises the possibility that telomere shortening is potentially modifiable (Bojesen, 2013).

Telomeres are DNA–protein complexes that cap chromosomal DNA ends, protecting chromosomes from damage. When telomeres reach a critically short length, cells undergo replicative senescence or apoptosis or can become genomically unstable (Blackburn, 2005). Telomere length is influenced by genetic factors (Broer et al., 2013), demographic factors and environmental exposure. Telomeres shorten with advancing age (Muezzinler et al., 2013) and are generally shorter in men than in women (Gardner et al., 2014). Telomeres also shorten with repeated mitosis in somatic cells, with replication- and nuclease-associated telomeric DNA damage, and with exposure to oxidative stress, certain cytotoxins, inflammation, and possibly stress hormones (Effros, 2011; Epel et al., 2004; Lindqvist et al., 2015; von Zglinicki, 2002; Wolkowitz et al., 2011). Among the most important lifestyle- and experience-related factors that may impinge on LTL are stress (Epel, 2009; Epel et al., 2004), tobacco use (Babizhayev et al., 2011), exercise (Puterman et al., 2010); and diet (Epel, 2009; Freitas-Simoes et al., 2016), as well certain medical risk factors, such as visceral adiposity (Epel, 2009) (but see (Diaz et al., 2010)), metabolic stress (Epel, 2009) and certain chronic viral infections (e.g., cytomegalovirus) (Effros, 2011). It is unknown if these genetic, lifestyle, and environmental factors also affect LTL in schizophrenia, or if they differ between women and men with schizophrenia.

The published literature on LTL in schizophrenia is based on cross-sectional studies. Because concomitants of aging, including changes in LTL with age, are processes taking place within individuals over time, with individual differences in time course, longitudinal studies are ultimately necessary to fully understand these phenomena. However, if the changes over time are generally monotonic (e.g., LTL decreasing within individuals over time), results shown to be age-related in cross-sectional studies are likely to be even more strongly age-related in longitudinal studies, as cross-sectional studies tend to attenuate time effects. Consequently, cross-sectional studies provide clues as to which factors may be considered in the design of such studies. Thus far, cross-sectional studies have reported mixed results. Several investigations found shorter LTL in persons with schizophrenia than in healthy comparison subjects (HCs) (Fernandez-Egea et al., 2009; Kao et al., 2008) or at least in subgroups of individuals with more chronic, severely psychotic, or treatment-resistant illness (Kota et al., 2015; Li et al., 2015; Rao et al., 2016; Yu et al., 2008) (but see (Lin, 2015)), possibly suggesting accelerated biological aging (Jeste et al., 2011; Kirkpatrick et al., 2008). However, one large study reported longer LTL in schizophrenia than in HCs (Nieratschker et al., 2013). Yet other studies have detected no difference in LTL between individuals with schizophrenia and HCs (Li et al., 2015; Malaspina et al., 2014; Mansour et al., 2011). Reasons for discrepancies in findings among these studies are not known, but may include inadequate sample sizes, differing gender distributions, quality of diagnostic evaluations, nature of the comparison sample, chronicity and severity of illness, medical illnesses, medication history, and history of treatment responsiveness, along with demographic and lifestyle factors such as age, diet, body-mass index (BMI), exercise, and tobacco use. Nonetheless, reviews and meta-analyses of these studies of LTL (Darrow et al., 2016; Lindqvist et al., 2015) support decreased LTL in schizophrenia compared to HCs, with an effect size of approximately d = 0.34, with the effect size being larger in subgroups of subjects who were either drug-naïve (d = 0.56) or poor responders to medication (d = 0.97) (Darrow et al., 2016; Lin, 2015; Polho et al., 2015).

The present study, using a relatively large sample size with adequate representation of women and men with schizophrenia and HCs, well matched in age from 26 to 65 years (mean age = 48), was designed to assess the simultaneous association of age, gender, and diagnosis with LTL. We hypothesized that shorter LTL would be associated with older age (Muezzinler et al., 2013), male gender (Gardner et al., 2014) and diagnosis of schizophrenia (Darrow et al., 2016; Lindqvist et al., 2015). Demographics as well as certain factors associated with schizophrenia or aging, such as cigarette consumption, physical exercise, nutrition, stress, psychiatric ratings, antipsychotic medication doses, and physical health, were also explored.

2. Methods

2.1. Study participants

This report is based on an analysis of baseline data from an ongoing longitudinal study of biological aging in schizophrenia (NIH R01 MH094151-01 [PI: Dilip V. Jeste]). Although we previously published data on high sensitivity C-reactive protein (hs-CRP) (Joseph et al., 2015), F2-isoprostanes (Lee et al., 2016), as well as cytokines (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IFN-γ) (Lee et al., In Press) and chemokines (Hong et al., In Press) in earlier subsets of this sample, the current report represents our first examination of LTL and its associations with demographic, psychiatric, and medical factors. The analyses were restricted to all participants who had LTL data available. These included 134 outpatients with either schizophrenia (N = 80, comprised of 61% women) or schizoaffective disorder (N = 54, comprised of 48% women), and 123 HCs (comprised of 48% women) with no history of major neuropsychiatric illness. All the subjects were recruited from the greater San Diego community and interviewed using the Structured Clinical Interview for the DSM-IV-TR (SCID) (Almeida and Xiao, 2007). Subjects were excluded if they had 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other substance (other than tobacco) abuse or dependence within 3 months prior to enrollment; 3) diagnosis of dementia, mental retardation, or a major neurological disorder; 4) or any medical disability that interfered with their ability to complete the study assessments. Most (91%) of the schizophrenia patients were receiving antipsychotic medication at the time of their assessment. The study protocol was reviewed and approved by the UC San Diego Human Research Protections Program (Project #101631). All study subjects provided written informed consent to participate.

2.2. Blood collection

Fasting blood samples were collected by trained nurses at the UC San Diego Clinical and Translational Research Institute (CTRI) lab. Whole blood was collected for telomere assays in 8.5 mL lavender top plastic EDTA tubes on ice. Samples were stored in a −80° freezer until transportation to UC San Francisco for assay in the Blackburn Lab.

2.3. Biological measures/assays

2.3.1. Telomere length

Total genomic DNA was purified using QIAamp® DNA blood Mini kit (QIAGEN, Cat#51106) from whole blood stored at −80 °C and quantified by measuring OD260. Quality comparison criteria for DNA was OD260/OD280 between 1.7 and 2.0. The telomere length assay was adapted from the published original method by Cawthon (Cawthon, 2002). Details of the assay can be found in Lin et al., (Lin et al., 2010). Lab personnel who performed the assays received de-identified samples and were blind to all demographic and clinical data.

To determine the conversion factor for the calculation of approximate base pair telomere length from T/S ratio, T/S ratios of a set of genomic DNA samples from the human fibroblast primary cell line IMR90 at different population doublings, as well as with the telomerase protein subunit gene (hTERT) transfected into a lentiviral construct. The mean TRF length from these DNA samples was determined using Southern blot analysis, and the slope of the plot of mean TRF length versus T/S for these samples served as the conversion factor for calculation of telomere length in base pairs from the T/S ratio. The equation for conversion from T/S ratio to base pairs for this study was base pairs = 3274 + 2413*(T/S).

2.3.2. Sociodemographic and clinical characteristics

Sociodemographic characteristics (age, education, gender, race/ethnicity), current smoking status, and physical health-related factors for both study samples were ascertained through participant interview and review of available research and medical records (with the appropriate HIPAA authorization from the study participants). Other self-rated scales included the Perceived Stress Scale (Cohen et al., 1983), the Short-Form Health Survey (SF-36) (Hays et al., 1993), International Physical Activity Questionnaire (Craig et al., 2003; Faulkner et al., 2006), and the Nutritional Screening Initiative Checklist (Posner et al., 1993). Antipsychotic medication daily dosages were converted to Defined Daily Doses (DDD) (Organization, 2003; Sweileh et al., 2014).

2.3.3. Current psychopathology and cognitive functioning

The severity of psychopathology was evaluated with the interviewer-administered Scales for Assessment of Positive Symptoms and Negative Symptoms (SAPS and SANS, respectively) (Andreasen et al., 1995; Andreasen and Olsen, 1982). Severity of depressive symptoms was assessed with the Calgary Depression Rating Scale (CDRS; Addington et al., 1990). Assessment of cognitive functioning was focused on executive functioning composite score (Delis et al., 2001; Fucetola et al., 2000; Wobrock et al., 2008).

2.3.4. Medical comorbidity

Medical comorbidity was measured with the total score from the Cumulative Illness Rating Scale (CIRS), which combines the presence and severity of common medical comorbidities (Parmelee et al., 1995). BMI was assessed as a measure of body fat based on height and weight that applies to adult women and men (kg/m^2). Waist-to-hip ratio was collected at time of blood draw and calculated as waist circumference (cm) divided by hip circumference (cm). Waist-to-hip ratio is a standard anthropometric measurement of visceral adiposity (Konarzewska et al., 2014).

2.4. Statistical methods

A multiple linear regression was done on LTL using age (centered at 48 years), gender, and diagnostic group (each coded as +1/2 and −1/2), and all interactions (Kraemer and Blasey, 2004). Thus the main effect of aging is the slope of LTL on age averaged across the four groups. The interactive effects of age by diagnosis, gender, and the diagnosis by gender interaction tested whether the slope of LTL on age differed by diagnosis and/or gender. The main effects of diagnosis, gender and their interaction compare groups at the centering (average) age, here 48 years. All tests were run at a two-tailed 5% significance level, and the effect sizes shown graphically.

Additionally, to explore the possible contribution of demographic and health factors to LTL within the four subgroups, LTL was correlated with each demographic and health variable using Spearman's r to deal with non-normal distributions.

3. Results

3.1. Demographics

We compared persons with schizophrenia and those with schizoaffective disorder, and found no significant between-group differences on socio-demographic, clinical, or lifestyle variables except that individuals with schizophrenia had lower levels of education than those with schizoaffective disorder. We combined those two groups for further analyses. The duration of illness for the men with schizophrenia was 23.6 ± 13.0 years and for women 23.5 ± 11.5 years. The Total antipsychotic dose (DDD) for the men with schizophrenia was 1.46 ± 1.32 and for women 1.91 ± 1.52.

Table 1 shows the baseline characteristics of subjects in the four groups: HC women, HC men, women with schizophrenia, and men with schizophrenia. There was no difference between the groups in age (overall mean 48 ± 1 years). The schizophrenia groups were less educated, more likely non-Caucasian, smoked more, took less exercise, had worse nutrition, and had less favorable outcomes on all the measures of psychological functioning, perceived stress, qand BMI.

3.2. Effects of diagnosis and gender and age on telomere length

3.2.1. Multiple linear regression

Table 2 shows the results of the regression of LTL on age, diagnosis, and gender including all interactions. The main effect of age is significant ($t = -6.237$, $df = 249$, $p < 0.001$), indicating that, in general, in these four groups, LTL decreases with age. There was also a significant age X gender interaction ($t = 2.20$, $df = 249$, $p = 0.029$). As seen in Fig. 1, LTL decreases more rapidly with age in men than in women. No significant diagnosis by age interaction was found ($t = -1.583$, $df = 249$, $p = 0.12$) nor the diagnosis by age by gender interaction ($t = 0.072$, $df = 249$, $p = 0.942$).

At age 48 (the centering age), there was a significant gender effect ($t = 3.59$, $df = 249$, $p < 0.001$), with women having longer mean LTL than men. No significant diagnosis effect was found ($t = 0.635$, $df = 249$, $p = 0.526$), but a significant gender X diagnosis effect was seen ($t = 2.43$, $df = 249$, $p = 0.016$). At age 48, the separation between schizophrenia and HC women is greater (with HC women having longer mean LTL than schizophrenia women) than is the separation between HC men and schizophrenia men. However, because of the gender difference in slopes, this result is specific to that age, and will vary with age.

3.2.2. Within-group exploration

Age, as expected from the regression results, was negatively correlated with LTL in all four groups, -.59 for HC men, -.38 for schizophrenia men both statistically significant with $p < 0.001$, lower for women, -.29 ($p = 0.02$) for HC women, -.18 ($p > 0.05$) for schizophrenia women. All the other within-group correlations (60 correlations) of LTL with the baseline factors presented in Table 1 were examined. There were very few significant correlations, and

Table 1
Baseline characteristics of subjects in four groups: Women and men healthy comparison subjects and women and men with schizophrenia.

	Healthy comparison women			Healthy comparison men			Schizophrenia women			Schizophrenia men		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Leukocyte Telomere Length (base pairs)	66	5813.5	515.3	57	5490.4	422.7	60	5623.2	387.2	74	5604.8	402.7
Age (years)	66	48.0	12.0	57	48.9	11.0	60	49.1	10.3	74	47.4	9.9
Ethnicity (% Caucasian)	66	61%		57	61%		60	40%		74	45%	
Education (years)	66	14.7	2.0	57	14.3	2.4	60	12.7	2.0	74	12.1	1.9
Cigarettes (CPPD)	66	0.02	0.09	57	0.02	0.08	60	0.29	0.45	74	0.44	0.49
IPAQ	66	2.08	0.73	57	2.40	0.70	60	1.68	0.70	73	1.82	0.71
NSIC	64	2.03	2.27	55	2.35	2.72	56	8.70	4.52	72	6.56	4.01
SAPS	66	0.41	0.89	56	0.13	0.33	60	6.53	4.05	74	6.46	4.44
SANS	66	1.44	2.18	56	1.30	2.31	60	7.45	4.27	74	7.36	4.51
CDRS	65	0.74	1.54	57	0.58	1.51	59	3.41	3.74	74	3.23	3.97
PSS	63	11.3	5.8	56	10.8	6.5	60	18.9	6.5	72	17.9	5.7
SF-36 Mental Composite	64	55.08	4.72	56	54.21	6.90	60	43.49	11.36	72	43.35	11.24
Executive Functioning Composite	66	0.55	0.52	57	0.34	0.65	60	−0.65	0.78	74	−0.42	0.67
SF-36 Physical Composite	64	51.41	8.39	56	51.59	9.43	60	41.71	10.12	72	44.41	9.89
CIRS - Total Score	60	3.17	3.20	43	3.05	3.23	46	7.85	5.56	70	6.03	4.25
BMI	64	27.4	7.9	55	28.1	5.9	59	34.3	8.5	73	30.5	6.0
Waist-to-hip ratio	63	0.87	0.07	51	0.95	0.07	55	0.94	0.08	67	1.0	0.08

Note: Sample sizes (N) reflect the number of subjects having data for that variable. Thus, in cases of missing data, N's differ across variables.
Abbreviations:
Cigarettes (CPPD) – Cigarettes Current Pack Per Day.
IPAQ – International Physical Activity Questionnaire; note: higher scores indicate higher levels of physical activity.
NSIC – Nutritional Screening Initiative Checklist; note: higher scores indicate worse nutrition/diet.
N/A- Not applicable.
SAPS/SANS- Assessment of Positive Symptoms and Negative Symptoms.
CDRS – Calgary Depression Rating Scale.
PSS – Perceived Stress Scale.
SF-36- Short-Form Health Survey.
CIRS- Cumulative Illness Rating Scale.
BMI- Body-mass index.

Table 2
Tests of between-subjects effects (multiple linear regression).

Parameter	Estimate	STD Error	t-value	p-value
Intercept	5680.13	26.61	213.45	<0.001
Age	−14.81	2.37	−6.24	<0.001
Age x Dx Group	−7.52	4.75	−1.58	0.115
Age x Gender	10.44	4.75	2.20	0.029
Age x Dx Group x Gender	−0.69	9.50	−0.07	0.942
Gender	131.88	53.22	2.48	0.014
Dx Group	70.22	53.22	1.32	0.188
Dx Group x Gender	259.05	106.44	2.43	0.016

Residual standard error: 403.8 on 249 degrees of freedom.
Multiple R-squared: 0.2088, Adjusted R-squared: 0.1866.
F-statistic: 9.389 on 7 and 249 DF, Model p-value: 2.505e-10.
Abbreviations:
Dx = Diagnostic Group.

in every such case, a significant correlation was at best of moderate magnitude (r = 0.3) and was seen in only one of the four groups. With correction for multiple testing, none are statistically significant at the 5% level. This does not exonerate these factors as influences on LTL, for it may be no single one of these variables has much impact on LTL, but collectively they might.

4. Discussion

The present results may suggest that gender, not the diagnosis of schizophrenia, is the major factor involved with LTL shortening across the age range studied. Because numerous studies have shown that the onset of schizophrenia tends to be later in life in women than in men (Howard et al., 2000), and the present results indicate that the separation between women with schizophrenia and HC women might differ from that between men with schizophrenia and HC men at various ages, understanding the effects of aging in schizophrenia will likely require studying LTL (and other aging parameters) separately in men and women (Ramsey et al., 2013).

This study also serves to clarify possible sources of the mixed findings in earlier cross-sectional studies. Use of a regression model with age as a covariate, but excluding interactions of age with gender and diagnosis, generates results based on the likely false assumption that the rate of decline of LTL is the same in all subgroups (particularly an absence of a gender effect on rate of LTL decrease). An interaction present in the population, but missing from a regression model, is remapped into the other effects and biases both estimation and testing. Our results strongly suggest that the effect of schizophrenia on LTL should be studied separately among men and women.

While the lack of a statistically significant difference in the rates of LTL decline among schizophrenia vs. HC groups in either gender cannot be interpreted as confirming there is none, the presence of a significant interactive effect of gender by diagnosis at age 48 suggests that there is some aspect of LTL change that differentiates the two groups, perhaps, for example, the initial LTL (time of birth), or the age at which decline in LTL becomes more rapid, or the age of onset of schizophrenia if that even impacts LTL level. Moreover, in a cross-sectional study, what is seen may be associated with menopause in women, or with survival differences in the four groups. Longitudinal studies are required to see individual differences in LTL course.

We also did not find evidence, either within HC or schizophrenia gender-matched groups, that LTL is correlated with demographic or health variables that have often, but not always, been associated with LTL in other studies, e.g., perceived stress (Epel et al., 2004), education (Adler et al., 2013), socioeconomic status (Cherkas et al., 2006), tobacco use (Babizhayev et al., 2011), exercise/activity

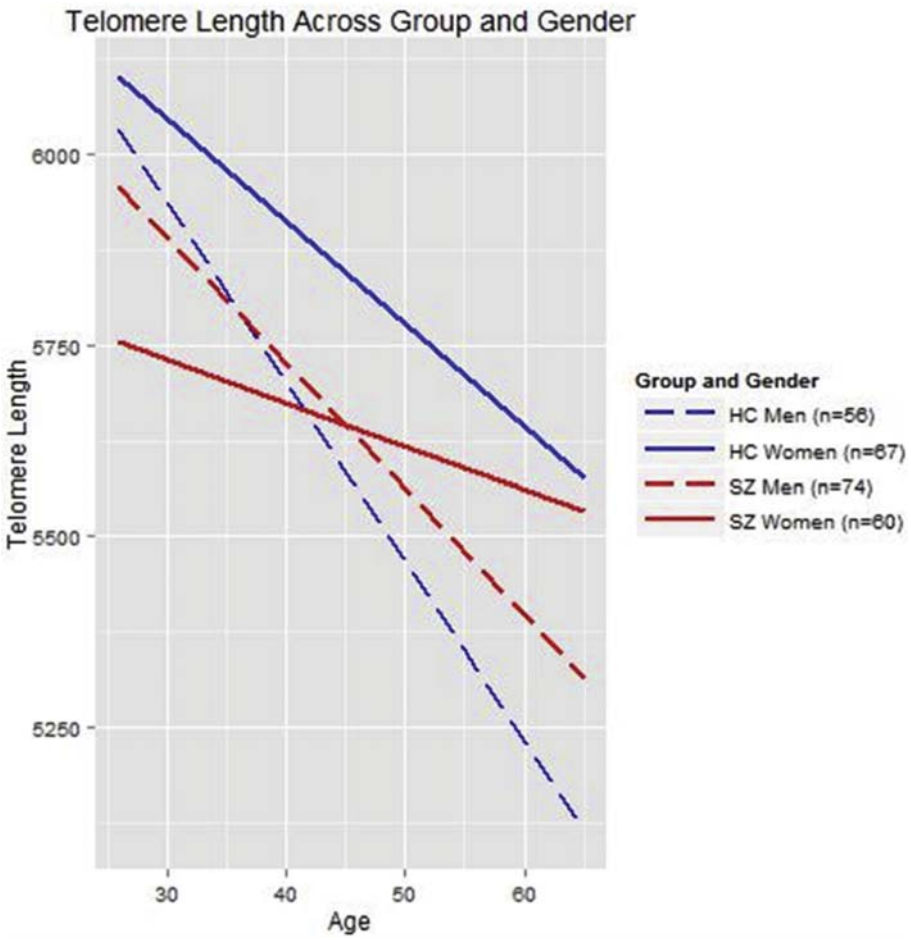

Fig. 1. Associations of age, diagnosis, and gender on leukocyte telomere length (LTL). Legend: Average LTL by diagnosis and gender. HC= Healthy comparison. SZ= Schizophrenia.

(Puterman et al., 2010), sleep (Prather et al., 2011), diet (Epel, 2009), depression (Wolkowitz et al., 2011), early life adversity (Price et al., 2013) and BMI (Epel, 2009). This suggests that each of these demographic, lifestyle, and health variables, despite the fact that they differed between groups, did not substantially contribute to our LTL findings.

Several putative mechanisms of telomere shortening have been proposed (Lindqvist et al., 2015). Approximately 70% of adult LTL is heritable (Broer et al., 2013), with the other 30% being environmentally induced post-partum. There is no evidence either way that the genetic contribution to telomere length is related to a genetic propensity to schizophrenia, or that this differs in men vs. women. However, certain polymorphisms in the gene for telomerase reverse transcriptase (TERT), a key component of telomerase, may affect risk for schizophrenia (Rao et al., 2016), although the specific effects of the risk single nucleotide polymorphisms (SNPs) in hTERT on TL are unknown. Other possible contributors to LTL shortening include inflammation, oxidative stress, and certain chronic viral infections (reviewed in: Lindqvist et al., 2015). These factors may be increased in schizophrenia compared to HCs (Emiliani et al., 2014; Muller et al., 2015; Shivakumar et al., 2014). This could, in theory, result in shortened LTL, but there is only mixed evidence that these factors are differentially prevalent in men vs women with schizophrenia (Joseph et al., 2015; Kunz et al., 2011; Lee et al., 2016; Ramsey et al., 2013; Reyazuddin et al., 2014).

While the reasons for the gender difference in LTL in schizophrenia vs. HCs remain unclear, this might help explain the greater standardized mortality ratio seen in women, compared to men with schizophrenia (Olfson et al., 2015). There may be several consequences of prematurely shortened LTL in women with schizophrenia. First, when T cells with short telomere lengths become senescent (e.g., $CD8^{+}CD28$- T cells), they hypersecrete inflammatory cytokines, further exacerbating the cellular aging process (Effros, 2009, 2011). Prematurely shortened TL can also lead to cellular apoptosis and genomic instability. Rapidly dividing cells (e.g., leukocytes undergoing clonal expansion or neuronal and other stem cells) are most prone to shortening of telomeres, unless acted upon locally by the enzyme telomerase. When these cells enter replicative senescence, their functional competence decreases and these stem cell pools can become depleted, leading to loss of ability to generate new cells and to repair tissues (Chou and Effros, 2013). Apart from directly contributing to cellular damage, LTL shortening may serve as an indicator of an endangering internal milieu (e.g., inflammation and oxidative stress; Effros, 2009). Thus, plausible mechanisms exist by which LTL shortening might contribute to, or reflect, disease or aging progression.

The strengths of this study include the relatively large sample size in each of the four groups defined by gender and diagnosis, simultaneous assessment of age, gender, and diagnosis, and their interactions on LTL, and assessment of potential confounders. Limitations of this study include the study of LTL in only leukocytes and inclusion of mostly medicated and relatively stable, low-acuity outpatients with schizophrenia. Thus, our findings may not apply to other cell types or tissues in the body or to acutely or severely ill

inpatients with the illness. Another limitation of this, and other published studies of LTL in schizophrenia, is the use of a cross-sectional design, which makes assessments of telomere trajectory or rate of telomere shortening in individual subjects impossible (Mather et al., 2011). Unless all trajectories of LTL with age parallel each other, the trajectory of LTL with age in cross-sectional studies does not well indicate the individual trajectories for subjects in the population (Kraemer et al., 2000; Louis et al., 1986; Vollmer, 1993). Indeed, based solely on cross-sectional data, we cannot say with certainty if differences in LTL are a product of an accelerated cellular aging process, or, of an initial "hit" (genetic or epigenetic), with no subsequent alteration of the normal trajectory of shortening with aging. This might be termed "premature," rather than "accelerated," biological aging. Consequently, cross-sectional and longitudinal studies address different research questions. Furthermore, cross-sectional studies can demonstrate LTL correlates with current diseases, but longitudinal studies are necessary to assess whether LTL at one time point predicts subsequent development of diseases (e.g., cardiovascular disease) and mortality (Cawthon et al., 2003; Epel et al., 2009). As an example of this difficulty, the starting points of the trajectories in the four groups in our study differed, and the trajectories of subjects with schizophrenia and HCs within each gender group crossed, men at about age 35, while women approach crossing at about age 65. It is unclear whether this is due to different starting values for those likely to be diagnosed later with schizophrenia, or to an acute effect on LTL at the age of diagnosis or to differential death risks either due to LTL or other diseases, or simply random errors.

Due to relatively high inter-individual variability in LTL at any time point, clearer interpretations are possible only from examining intra-individual, rather than between-individual or between-group, patterns longitudinally (Mather et al., 2011). Such studies should always include an HC group, separate analyses of men and women, adequate sample sizes within each group, consideration of possible differences in the aging process in each group (gender and diagnosis), and careful consideration of other covariates either interacting with, or collinear with gender, age, or diagnosis. It would also be important to include diverse groups of persons with schizophrenia – e.g., first-episode antipsychotic-naïve patients, chronic treatment-resistant patients, and patients from countries with different health care systems, in case the aging process may be different with different manifestations, or at different stages, of the illness, or with different treatment choices.

Conflicts of interest

Jue Lin is a cofounder and consultant to Telomere Diagnostics, Inc. The company played no role in the current study.

Other authors have no other conflicts of interest to report.

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