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# No alteration of leukocyte telomere length in first episode psychosis

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ABSTRACT

Both shorter telomeres and schizophrenia have been associated with a decrease in life expectancy. Furthermore, several studies found a shorter telomere length (TL) in schizophrenia. Understanding whether or not telomere shortening is directly related to pathophysiology of schizophrenia or is a consequence of a cumulative exposure to chronic stress is of major importance. Comparing the TL of subjects at the very beginning of the disease (FEP) and control subjects could help to decide between these two hypotheses. The aim of the present study was to compare TL between FEP subjects (N=91) and controls (N=137). After accounting for multiple potential confounders, no significant association was observed between FEP and TL. Our result is consistent with the hypothesis that psycho-social stress / adversities and stressful situations in people with schizophrenia affect TL rather than that telomere erosion contributes to the development of this disorder.

## 1. Introduction

Schizophrenia is associated with a weighted average of 14.5 years of potential life lost according to a recent meta-analysis (Hjorthøj et al., 2017). This is partly explained by high rates of suicide and an increased risk of cardiovascular diseases. However, all these causes could not fully explain the loss of life expectancy in people suffering from schizophrenia (Galletly, 2017).

On the other hand, life expectancy has been strongly correlated with telomere length (Whittemore et al., 2019). Telomeres are noncoding structures consisting of DNA TTAGGG tandem repeats and associated proteins located at the end of the chromosomes (de Lange, 2005). Their role is to help preserve genome stability by protecting chromosomal ends from the loss of genetic material (Harari and Kupiec, 2018). The progressive loss of telomeric repeats during cell divisions has led researchers to consider telomeres as molecular clocks that count down to the end of cell growth (Blackburn et al., 2010).

Age is not the unique factor influencing telomere's length (TL). TL is also influenced by genetic factors (Slagboom et al. 1994) and environmental factors such as smoking (Verde et al., 2015) or psychological stress (Mathur et al., 2016). Telomere shortening has been observed in many diseases such as cardiovascular diseases (D'Mello et al., 2015), type 2 diabetes (Gurung et al., 2018), high blood pressure (Tellechea and Pirola, 2017). Interestingly, these medical conditions that show a high prevalence in subjects with schizophrenia tend to be associated with aging. Schizophrenia itself and its course are associated with physiological changes, which have been associated with normal aging. Such changes include hyperlipidemia, decreased bone density, insulin resistance, cortical atrophy, thinning and wrinkling of the skin, increased blood pressure and decreased muscle mass (Kirkpatrick and Galderisi, 2008). Another potential link between schizophrenia and shortening TL might be through oxidative stress, which is suspected to play a role in the pathophysiology of schizophrenia (Hardingham and Do, 2016; Steullet et al., 2016) and might also accelerate the physiological process of telomere erosion in schizophrenia.

The fact that both shorter telomeres and schizophrenia have been associated with a decrease in life expectancy has fueled the interest in the study of TL in schizophrenia. Indeed, demonstrating such a relation might improve understanding of the increased mortality and morbidity, improve diagnosis and hopefully suggest means for prevention and/or treatment.

To date, the majority of the studies found a decrease in TL in subjects

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with schizophrenia compared to control subjects (Galletly, 2017; Rao et al., 2016; Czepielewski et al., 2016; Pawelczyk et al., 2015; Kota et al., 2015; Fernandez-Egea et al., 2009; Kao et al., 2008; Yu et al., 2008) suggesting that telomeres play a role in the pathophysiology of schizophrenia. However, other studies (Riley et al., 2018; Monroy-Jaramillo et al., 2017; Wolkowitz et al., 2017; Li et al., 2015; Malaspina et al., 2014; Mansour et al. 2009) have not been able to demonstrate a significant difference in TL between subjects with schizophrenia and controls. In addition, four studies (Zhang et al., 2018; Cui et al., 2017; Maurya et al., 2017a; Nieratschker et al., 2013) found an opposite result: increased TL in subjects with schizophrenia. Several meta-analyses have been published on TL in schizophrenia leading to different conclusions (Omidpanah et al., 2019; Russo et al., 2018; Polho et al., 2015; Rao et al., 2016; Lin, 2015). Three of them conclude that TL is decreased in schizophrenia while, two others (Omidpanah et al., 2019; Li et al., 2015) do not. To explain, these discrepant results, the most recent meta-analysis (Omidpanah et al., 2019) suggests that different subtypes of schizophrenia could have specific relationship with TL, while in the studies used for meta-analyses, patients were not categorized according to disease sub-types. *It has also been suggested that in schizophrenia, shorter TL was specifically observed in patients reporting childhood abuse (Aas et al., 2019)*.

Furthermore, the classic case-control studies that include subjects in different stages of the disorder might add to the confusion because of the presence in variable proportion or for variable durations of potential confounding factors like medications (Rao et al., 2016; Porton et al., 2008), duration of illness and unhealthy lifestyles (e.g., poor diet, smoking). All these factors may impact upon rates of telomere shortening (Maurya et al., 2017a; Yu et al., 2008) and confound the association between schizophrenia and TL.

In order to overcome these difficulties, some authors (Çevik et al., 2019; Czepielewski et al., 2016) have studied TL, considered as an intermediate phenotype, in non-affected first-degree relatives of schizophrenia subjects. This strategy offers several advantages, since subjects are not impacted by any of the afore-mentioned confounding factors (Braff et al., 2007; Gottesman and Gould, 2003). Çevik et al. (2019) found that first-degree relatives of schizophrenic subjects had significantly longer TL compared to both subjects with schizophrenia and controls. Conversely, Czepielewsi et al. (2016) found that unaffected relatives did not significantly differ in TL from subjects with schizophrenia, whereas individuals with schizophrenia had shorter TL compared to controls. Only one study has been conducted in ultra-high risk (UHR) subjects for psychosis and found that they had shorter TL compared to control subjects (Maurya et al., 2017b). Although this study avoids confounding from medication, it's relevance to schizophrenia is diminished by the fact that most of UHR subjects do not develop schizophrenia (Addington et al., 2015). Thus, the interpretation of this finding is not clear and needs to be further explored.

Comparing the TL of subjects at the very beginning of the disease (FEP) to the general population could help to minimize potential biases (medication, hospitalizations, etc.) and may be more informative about a causative risk mechanism for schizophrenia. To our knowledge, only two studies have investigated the TL in FEP subjects (Maurya et al., 2017a; Li et al., 2015). In both studies, the TL of FEP subjects was not significantly different from TL in control subjects. However, these two studies had also limitations that might explain the negative results. For example, one of the studies excluded subjects with comorbid addiction, which given the high frequency of substance use disorders in schizophrenia, might have rendered the sample non-representative of the disorder (Li et al., 2015). In the other sample, the authors did not account for potential differences in ethnicity, which might have influenced the result (Maurya et al., 2017a). The aim of the present study was to further explore the relationship between TL and psychotic disorders by comparing TL between FEP subjects and controls after adjusting for several potential confounding factors. We hypothesized that TL is similar between FEP and controls, suggesting that telomeric erosion occurs during the course of the disease.

## 2. Material and methods

### 2.1. Subjects

The present study is part of a large effort designed to explore gene-environment interactions in the aetiology of psychosis (European network of national schizophrenia networks studying Gene-Environment interaction: http://www.eu-gei.eu). Our study is based on the data collected in the French centers. Data were collected between June 1st 2010 and May 31st 2014 in three French catchment areas: Clermont-Ferrand surroundings, Créteil (in the suburb of Paris) and Paris.

Patients presenting with their first episode of psychosis were identified by trained researchers who carried out regular checks across the mental health services within the 3 catchment areas. Patients were eligible if they were aged 18-65 years and resident within the study areas at the time of their first presentation with a diagnosis of psychosis (diagnosis of psychotic disorder or mood disorders with psychotic features) by ICD-10 criteria (F20-F33); details are provided in previous publications (Di Forti et al., 2019; Jongsma et al., 2018; Szöke et al., 2014). Cases that accepted to participate were interviewed using the Diagnostic Interview for Genetic Studies (DIGS) (Preisig et al., 1999; Nurnberger et al., 1994) and received a research-based diagnosis. All patients suffering from psychosis due to medical general conditions (ie when there was evidence that the delusions or hallucinations were the direct consequence of a general medical condition) or from substance / medication-induced psychotic disorder were excluded.

Controls were recruited using quota sampling strategies. Accurate local demographic data were used to ensure the sample's representativeness of the three catchment areas in terms of age, gender and ethnicity. Control subjects were also between 18 and 65 years old and were excluded if they had previously received a diagnosis of a psychotic disorder. Given the general aims of the global European study, subjects born outside mainland France were oversampled (twofold).

All participants provided informed written consent. Ethical approval was provided by the Comité de Protection des Personnes (CPP Ile de France IX) under the project number: 2010-A00161-38. The EU-GEI project is funded by the European Community's Seventh Framework Program under grant agreement n° HEALTH-F2-2010-241909. The funder had no involvement in the study design, data collection, analysis, interpretation of findings, manuscript preparation or the decision to submit the paper for publication.

### 2.2. Assessments

Data collected from FEP and control subjects which included variables of interest for the present study were: age, gender, weight, smoking status, ethnicity, paternal and maternal ages at birth of the subject. *We also assessed childhood trauma with the French version of the Childhood Trauma Questionnaire (CTQ), a 25 item questionnaire. All items are answered on a five point Likert scale (1: Never to 5: Very often).CTQ provides six different scores: CTQ total score and five sub-scores: physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect. The CTQ total score is the sum of all items (Paquette et al. 2004)*. All participants provided a blood sample for measurement of leukocyte telomere length.

### 2.3. Measurement of leukocyte telomere length

Leukocyte DNA was extracted from peripheral blood samples and kept at -80°C before use. The genomic DNA was isolated from whole blood using Maxwell 16 semi-automated system (Promega) following the manufacturer's instructions.

The telomere length was measured by realtime PCR (qPCR)

according to the original method by Cawthon (Cawthon, 2002). The samples were all run in triplicates in a real time PCR system with QuantStudio™ 6 Flex *Real-time PCR* System. The sequences for the primers for telomeres et 36B4 were: Tel F, 5' CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3', 300 nM; Tel R, 5'-GGCT TGCCTTACCCTTACCCTTACCCTTACCCT-3', 300 nM; 36B4F, 5'CAGCA AGTGGGAAGGTGTAATCC-3', 300 nM; and 36B4R, 5'-CCATTCTATCAACGGGTACAA-3', 300 nM.

The measurement consists of determining the relative ratio (T/S ratio) of number of telomeric copies to a single copy gene, using the comparative Ct method ($T/S = 2^{-\Delta\Delta Ct}$), which reflects the number of copies of telomere in each cell in a assay. This method amplifies the telomeric (T) DNA and a single-copy (S) control gene (36B4) was used to normalize values.

### 2.4. Statistical analyses

Demographic and clinical characteristics were compared between FEP and controls using the chi-square, Mann-Whitney's or Student's t test, as appropriate. Due to a skewed distribution of TL (assessed by The Shapiro-Wilk test), non-parametric tests were used to study the relationships between TL and other variables. Spearman correlation analyses were used to study the relationship between TL and continuous variables. For multivariate analyses, a logarithmic transformation of TL was performed to achieve the normality assumed for parametric procedures. *Linear regression model was used to examine the relationship between TL and the group as the predictive variable. Age, gender, ethnicity, smoking status, childhood trauma, paternal and maternal ages were included as the confounding factors.* A p-value of $\leq 0.05$ was considered statistically significant. Analyses were performed using R software (version 3.6) (R Core Team, 2013).

## 3. Results

The sample was composed of 91 FEP subjects and 137 control subjects. Demographic and clinical characteristics of the two samples are summarized in Table 1. The control group were significantly older than the FEP group (38.7 +/- 14 and 31.5 +/- 10.7, respectively, $p < 0.001$). The groups also differed significantly according to gender ($p = 0.01$), smoking status ($p < 0.01$) and ethnicity ($p < 0.001$). Cigarette smoking status were defined as either "never" or "current/past" as in Malaspina et al., (2014). *FEP group has significantly higher CTQ total scores and sub-scores than controls.* Leukocyte TL was negatively correlated with age (Spearman rho = - 0.19, $p = 0.03$) and positively correlated with paternal age (Spearman rho = 0.16; $p = 0.01$). *There was no significant correlation between TL and the other potential confounding variables (maternal age, weight, smoking status, gender, ethnicity and childhood trauma).*

In an unadjusted model, the groups did not differ significantly according to T/S ratio (0.76 +/- 0.26 vs. 0.71 +/- 0.25 for FEP cases and controls respectively; $p = 0.23$) (Fig. 1). *After adjustment for age, maternal and paternal ages, gender, smoking status, childhood trauma and ethnicity, the results were the same, i.e. TL did not show a significant difference between groups (beta coefficient = - 0.39, p = 0.56).* Subgroup analyses (affective FEP ($n = 22$) vs. controls and non-affective FEP ($n = 69$) vs. controls) did not show any significant differences of TL between subgroups and controls ($p = 0.19$ and $p = 0.73$ respectively).

## 4. Discussion

We did not find any significant differences of TL in FEP compared to healthy controls. This finding is consistent with the two previous studies investigating TL in FEP subjects and raises several questions regarding the relationship between telomere erosion and schizophrenia. Indeed, the fact that the majority of studies report shortened TL in schizophrenia (Kota et al., 2015; Fernandez-Egea et al., 2009; Kao et al., 2008; Yu et al.,

**Table 1**
Description and comparison of the FEP subjects vs. control subjects.

| | FEP (n = 91) | Controls (n = 137) | IC 95% | $Chi^2$ or Mann-Whitney statistic test | p |
|---|---|---|---|---|---|
| Age (years) | 31.5 (+/- 10.8) | 38.7 (+/- 14.1) | (29.3 - 33.7)* (36.4 - 41.1) | 3.80 | p < 0.001 |
| Sex (% of men) | 37.4% | 54.7% | (28 – 47.8)* (46.3 - 63) | 6.6 | p = 0.01 |
| Smoking (% of smokers) | 60.9% | 34.1% | (50.2 - 70.7)* (26.5 - 42.5) | 15.4 | p < 0.01 |
| Number of years of education completed | 12 (+/- 4.1) | 14.2 (+/- 3.2) | (11.1 – 12.9)* (13.6 – 14.7) | 0.34 | P < 0.001 |
| Global Assessment of Functioning (GAF) score: symptoms | 42.7 (+/- 15.3) | 87.9 (+/- 11) | (38.4 – 46.9)* (95.9 – 89.8) | 0.95 | P < 0.001 |
| (GAF) score: disability | 51.4 (+/- 13.9) | 87.3 (+/- 9.7) | (47.5 – 55.2)* (85.5 – 89) | 0.93 | P < 0.001 |
| Childhood Trauma Experiences | | | | | |
| - CTQ total score | 45.9 (+/- 14.7) | 35.2 (+/- 11) | (42.8 – 48.9)* (33.3– 37.0) | 5.91 | P < 0.0001 |
| - CTQ Physical abuse | 7.7 (+/- 4) | 6.1 (+/- 2.5) | (6.8 – 8.5)* (5.67– 6.52) | 3.67 | P < 0.0002 |
| - CTQ Emotional abuse | 9.3 (+/- 4.3) | 7.4 (+/- 4.1) | (8.4 – 10.2)* (6.7– 8.1) | 4.26 | P< 0.0001 |
| - CTQ Sexual abuse | 6.8 (+/- 3.5) | 5.3 (+/- 1.4) | (6 – 7.5)* (5– 5,5) | 5.23 | P < 0.0001 |
| - CTQ Physical neglect | 9.3 (+/- 3.6) | 6.8 (+/- 2.6) | (8.5 – 10)* (6.3– 7.2) | 5.60 | P < 0.0001 |
| - CTQ Emotional neglect | 12.4 (+/- 4.8) | 9.9 (+/- 4.3) | (11.4 – 13.4)* (9.1 – 10.6) | 3.56 | P < 0.0004 |
| Lifetime cannabis use (yes/no) | 55.8% | 7.2% | (45.3 – 65.8)* (3.9 – 12.8) | 65.1 | p < 0.001 |
| Paternal age (Years) | 33.2 (+/- 9.2) | 31.1 (+/- 9.2) | (31.1- 35.4)* (29.7 - 32.5) | 1.50 | p = 0.13 |
| Maternal age (years) | 27.7 (+/- 6.6) | 26.9 (+/- 5.9) | (26.2 - 29.2)* (25.9 - 27.9) | 0.69 | p = 0.49 |
| Ethnicity (% of Caucasians) | 37.1% | 70.8% | (27.6 - 47.7)* (62.7 - 77.8) | 25.11 | P < 0.001 |
| Weight (kgs) | 70.4 (+/- 13.7) | 73.1 (+/- 16) | (67.2 - 73.5)* (69.9 - 76.4) | 1.06 | p = 0.29 |
| Telomere length (T/S) | 0.76 (+/- 0.26) | 0.71 (+/- 0.25) | (0.71 - 0.82)* (0.67 - 0.76) | 1.20 | p = 0.23 |

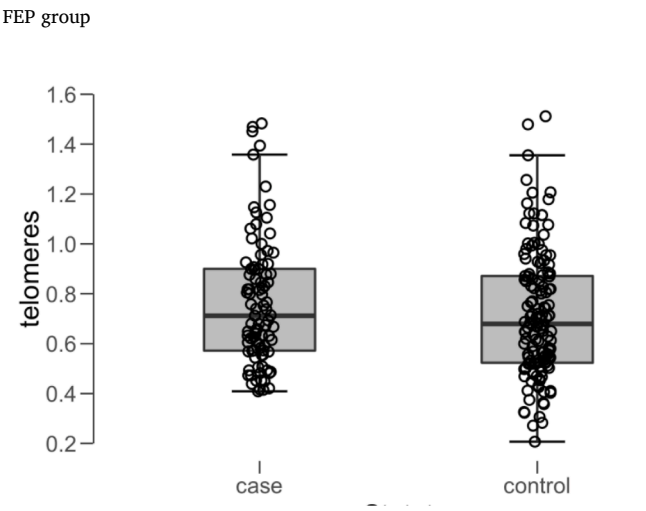


**Fig. 1.** Telomere Length (TL) in FEP (case, N = 91) and healthy controls (N = 137).
Bold line as mean and error bars as standard deviation.

2008) but not in FEP subjects could lead to several explanations. It is possible that some confounders that occur or increase after the first episode, including age of subjects, lifestyles, medical comorbidities and antipsychotics use might partly explain a shortened TL in schizophrenia. The inconsistent results in the literature might also suggest that shortened TL is associated only with a specific subtype of schizophrenia (Vaez-Azizi et al., 2015) or depend on the exposure to specific risk factors such as a history of childhood trauma (Aas et al., 2019). Thus, the association between TL and schizophrenia would depend on the proportion of this subtype and/or of the frequency of exposure to specific risk factors in the different samples. It is therefore possible that the absence of shortened TL in our study is due to the clinical and/or etiological heterogeneity of this population.

However and more convincingly, two pathophysiological, non-mutually exclusive mechanisms can be proposed to explain the observed data. A first hypothesis is that the acceleration of the physiological process of telomere erosion in schizophrenia is due to the activation of inflammatory processes and oxidative stress as a consequence of schizophrenia *per se. The second hypothesis is that reduced TL may be a result of cumulative exposure to chronic stress related to schizophrenia. Indeed, subjects suffering from schizophrenia are often exposed to stigma, discrimination and other social stressors such as poverty, inequality and social deprivation (Kirkbride et al., 2011). In addition, they exhibit a higher sensitivity to stress than healthy individuals including events not experienced as stressful by healthy individuals (Taylor et al.,. 2019) We hypothesized that in schizophrenia, telomere erosion is in part due to a longer period of exposure to these stressful situations*. According to these two hypotheses, telomere erosion may be mild in the early-phase of schizophrenia, since these individuals have short-term exposure to stress and a shorter duration of the illness. Indeed, in healthy individuals, a growing body of evidence has linked chronic stress, inflammatory process, oxidative stress to accelerated shortening of TL (Tyrka et al., 2015; Price et al., 2013; Epel et al., 2004) and it is possible that the stress-mediated telomere erosion might be too small to be detected in FEP patients because they had younger age and shorter duration of illness than subjects with schizophrenia. Based on these both explanations, telomere alterations may be considered as a biomarker of illness progression and might be useful for illness staging.

It is unlikely that our results and those previously reported in FEP could be explained by a lack of statistical power or by the presence of psychotic affective disorders. Indeed, several studies reporting significant reduced TL in non FEP schizophrenia samples have similar or smaller sample sizes than the FEP studies and shorter telomeres have also been described in subjects with affective disorders (Barbé-Tuana et al., 2016; Lima et al.,2015; Simon et al., 2006). However, several limitations should be considered in the interpretation of our results. Leukocyte TL is highly correlated with TL of other tissues, however, we still cannot exclude significantly shorter TL in neural cells. The cross-sectional design of the study makes assessments of telomere trajectory or rate of telomere shortening in individual subjects impossible. The percentage of women is high in the FEP group, and thus, our sample is probably not representative of FEP population. Although, our multivariate analysis has been adjusted for these two socio-demographic variables, the fact that the two groups differ in terms of age and sex remains a limitation of the study. Lastly, although adjustments were made for potential confounding variables, the possibility of the influence of unmeasured covariates cannot be excluded.

Overall, our result suggests that reduced TL may not be an intrinsic feature of schizophrenia or associated with risk factors for schizophrenia but rather the result of cumulative exposure to chronic stress (Savolainen et al., 2012; Epel et al., 2004) after the onset of the disorder. In other words, our result is consistent with the hypothesis that psycho-social stress / adversities and stressful situations in people with schizophrenia affect TL rather than that telomere erosion contributes to the development of this disorder. In this case, treatments that prevent exposure and/or vulnerability to stressful life events that ameliorate schizophrenia may also prevent or decelerate telomere erosion. In this perspective, by engaging in a healthy diet and regular activity subjects suffering from schizophrenia could be both promising strategies to protect telomere maintenance and improve health span at old age. It is clear that schizophrenia is associated with a greater exposure to stress factors, altering hypothalamic-pituitary-adrenal axis function, which may produce altered cognition and behaviors (Ruby et al., 2017; Cherian et al., 2019). It remains to be determined how stress and the activity of the hypothalamic-pituitary-adrenal axis influence TL. In addition, the inflammatory process involved in the physiopathology of at least a subgroup of subjects with schizophrenia (for review, see Müller (2018)) could be also responsible of telomere erosion as suggested by previous research (Steullet et al., 2016; Carrero et al., 2008; Damjanovic et al., 2007). Further illuminating the relationship between stress, inflammation and TL is of great interest for psychiatric research and for understanding stress effects in this population.

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## CRediT authorship contribution statement

**Franck Schürhoff:** Writing - review & editing. **Cécile Corfdir:** Writing - review & editing. **Baptiste Pignon:** Data curation. **Mohamed Lajnef:** Formal analysis. **Jean-Romain Richard:** Formal analysis. **Elisabeth Marcos:** Formal analysis. **Antoine Pelissolo:** Data curation. **Marion Leboyer:** Data curation. **Serge Adnot:** Formal analysis. **Stephane Jamain:** Formal analysis. **Andrei Szöke:** Writing - review & editing.

## Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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