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# Leukocyte telomere length and accelerated aging as predictors for the onset of psychosis

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**LEUKOCYTE TELOMERE LENGTH AND ACCELERATED AGING AS  
PREDICTORS FOR THE ONSET OF PSYCHOSIS**

by

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B.A., University of California Berkeley, 2015

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**ABSTRACT**

Leukocyte telomere length is an emerging marker for pathologically accelerated cellular aging. First discovered to be associated with aging-related disorders, such as type 2 diabetes mellitus and cardiovascular disease, in young individuals, leukocyte telomeric degeneration is also garnering growing attention in psychiatric illnesses. Comorbid metabolic symptoms and physiological dysregulation observed in schizophrenia patients imply a plausible association between pathological telomere biology and psychosis. Available data on the relationship between leukocyte telomere length and schizophrenia is limited largely to small-sample, cross-sectional studies unable to fully account for the large body of potentially confounding factors on telomere length (psychotropic medication, chronic stress and history of trauma, comorbidities, paternal age, substance use, subject-level variables). The most comprehensive meta-analysis to date reveals a significant trend of shortened telomeres in schizophrenia patients as compared to healthy controls. Some findings suggest a linear relationship between telomeric attrition and disease chronicity/severity. However, overall findings are insufficient to gauge the potential of leukocyte telomere length as a predictive, diagnostic biomarker in this patient population. Future longitudinal studies with carefully controlled covariates are required to verify the promising potential of a new marker for schizophrenia onset and a possible new direction for adjunctive antipsychotic treatment.

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## LIST OF ABBREVIATIONS

eLTL	elongated Leukocyte Telomere Length
LTL	Leukocyte Telomere Length
MDD	Major Depressive Disorder
PBMCs	Peripheral Blood Mononuclear Cells
PTSD	Post-Traumatic Stress Disorder
SMD	Standardized Mean Difference
SNP	Single-Nucleotide Polymorphism
SZ	Schizophrenia
TERT	Telomerase Reverse Transcriptase
TL	Telomere Length
T/S Ratio	Telomere/Single Copy Gene Ratio
UHR	Ultra-High Risk

## INTRODUCTION

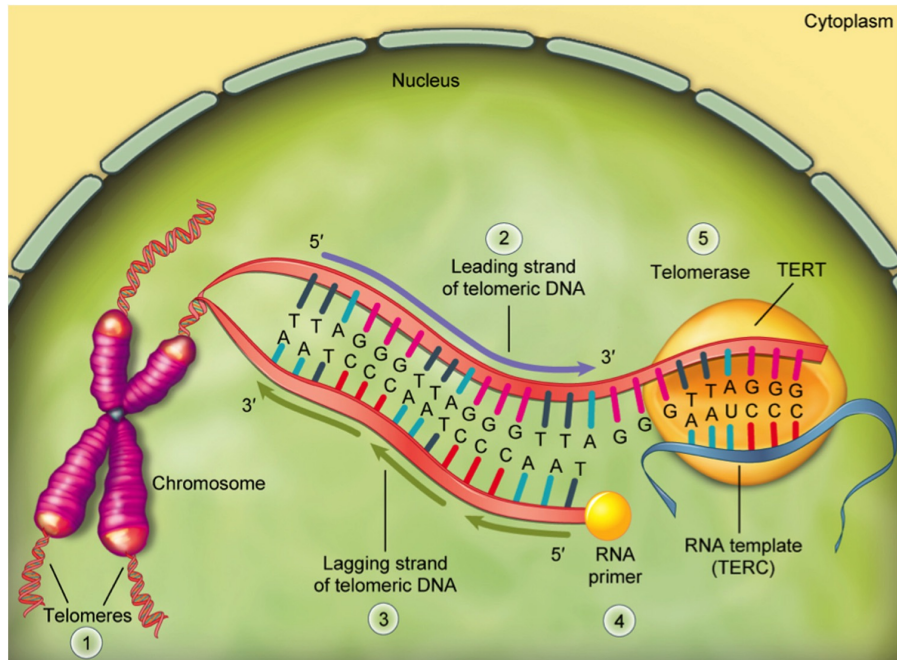
Schizophrenia is an enigmatic disorder that affects 1% of the population and for which no discrete biological etiology has been discovered.<sup>1</sup> The diagnosis is based on positive symptoms (delusions, hallucinations, persecutory ideation), negative symptoms (social withdrawal, affective flattening, impaired motivation), as well as cognitive deficits.

Though early detection is crucial in the treatment of psychotic disorders, the identification of individuals at risk is complicated by a wide array of associated genetic and environmental factors.<sup>2</sup> Despite continued disagreements in the field surrounding the causality and significance of various potential biomarkers for psychosis, studies began identifying prominent neurodevelopmental and neurodegenerative aspects of schizophrenia as early as two decades ago.<sup>3,4</sup> There continues to be support for two opposing models regarding whether psychotic disorders are the result of an initial neurodevelopmental insult or progressively worsen throughout a patient's lifetime.

Certain sources are arguing, however, that the two concepts are not mutually exclusive, and that schizophrenia should be viewed as a progressive neurodevelopmental disorder.<sup>4</sup>

Through an upsurge in longitudinal cohort studies, advanced brain imaging techniques, and genetic analyses, new evidence of such progressive neurodevelopmental traits in schizophrenia patients has been reported in recent years.<sup>5</sup>

In combination with the similarly growing body of evidence in support of accelerated aging in patients with psychotic disorders<sup>6</sup>, these findings of neurodegenerative pathophysiology suggest a plausible association between schizophrenia and heightened



**Figure 1 – Telomeres and Telomerase**

In humans, telomeres are comprised of repeating, noncoding TTAGGG sequences and are about 10,000 nucleotides long. Unless acted upon by telomerase, they lose roughly 50-100 nucleotides per DNA replication cycle. Telomerase is comprised of a telomerase reverse transcriptase (TERT) and a telomerase RNA component (TERC).<sup>9</sup>

Figure adapted from *Lindqvist et al. (2015)*

telomeric shortening. Telomeres can be defined as DNA repeat structures on the ends of chromosomes that regulate cellular replication and protect against loss of genetic information.<sup>7</sup> The inability of DNA polymerase to fully replicate the 3' end of a given strand of DNA causes telomeres to shorten by a substantial number of base pairs with every cell division.<sup>7,8</sup> In most eukaryotic cells, once telomeres attain a critically short length, the body induces cellular senescence or apoptosis. Cell types that continuously replicate throughout the lifespan contain the enzyme telomerase, which replenishes lost DNA base pairs not replicated by DNA polymerase. [Figure 1] Even though peripheral

blood mononuclear cells (PBMCs) are among these cell types, leukocyte telomere length (LTL) consistently shortens by about 32.2-45.5 base pairs per year according to several longitudinal studies.<sup>9</sup> LTL is therefore being considered an emerging marker for cellular aging.<sup>9,10</sup> Despite being a peripheral marker, it is plausible that LTL is correlated with telomere length (TL) in certain brain tissues.<sup>9</sup> However, data on concrete correlations of LTL to brain tissue TL, brain structural volume, or brain tissue telomerase activity are still largely inconclusive.<sup>9,11</sup> Further investigations will need to be conducted in order to determine how accelerated leukocyte telomere degeneration is related to brain tissue. Acknowledging that LTL does not equate to mean brain tissue TL, the remainder of this thesis will not focus on studies of TL in various brain regions and will instead discuss the more readily measured peripheral blood cell TL as an indicator for cellular aging and accompanying pathologies.

## **Possible Mechanisms of Telomere Shortening**

### **a) Inherited Telomerase Deficiencies**

Continued cell division in the absence of telomerase activity is possibly the most intuitive potential cause of pathological leukocyte telomere degeneration in psychiatric illnesses. Inherited telomerase deficiencies have therefore been found to be a major cause of shorter leukocyte telomeres.<sup>9</sup> For instance, an autosomal dominant mutation in hTERC, the human telomerase RNA component, causes markedly decreased LTL and is associated with dyskeratosis congenita.<sup>12</sup> Interestingly, some studies have found an increased incidence of neuropsychiatric conditions in patients with dyskeratosis

congenita.<sup>9,12</sup> Conversely, an increased ratio of telomerase activity to LTL, especially in combination with lowered LTL, is indicative of cellular stress and/or failed compensatory attempts by telomerase to maintain LTL.<sup>9,13</sup> While telomerase activity could be considered its own biomarker and is not the focus of this thesis, it is nonetheless intimately tied to the accelerated attrition of LTL.

### **b) Inflammation**

Acute inflammation is a protective response to injury and a process that delivers leukocytes and antibodies to the site of infection or tissue damage.<sup>9,14</sup> The inhibition of negative regulators forces this response to persist and is therefore characteristic of a chronic inflammatory state. In this state, leukocytes are constantly proliferating, and it is plausible that a rate of leukocyte proliferation greater than the rate of telomerase activity could be responsible for leukocyte telomere shortening. In support of this theory, a remarkable incidence of telomere shortening has been cited in chronic inflammatory disorders, a broad umbrella term encompassing chronic lung diseases, diabetes, autoimmune diseases, renal failure, cardiovascular disease, and chronic infections.<sup>14</sup> Despite this significant coincidence of LTL shortening and chronic inflammation, a causal relationship between LTL and inflammation has not been established. On the one hand, inflammation increases leukocyte proliferation thereby feasibly causing LTL degeneration. Alternatively, accelerated loss of telomeric sequence has been found to signal the production of pro-inflammatory cytokines, thereby in turn causing inflammation. Due to the significant coincidence of both phenomena across distinct

pathologies, inflammation likely both contributes to and persists as a result of telomere degeneration.

### **c) Oxidative Stress**

Oxidative stress is a known trigger for cellular senescence. Specifically, it has been shown to induce DNA damage at the 5' end of 5'-GGG-3' telomere sequences.<sup>15</sup> This suggests that oxidative stress has a causative effect on increasing the rate of telomere shortening. Oxidative stress may in fact play the most intrinsic role in LTL shortening, due to this heightened susceptibility of telomeric DNA to oxidative damage and the fact that the repair of oxidative damage is relatively inefficient in telomeres.<sup>9</sup> It is well established that oxidative stress markers are inversely correlated with LTL in Major Depressive Disorder (MDD),<sup>16</sup> suggesting that a similar association could plausibly be found in schizophrenia.

### **Telomeric Degeneration in Major Psychiatric Illnesses**

An association between TL and psychiatric disorders is widely accepted in scientific literature. A meta-analysis published in 2016 involving 14,827 participants reported a robust effect size showing LTL shortening as a whole across all psychiatric disorders analyzed (depressive disorders, post-traumatic stress disorder, psychotic disorders, anxiety disorders, and bipolar disorder).<sup>10</sup> Various studies interestingly also cite increased incidences of inflammation and oxidative stress in certain psychiatric illnesses.<sup>16</sup> A review by Raza et al (2016), for instance, reports a strong association between oxidative damage to DNA and the development of psychiatric symptoms.<sup>17</sup> Considering that



inflammation and oxidative stress, especially in combination,<sup>9</sup> are underlying physiological mechanisms of telomeric degeneration, this reported association further validates the need for more exhaustive investigations into the relationship between LTL and psychiatric disorders.

Research within some psychiatric populations has begun to show conclusive results. Meta-analyses of MDD studies typically suggest that LTL is decreased in diagnosed patients compared to controls, especially in those displaying chronic or severe symptoms.<sup>9,10</sup> Findings in anxiety disorders are more mixed, but meta-analyses seem to agree that evidence supports significant LTL shortening, especially within more severe anxiety disorders.<sup>9,10</sup> Though not entirely conclusive due to a small number of published studies and prevalence of confounding factors, existing evidence supports the shortening of LTL in PTSD patients.<sup>9,10</sup> Recent meta-analyses report the overall findings on LTL in bipolar disorder to be inconclusive, perhaps due to a particularly significant confounding effect of psychotropic medication in these patients.<sup>9,10</sup> In conclusion, there is suggestive evidence that accelerated telomeric degeneration is implicated in many psychopathologies. The remainder of this discussion will examine the currently published data on LTL in psychosis patients, consider potential limitations and confounds to the concept of LTL as a reliable biomarker in this population, and suggest exciting future directions for this field of research.

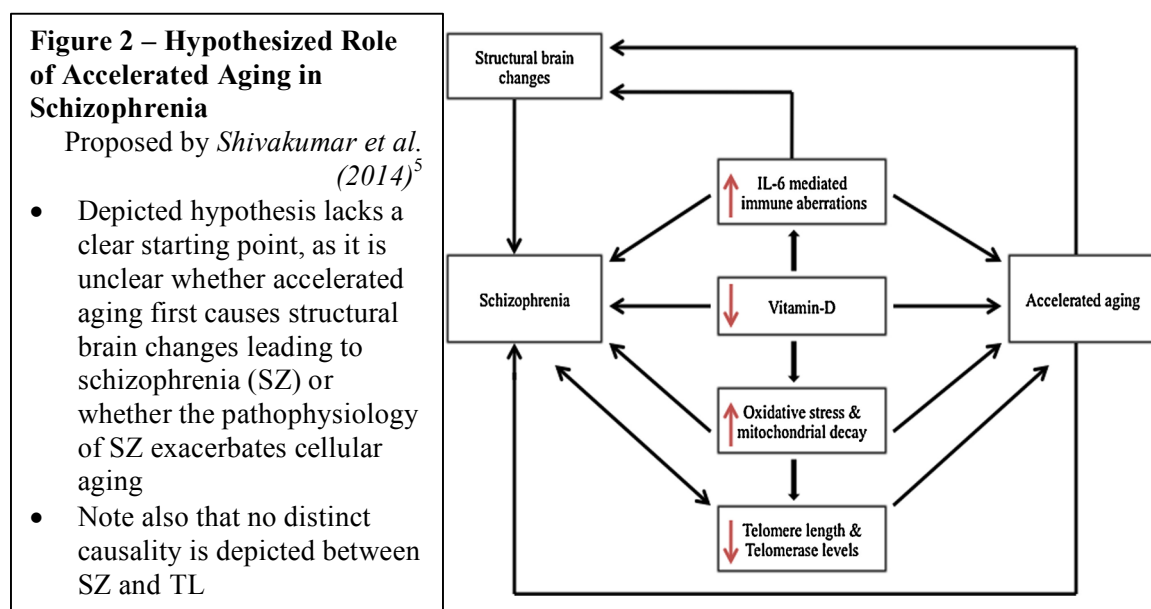
## **SPECIFIC AIMS**

The specific aims of this thesis include:

- 1) To conduct a comprehensive review of the literature in order to better understand the relationship of leukocyte telomere length and psychosis
- 2) To determine of how reliably telomere degeneration in psychosis can be utilized to make predictions on disease chronicity, severity, and recurrence
- 3) To address the need for investigation of leukocyte telomere shortening in prodromal and recent-onset patients, in order to determine whether the phenomenon could act as an early predictive biomarker

## ACCELERATED AGING IN SCHIZOPHRENIA

Accumulating evidence suggests that patients diagnosed with schizophrenia have lower life expectancies and more comorbid medical issues than other psychiatric patients.<sup>6</sup> While unhealthy lifestyle choices, substance abuse, and poor access to care have a significant impact on the mortality rate of this population, more findings are beginning to suggest that these factors do not fully account for the lowered life expectancy.<sup>6,18</sup> The prevalence at which illnesses such as type 2 diabetes, cardiovascular disease, and other metabolic irregularities are observed in schizophrenia patients at abnormally young ages has frequently been attributed to side effects of antipsychotic medication.<sup>19</sup> However, the relationship between schizophrenia and type 2 diabetes mellitus has been known since the 19<sup>th</sup> century, long before the discovery of antipsychotic therapeutics.<sup>18</sup> This has caused some investigators to suggest that early metabolic dysregulation in schizophrenia is independent of medication, implying instead that accelerated pathological aging plays a



role in psychosis.<sup>6,18,20,21</sup> The constellation of issues such as abnormal blood pressure, dyslipidemia, and increased adiposity that predispose comorbidities such as cardiovascular disease and diabetes in schizophrenia patients are collectively referred to as the metabolic syndrome.<sup>20</sup> Metabolic syndrome is a pro-inflammatory state that increases oxidative stress systemically, affecting roughly 32.5% of schizophrenia patients.<sup>22</sup> Shivakumar et al (2014) uses this markedly early incidence of aging-related metabolic dysregulations in addition to novel neuroimaging findings, immunological studies, and LTL analyses to hypothesize a plausible connection between accelerated aging and schizophrenia<sup>5</sup> [Figure 2]. The review prescribes a central role in this hypothesized connection to vitamin D, the validity of which remains to be tested. Of greater interest is the idea that chronic inflammation, oxidative stress, and telomeric degeneration simultaneously impact pathophysiological aspects of schizophrenia and accelerated aging, as this avoids the unresolved question of whether pathological aging and the metabolic syndrome precede or result from psychosis. A growing body of literature is reporting an association between chronic inflammation, oxidative stress, and schizophrenia, thereby supporting the coincidence of accelerated aging and psychosis. For instance, a review article analyzing the role of neuroimmunological defects in schizophrenia found substantial evidence suggesting that an altered expression of immune system genes and the resultant imbalance of anti-inflammatory cytokines contribute to both structural and functional brain abnormalities in schizophrenia patients.<sup>23</sup> Additionally, there have been studies finding positive therapeutic effects of anti-inflammatory agents on cognitive, negative, and even positive psychotic symptoms.<sup>24,25</sup> Okusaga (2014) focuses on the potential role

of oxidative stress on pathological aging in schizophrenia.<sup>26</sup> The study concludes that, due to common confounding factors of this population that feasibly could have an effect on oxidative stress (smoking, diet, antipsychotic medication), the currently available data precludes an unequivocal prescription of symptoms of premature aging to a schizophrenia diagnosis. However, Okusaga (2014) does attribute chronic inflammation to be in part responsible for the increased oxidative stress in schizophrenia, which would explain the prevalence of metabolic changes and premature aging-related pathologies in these patients. Lastly, there have been investigations showing significantly higher numbers of markers for irreversible protein oxidation in schizophrenia patients than healthy controls,<sup>26,27</sup> as well as adjunctive antioxidant therapies reducing the symptoms of schizophrenia.<sup>26,28,29</sup> Both of these findings once again suggest that the relationship between schizophrenia and its metabolic symptoms related to pathological aging is complex and cannot be accounted for solely by the side effects of antipsychotic medications.

Recent investigations provide support for the theorized link between psychosis and pathological aging. Czepielewski et al (2017) evaluates the relationships between age, TL, biomarker CCL11, gray matter volume, and episodic memory performance in 48 schizophrenia patients compared to 64 healthy controls.<sup>30</sup> Previous findings of an increase in CCL11 in patients with chronic but not recent-onset schizophrenia imply that the pro-inflammatory chemokine acts as a biomarker for worsening, degenerative pathological aging.<sup>31</sup> Czepielewski et al (2017) reports that, compared to

demographically similar controls, schizophrenia patients had worse memory performance, increased CCL11, reduced TL, and decreased total gray matter volume.<sup>30</sup> These parameters behaved, with the exception of gray matter volume, independently from participant age, implying that the worsened outcomes summarized above reflect not age itself, but the impact of disease-associated accelerated aging. The study's major shortcomings were its cross-sectional design and small sample size. Future large scale longitudinal investigations are required in order to definitively ascertain the relationship between psychosis and accelerated aging.

A study on cerebral white matter aging in schizophrenia and major depression, Kochunov et al (2013), reveals an interesting discordance between the two psychiatric disorders. As stated in the introduction, the current findings of studies in depressive disorders on LTL shortening suggest that advanced cellular aging is positively linked to depressive symptom severity and chronicity. However, Kochunov et al (2013) reports findings that only show significant accelerated cerebral white matter aging in schizophrenia, not Major Depressive Disorder (MDD).<sup>32</sup> Additionally, white matter tracts that matured later in life showed heightened sensitivity to the effects of schizophrenia and were more susceptible to disorder-related accelerated degeneration. No such trend was observed in MDD. This implies a potential difference in the pathophysiology of the two psychiatric disorders and suggests that the relationship between psychosis and premature aging should be studied independently from the influence of results in other disorders. This trend of differentially accelerated cellular aging among psychiatric disorders is replicated by Koutsouleris et al

(2014). The study analyzes deviation from the trajectory of normal brain maturation, as measured by the difference between chronological and neuroanatomical age, in various psychiatric patient cohorts.<sup>33</sup> The findings report the highest deviation to be in the schizophrenia patient group with smaller, yet still significant deviations seen in MDD and bipolar disorder patients. There is no significant association between abnormal trajectory of brain maturation and illness duration cited in any of the groups studied, contradicting the idea that accelerated aging manifests as a result of progressive neurodegeneration. This could simply be explained by the limitation of the study's cross-sectional designs. The authors do however report a linear increase of deviation from normal trajectory starting from patients experiencing early, attenuated psychotic symptoms all the way to chronic schizophrenia patients. This suggests a possible correlation between severity of pathological aging and severity of psychotic symptoms. None of these findings were attributed to common confounds such as psychotropic medications, alcohol, smoking, or socioeconomic status.

Several studies have used this noteworthy incidence of accelerated aging-related symptoms to reframe schizophrenia as a somatic disorder. As previously alluded to, schizophrenia is associated with a striking increase in mortality.<sup>34</sup> It is generally accepted that increased risk of suicide, poor health habits, and the metabolic side effects of antipsychotics play a significant role in this mortality rate.<sup>18,34</sup> However, Kirkpatrick et al (2008) hypothesizes that the physiological abnormalities associated with schizophrenia themselves contribute to this increased mortality.<sup>18</sup> This would implicate schizophrenia in

serious somatic health risks. Jeste et al (2011) rejects the idea of aging as a uniform process and cites a marked divergence in physical, cognitive, and psychosocial aging, especially in psychosis patients.<sup>35</sup> Despite persistent, mild cognitive impairment starting in the premorbid period, the study cites a normal rate of cognitive aging in schizophrenia patients. Psychosocial functioning notably improves with age in the overall population according to this study. The only pathological increase was observed in physical aging. The authors therefore suggest that the targeted treatment of these biological symptoms could lead to improved long-term prognoses and would eliminate the conception of schizophrenia as a life sentence. Finally, a study by Papanastasiou et al (2011) reclassifies schizophrenia as a whole-body disorder caused by segmental progeria (degenerative aging), citing similar genetic and clinical similarities between schizophrenia and aging-related disorders as observed by the aforementioned studies.<sup>36</sup> The authors argue that the growing body of evidence in support of this reformulation shatters the prevailing mind/body dualism, encourages future investigations into somatic-based therapies, and highlights the impact that definitive biomarkers can have on the more confident diagnosis of this complex disorder.

In conclusion, psychosis and accelerated biological aging appear to be sufficiently linked to warrant research into reliable markers predictive of the two phenomena. As indicated in earlier sections, findings in related fields suggest that LTL and telomeric degeneration have the potential to serve as this type of marker.



## LEUKOCYTE TELOMERE LENGTH IN SCHIZOPHRENIA

### **Shorter LTL in Schizophrenia**

The majority of studies on LTL in schizophrenia report shortened telomeres in patients compared to healthy controls. Kao et al (2008) summarizes two study designs: one independent group analysis of schizophrenia patients, unaffected family members, and unrelated healthy controls, as well as an age-matched analysis of male schizophrenia patients and controls.<sup>37</sup> Both analyses ultimately control for age and sex and report findings of significantly reduced LTL in the patient groups. The examination of family members in the first study aims to eliminate potential confounding genetic factors. Based on these findings, the authors estimate that the rate of telomeric degeneration is more than doubled upon the onset of schizophrenia. This estimation is most significantly limited by the cross-sectional nature of the study. A true determination of telomeric degeneration rate throughout the course of illness can only be attained through future longitudinal studies. Fernandez-Egea et al (2009) supports this trend with findings of decreased leukocyte telomere content and increased pulse pressure in patients with nonaffective psychosis.<sup>38</sup> The authors use this measured decrease in LTL and the increased indices linked to accelerated aging, diabetes, and hypertension, to support a hypothesis of the concrete pathophysiological aspects of schizophrenia directly impacting an increased rate in mortality. Galletly et al (2017) replicates these exact findings of shortened LTL in schizophrenia patients as compared to healthy controls.<sup>39</sup> Due to the

study's recent date of publication, the authors are highly conscious of previous studies' limitations and aim to control for as many potential confounds as possible. Patients and controls are therefore all male, aged-matched, fall into a narrow range of ages, and originate from the same geographic area. This study sets an important precedent for the exclusion of independent factors, however continues to leave room for future (longitudinal) investigations to determine whether the relationship holds over time. Czepielewski et al (2016) also reports shortened LTL in schizophrenia patients compared to controls, while adding a unique, noteworthy finding.<sup>40</sup> It is the first study to show that unaffected siblings did not differ in telomere length from subjects with schizophrenia. This implies the possibility of an underlying, inheritable accelerated telomeric attrition endophenotype, which increases one's risk of developing a psychotic disorder. Although these findings have yet to be replicated, the authors suggest that these results could open a venue for increased investigations into peripheral aging markers in at-risk populations. One should also note that the sample sizes employed in this study are small (36 patients/36 siblings/ 47 controls), and that the authors did not address several common confounding factors.

Of the numerous studies citing significantly shortened LTL in schizophrenia, a handful report additional findings on potential relationships between LTL and disease chronicity, symptom severity, or treatment route. Pawelczyk et al (2015), for instance, compares LTL in chronic and early schizophrenia cohorts in order to assess the relationship between telomere length and disease chronicity/severity.<sup>41</sup> The results elucidate

significantly higher telomere erosion in chronic schizophrenia, symptom severity to be negatively associated with TL, as well as a significant correlation between LTL shortening and the number of psychotic episodes/hospitalizations. A regression analysis proposed that knowledge of the study group (chronic vs. early), age, sex, and number of episodes/hospitalizations allows one to significantly predict TL, with over 50% of variance explained by these factors alone. Important limitations of this study include the authors' inability to control for certain residual confounding covariates (parental age, physical activity, systemic inflammation, obesity, and red meat consumption) as well as the fact that all participants were recruited upon hospitalization for psychotic exacerbation and may therefore not be representative of the general population of individuals with schizophrenia. Yu et al (2008) additionally sheds light on the impact of duration of illness and symptom severity on telomeric degeneration.<sup>42</sup> The study separates participants with chronic schizophrenia into "good responders" and "poor responders" to treatment, based on their Global Assessment of Function score. It reports significantly shorter LTL within the "poor responder" group as compared to both "good responders" and healthy controls. The findings suggest that treatment-resistant patients with chronic schizophrenia have significantly shorter telomeres due to uncontrolled factors such as oxidative stress that also leads to ensuing cellular dysfunction. This relationship is still purely speculative, and the study's results are limited by sample size and the potentially confounding covariates. However, Kota et al (2015) replicates similar findings.<sup>43</sup> The study classified 35 subjects as remitted schizophrenia patients and 36 subjects as unremitted, based off the Clinical Global Impression Severity scale. The

results reveal telomeric degeneration to be significantly higher in unremitted schizophrenia patients than in either controls or their remitted counterparts. Therefore, there have now been replicated reports of worsened LTL shortening in unremitted/poor responder patient cohorts. Future longitudinal studies would help determine whether remission potentially slows down the rate of telomeric degeneration, whether telomeric shortening is indicative of the likelihood of remission, or whether both TL shortening and poor response are driven by a third common factor.

#### *Reduced Telomerase Activity in Schizophrenia*

The group of researchers behind the Kao et al (2008) paper followed up on their initial findings with an analysis of telomerase activity in schizophrenia patients, unaffected family members, and unrelated healthy controls.<sup>44</sup> In this follow-up paper, Porton et al (2008) demonstrate a nominally significant reduction in telomerase activity in schizophrenia patients as compared to unaffected individuals. Significant variation in lymphocyte telomerase levels within the diagnostic groups suggests that this enzymatic activity is subject to physiological fluctuations and does not follow the same typically clear neurodegenerative trends with age as LTL. Nonetheless, these findings imply that a reduction in telomerase activity plays a role in the process of accelerated cellular aging in schizophrenia, though it is not likely to be the main cause of LTL shortening. Rao et al (2015) supports this hypothesis in finding an association between several single-nucleotide polymorphisms (SNPs) within the telomerase reverse transcriptase (TERT)

gene and paranoid schizophrenia.<sup>45</sup> Their findings also report a significantly shorter mean LTL in paranoid schizophrenia cases compared to healthy controls. However, the two results were not significantly associated, implying that the schizophrenia-risk associated SNPs might have no direct effect on LTL. Though there is therefore some support for reduced telomerase activity in schizophrenia, the exact relationship remains inconclusive.

### **Inconclusive Findings**

Several studies have null findings regarding LTL in schizophrenia. Mansour et al (2011) responds to prior reported findings of shortened LTL in schizophrenia patients by testing TL as a potential link between the disorder and consanguinity, a supposed risk factor for certain psychopathologies.<sup>46</sup> The results are largely inconclusive and neither show an overall association between inbreeding and TL nor replicate shorter LTL in the schizophrenia group. Malaspina et al (2014) also did not observe a significant difference in LTL between patient and control groups, despite a higher incidence of smoking in the schizophrenia participants in their sample, which should be indicative of an increased oxidative stress and likelihood of telomeric degeneration.<sup>47</sup> A follow-up study by the same research team, Malaspina et al (2016), analyzes the effect of paternal age on odor sensitivity in schizophrenia patients and healthy controls.<sup>48</sup> The study measures LTL as a potential explanatory factor for the two variables in question, but is once again unable to report a significant difference in LTL between patients and controls. A prospective longitudinal study, Li et al (2015), analyzing the association of PBMC telomere length and mitochondrial DNA copy number with risperidone treatment in first-episode,

antipsychotic-naïve schizophrenia patients is similarly unable to report a significant difference in TL between patients and controls both at baseline and 8 weeks after initial medication administration.<sup>49</sup> While a markedly lower mitochondrial DNA copy number, a related biomarker of cellular aging, is reported in schizophrenia patients compared to controls, the expected association between TL and mitochondrial DNA copy number was only observed in healthy controls. The authors address several factors that could have had a confounding effect on the TL findings, but also postulate that telomeric degeneration could simply be largely influenced by chronic levels of oxidative stress that are not yet seen in this cohort of patients with shorter durations of illness. Wolkowitz et al (2017) analyzes a relatively large sample (134 psychosis patients/123 healthy controls) and reports that gender, not the diagnosis, was the major factor involved in LTL shortening.<sup>50</sup> It is of the note that the study enrolled patients with schizophrenia and schizoaffective disorder diagnoses, in contrast to other studies that either focus exclusively on schizophrenia or exhibit less well-defined inclusion criteria. Despite the potential difference in incidence of depressive symptoms having a plausible influence on LTL, the publication cites no significant between-group differences for schizoaffective and schizophrenia patients. While the results fail to elucidate a significant difference in LTL between patients and controls overall, they do reveal shorter LTL in women with a psychotic disorder compared to female controls. In addition, men are shown to have shorter LTL than women at any given age, and LTL declines more rapidly in men. The authors use these findings to emphasize the importance of analyzing the effect of psychosis on LTL separately for each gender and go as far as to suggest that the

previously discussed inconclusive studies (Mansour et al, Malaspina et al, Li et al)<sup>46,48,49</sup> operated under the likely false assumption that the rate of decline in LTL is constant between the two genders. Lastly, Monroy-Jaramillo et al (2017)<sup>51</sup> analyzes a relatively large sample of schizophrenia patients of Hispanic descent (170 patients/126 controls), but fails to find a significant correlation between LTL and the disease status.

### **Longer LTL in Schizophrenia**

As of this date, only two studies have reported significant findings of longer LTL in schizophrenia patients as compared to healthy controls. Nieratschker et al (2013) sets out to replicate previously reported findings of shortened LTL in schizophrenia patients with a large sample analysis (539 patients/519 controls).<sup>52</sup> However, the results reveal LTL to be significantly longer in the patient group than in the control group, before and after adjusting for incidence of smoking. Separate age-subgroup analyses suggest that these unusual findings are not attributable to mortality bias. Similarly, a significant reported correlation between age and LTL suggests that telomere length measurement and analysis methods were valid. This result is nonetheless unexpected even for the authors, who address possible confounding effects of advanced paternal age and psychotropic medications. Data on lifetime quantities of psychotropic medication or paternal age were not available, making it impossible to rule out these confounds. There is therefore a significant amount of uncertainty surrounding this well-powered analysis. This unexpected result of elongated LTL has been replicated in one additional, fairly recent study, Cui et al (2017).<sup>53</sup> In this case, both early and chronic psychosis patients cohorts

exhibit significantly longer TL than healthy controls after controlling for a large subset of confounds. It is important to note that the study measures TL in only a subset of leukocytes, T lymphocytes, in order to attain more consistent results. While the authors portray this decision as a strength of the study, as it will hopefully usher in a future standard of more reliable TL measurements, one should also consider that this difference in measurement techniques could render the findings of this particular study slightly less comparable to previous results. This possibility becomes increasingly important upon the realization that the results fail to replicate significant correlations between TL and chlorpromazine-equivalent antipsychotic dosages, duration of illness, or even age. The authors address the lack of correlation between TL and age by citing a relatively young average sample age in addition to reports from prior studies failing to find a correlation. With the inverse relationship between age and TL becoming increasingly established, however, one is left to inquire if the results of Cui et al (2017) are not more plausibly influenced by independent factors.

### **Meta-Analyses**

Two meta-analyses have been published, to date, analyzing the overarching association between schizophrenia and LTL reported in case-control studies. Studies referenced above that strictly focus on telomerase activity or did not employ a healthy control comparison group are therefore not included in these analyses. The earlier analysis, Polho



	Method	Control	Schizophrenia	Conclusion
		N (mean ± SD)	N (mean ± SD)	
Kota et al. (2014)	qPCR	73 (1.05 ± 0.6)	71 (0.79 ± 0.69)	Bad responders have shorter telomere than control; telomere length of good responders equals control's telomere length
Malaspina et al. (2014)	qPCR	20 (1.80 ± 0.65)	53 (1.91 ± 0.74)	No difference in telomere length between schizophrenia and control
Nieratschker et al. (2013)	qPCR	519 (1.30 ± 0.32)	539 (1.36 ± 0.38)	Telomere length in schizophrenia is larger than control
Mansour et al. (2011)	qPCR	60 (0.87 ± 0.26)	60 (0.89 ± 0.3)	No difference in telomere length between schizophrenia and control
Fernandez-Egea et al. (2009)	FISH	41 (100.9% ± 15.20%)	41 (93.10% ± 12.10%)	Telomere content in patients with schizophrenia is shorter than control
Kao et al. (2008)	qPCR	76 (1.51 ± 0.33)	51 (1.14 ± 0.3)	Telomere length in schizophrenia is diminished compared to control
Yu et al. (2008)	Southern Blot	76 (8.91 ± 1.36)	68 (8.14 ± 0.93)	Bad responders have shorter telomere than control; telomere length of good responders equals control's

**Table 1: Meta-Analysis 1 – Leukocyte Telomere Length in Case-Controlled Schizophrenia Studies**

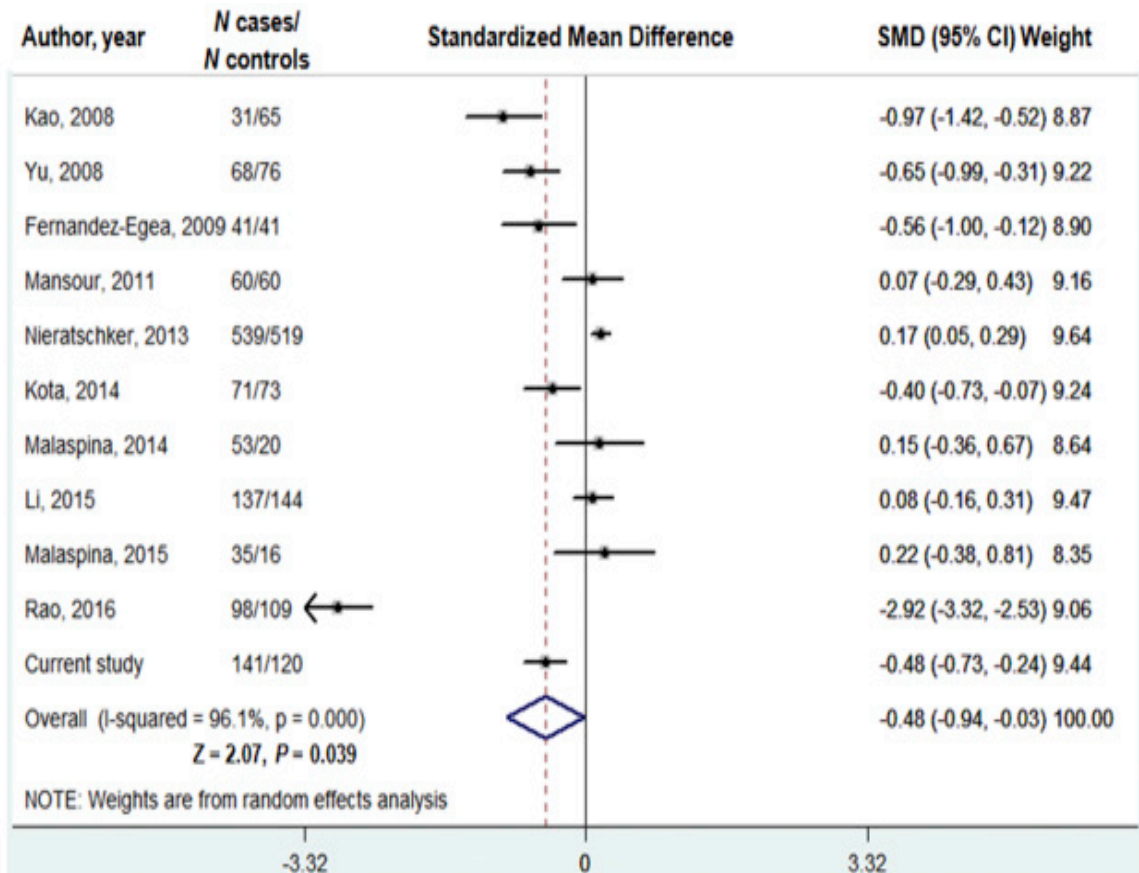
Seven case-control studies were included in this analysis. This table summarizes measurement methods, sample sizes, mean LTL, and study conclusions.<sup>54</sup>

Adapted from *Polho et al. (2015)*

et al (2015), is limited to the seven studies available at the time [Table 1] which utilize diverse methodologies and do not contain perfectly comparable samples.<sup>54</sup> The initial results do not reveal a significant difference in LTL between patient and control groups ( $p=0.074$ ). Crossvalidation shows that Nieratschker et al (2013),<sup>52</sup> the only study at the time reporting longer LTL in patients, is responsible for the majority of heterogeneity of the model. Exclusion of this study results in a significant model in which LTL is shortened in schizophrenia patients compared to controls ( $p = 0.027$ ). Despite a lack of statistically significant findings, the study cites sufficient suggestive evidence in support of a hypothesis of diminished telomere length in schizophrenia. There are serious

limitations to this hypothesis. Firstly, while the exclusion of Nieratschker et al (2013)<sup>52</sup> does produce a significant trend, this particular investigation features the largest sample size among all of the studies analyzed. The analysis also pools medicated and antipsychotic-naïve patients as well as responders and non-responders to treatment into a single analysis cohort, even though these subgroups have displayed alternate associations to LTL in individual analyses. Lastly, this model of pooled studies is unable to account for several potentially confounding variables, such as oxidative state, medical comorbidities, smoking habits, and paternal age. In a letter to the editors of *Schizophrenia Research*, Pao-Yen Lin argues that Polho et al (2015) neglected valuable information in their publication due to an insufficiency in meta-analytic methods employed.<sup>55</sup> Lin's analysis methods applied to the same pool of seven studies yield a marginal decrease in TL in the patient group ( $p = 0.051$ ) and notably attribute the pool's heterogeneity to the fact that poor-responders and antipsychotic-naïve patients displayed significant LTL reduction, whereas other medicated patients did not differ significantly from controls. This implies that disease status (i.e. severity, resistance to pharmacotherapy) rather than a schizophrenia diagnosis in general may be associated to leukocyte telomere shortening. More recently, Rao et al (2016) aimed to reconcile the controversy around telomere length in schizophrenia by first measuring LTL in an independent sample of patients and controls, and then incorporating their results into a comprehensive meta-analysis.<sup>56</sup> The authors' own sample displays a significant overall decrease in LTL in individuals with schizophrenia compared to healthy controls. Subgroup analyses reveal that paranoid schizophrenia is associated with LTL, whereas no significant difference is observed

between nonparanoid schizophrenia and controls. In their meta-analysis, 11 studies encompassing 1243 patients and 1274 healthy controls were pooled into a final analysis model [Figure 3].

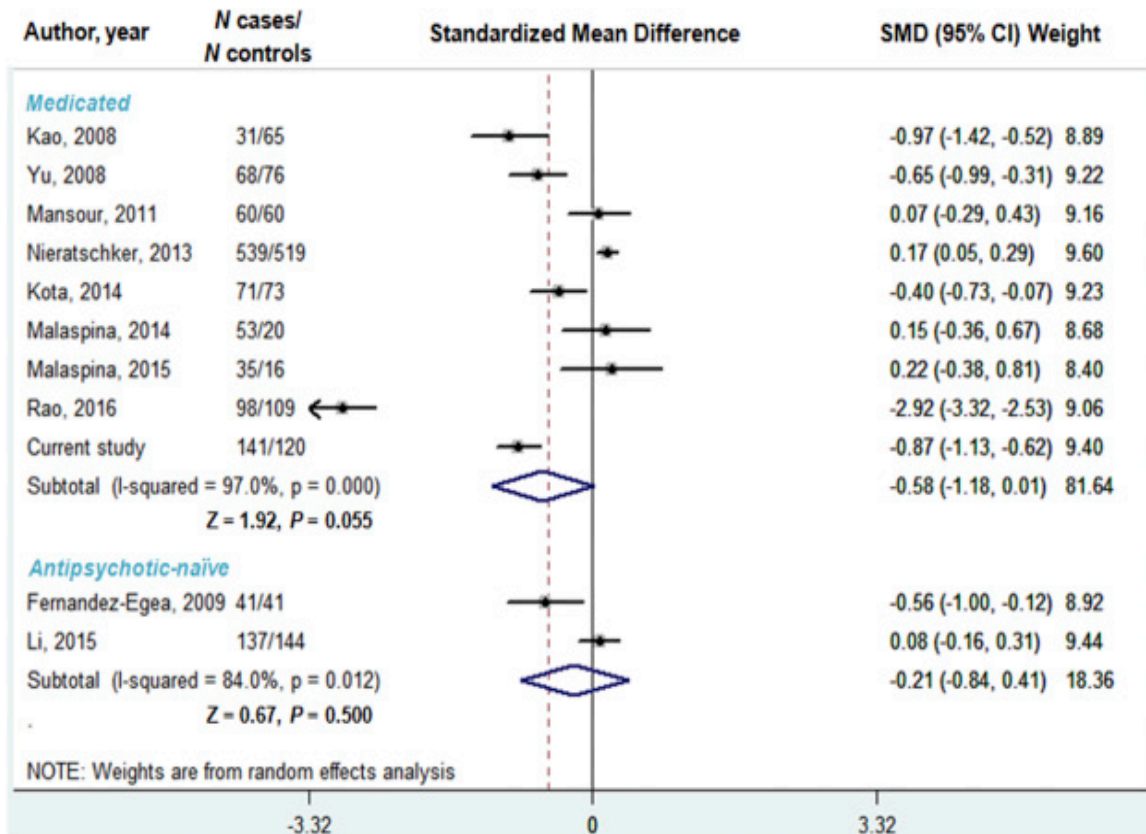


**Figure 3 – Meta-Analysis Forest Plot: LTL in Patients vs. Controls**

A list of studies included in the meta-analysis, Rao et al (2016). Standard Mean Difference (SMD) scores of LTL measurements are displayed. The dashed red line signifies the SMD of the of the overall analysis pool. A significant overall decrease in LTL is observed in schizophrenia patients.

Figure adapted from Rao et al. (2016) <sup>56</sup>

Despite heterogeneity within the pooled sample, a significant decrease in LTL is reported overall in schizophrenia patients compared to controls ( $p = 0.039$ ). In an attempt to explain the observed heterogeneity, subgroup analyses were conducted and revealed a marginal decrease ( $p = 0.055$ ) in LTL in medicated patients as compared to anti-psychotic-naïve patients and controls [Figure 4].



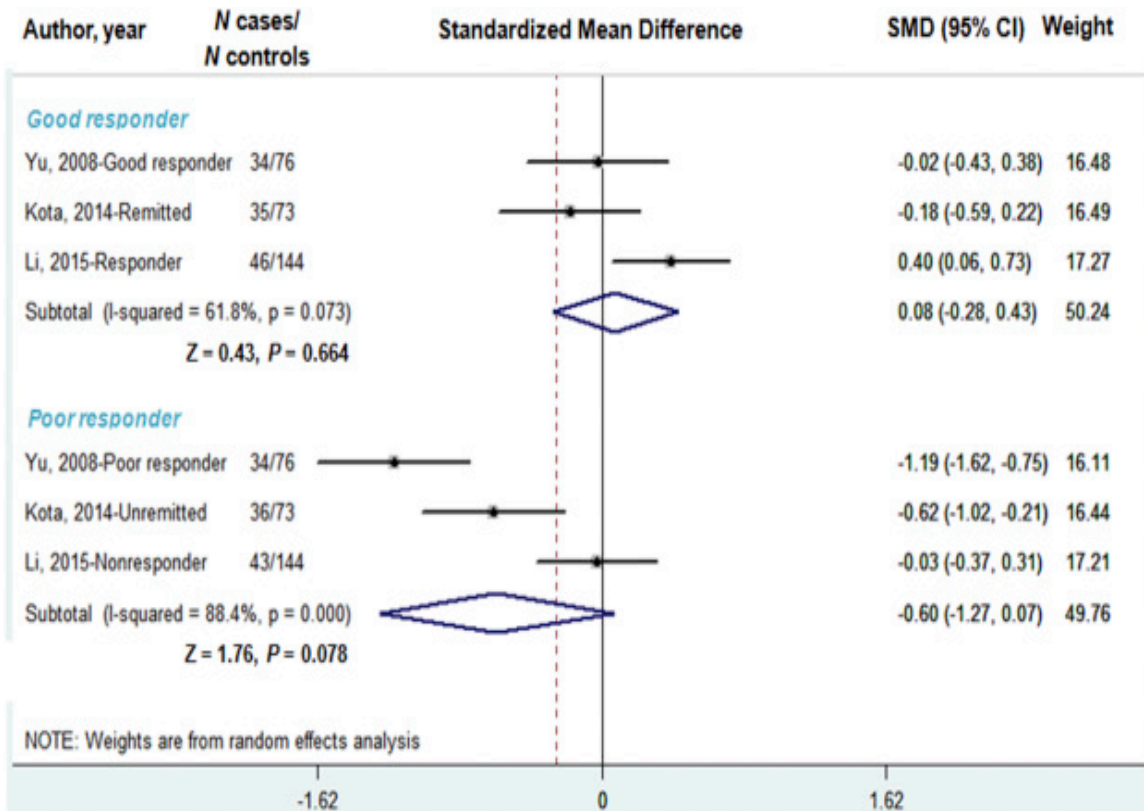
**Figure 4 – Subgroup Analysis Forest Plot:**

**LTL in Medicated/Antipsychotic-Naïve Patients vs. Controls**

The dashed red line signifies the SMD of the overall analysis pool. A marginal decrease in LTL is observed in medicated patients. No significant difference between antipsychotic-naïve individuals and control group.

Figure adapted from Rao et al. (2016)<sup>56</sup>

Similarly, patients with a reported poor response to antipsychotic treatment displayed a marginal decrease ( $p = 0.078$ ) in LTL compared to the remaining subjects within the analysis [Figure 5].



**Figure 5 – Subgroup Analysis Forest Plot:**

**LTL in Good Responder/Poor Responder Patients vs. Controls**

The dashed red line signifies the SMD of the of the overall analysis pool. A marginal decrease in LTL is observed in poor responder patients. No significant difference between good responders and control group.

Figure adapted from *Rao et al. (2016)*<sup>56</sup>

Any study published after 01/01/2016 postdate this analysis. Of the studies outlined above, five were published past this date. Czepielewski et al (2016) and Galletly et al (2017) report shorter LTL in schizophrenia patients compared to controls; Cui et al (2017) reports longer LTL in patients; and Wolkowitz et al (2017) and Monroy-Jaramillo et al (2017) find no difference.<sup>40,39,53,50,51</sup> This broad range of results does not suggest any directionality and therefore highlights the importance of additional future investigations and meta-analyses.

In conclusion, the most comprehensive meta-analysis to date reports a significant incidence of leukocyte telomeric degeneration in patients with schizophrenia, supporting the hypothesis that pathological accelerated aging is significantly associated with psychosis.

## LEUKOCYTE TELOMERE LENGTH IN EARLY PSYCHOSIS

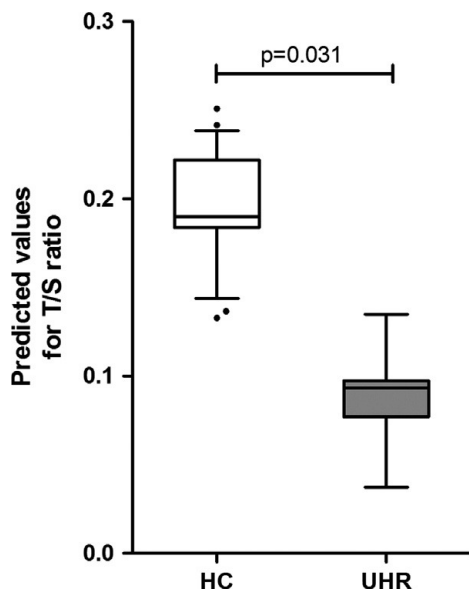
There appears to be an association between LTL shortening and schizophrenia. However, in order to determine whether LTL could potentially serve as a biomarker for the onset or worsening of psychosis, the relationship between LTL and duration of illness has to be studied. Schizophrenia is not a static disorder, but has rather been categorized into progressive clinical stages.<sup>57</sup> These range from attenuated, prodromal psychotic symptoms all the way to chronic, debilitating conditions. It is well established that the improvement observed in patients with chronic schizophrenia is lower than that in patients with a shorter duration of symptoms, suggesting a potential link between disease chronicity and severity.<sup>41</sup> Duration of illness is therefore an important variable in this patient population, and yet it is often overlooked when grouping patients into broad diagnostic groups. Only one study reviewed above, Pawelczyk et al (2015), currently investigates a potential difference in LTL between early and chronic schizophrenia patients.<sup>41</sup> Though its findings strongly suggest an association between duration of recurrent or heightened psychotic symptoms and leukocyte telomere degeneration, these results have yet to be replicated. Only three publications currently describe case-control studies in which LTL is analyzed in first-episode/recent-onset schizophrenia patients. Fernandez-Egea et al (2009) reports significant LTL shortening in this specific subpopulation, whereas Cui et al (2017) reports a significant increase in LTL, and Li et al (2015) finds no conclusive association whatsoever.<sup>38,53,49</sup> There is therefore an unequivocal need for further investigation into whether LTL is linked to some underlying

neurodegenerative pathophysiology of schizophrenia or is significantly shortened even within the early stages of the disorder.

An important aspect of early psychosis research is the ultra-high risk (UHR) concept, based on the observation that schizophrenia is usually characterized by a prodromal period that precedes the onset of full-blown psychotic symptoms.<sup>58</sup> Subthreshold positive symptoms, a decline in functioning, and a family history of psychotic disorders are the most common criteria of the UHR label. Identification of the prodrome and early intervention are thought to be the key to preventing or at least improving the prognosis of a schizophrenia diagnosis. The early identification of psychosis is complicated by the fact that not every individual meeting UHR criteria will transition to develop a psychotic disorder and that the attenuated psychosis-like experiences exhibited by this population are often merely clinical noise, unrelated to the risk of developing schizophrenia. The identification of a definitive biomarker such as LTL within UHR individuals would therefore greatly advance the detection and treatment of psychosis. As alluded to earlier, Koutsouleris et al (2014) notes a significant deviation from the trajectory of normal brain maturation in schizophrenia patients.<sup>33</sup> Though the deviation was the most pronounced in schizophrenia, the authors replicated these findings in MDD, borderline personality disorder, and UHR individuals. Additionally, this deviation showed a linear increase from individuals having recently met UHR criteria to recurrently ill, chronic schizophrenia patients. Though unique and unreplicated, this study therefore implies that pathological accelerated aging can feasibly be detected in individuals at-risk for psychosis and



progressively worsens as symptoms progress. This emphasizes the need for research in telomeric degeneration within this population. However, only one study to date has analyzed TL attrition in UHR subjects.<sup>59</sup> Maurya et al (2017) provides significant evidence that shorter LTL could be associated with UHR status compared to healthy controls. However, the study's sample is relatively small (22 UHR subjects, 88 healthy controls), and no other measures of pathological aging (oxidative stress, immune-inflammatory agents) were collected in support of these findings.



**Figure 6 – Decreased LTL in UHR Patients compared to Healthy Controls**

Data shows the predicted values for T/S (telomere/single copy gene) ratio after controlling for age, sex, ethnicity and years of education.

Figure adapted from *Maurya et al. (2017)*<sup>59</sup>

In conclusion, while there is emerging conclusive evidence of LTL shortening in the early stages of psychosis, future investigations are needed to elucidate the relationship between telomeric degeneration and the progression of schizophrenia. In order to truly assess the potential of LTL as a predictive biomarker for psychosis, longitudinal studies following individuals from the prodrome into subsequent stages of full-scale schizophrenia are needed.

## CONFOUNDING FACTORS

With the growingly accepted association between schizophrenia and pathological aging, additional studies are driven to investigate the potential link between LTL attrition and psychosis. The currently most comprehensive meta-analytical data is in support of this link, and yet results in this field of study have been relatively incongruous. A growing body of studies is failing to replicate findings of a significant correlation, and two publications are now in support of longer LTL in schizophrenia patients compared to healthy controls. While this apparent disagreement has encouraged future clarifying investigations, a number of potentially confounding covariates need to be eliminated in order to elucidate the true relationship between telomere length and schizophrenia.

### **1. Age**

The negative correlation between LTL and age is well established.<sup>9</sup> Despite this inherent difficulty in comparing telomere length in two non-age matched groups, not all investigations are able to perfectly control for age differences between their patients in controls. Rao et al (2016), for instance, in conducting a meta-analysis that pools together vastly heterogeneous patient and control samples, is unable to control for the resulting discordance in mean age between the two pooled groups.<sup>56</sup> Future case control studies investigating LTL as a potential marker for pathological aging in schizophrenia should ensure to control for age, in order to eliminate any potential confounding effect of normal age-associated telomeric attrition.

## **2. Study Design**

Age can continue to be an issue even in a perfectly age-matched study, due to the fact that in controlling for age, one is typically forced to operate under the assumption that all trajectories of LTL with age parallel each other.<sup>50</sup> Should this assumption be false and LTL trajectories were actually to vary significantly with age in healthy individuals, there would be a considerable, inherent flaw in cross-sectional study designs. It is difficult to identify pathological LTL shortening when no standard of normal age-related LTL shortening exists. This highlights the importance of future longitudinal studies within this field. With large enough sample sizes, cross-sectional studies are able to reveal significant standardized mean differences. In order to determine whether at one point LTL predicts subsequent development or worsening of disease, longitudinal investigations are needed. All studies discussed above utilized a cross-sectional design. Many therefore cite this as a major limitation to their findings, as they are unable to account for any subject-level covariates or to postulate anything beyond a significant correlation between schizophrenia and LTL degeneration.

Other study design-related, potentially confounding covariates include DNA extraction and telomere length analysis methods. While these factors may theoretically be the most feasibly controlled, they can produce a significant amount of variability from study to study. For instance, longer telomeres have been observed in DNA that is extracted automatically compared to manually extracted samples.<sup>52</sup> Analysis methods surrounding LTL data have also been suggested to have a substantial impact on a study's end result.<sup>55</sup>

While often negligible, these potentially confounding factors should especially be considered when performing cross-study analyses.

### **3. Sex**

Aside from age, sex is the most widely acknowledged potential confound in LTL analyses. Studies have shown greater telomere lengths in women compared to age-matched men, suggesting that for a given chronological age, biological aging of men is more advanced than that women.<sup>9,60</sup> Some studies have expanded on this observation in order to investigate whether these sex-related differences in TL are present at birth or develop over the course of the lifespan. Typical findings report no evidence for the effect of sex on telomere length at birth, rather suggesting that the longer telomeres in women than men arise from a slower rate of telomeric attrition in women.<sup>61</sup> The outlined delay in telomere shortening interestingly mirrors a later average age of disease onset in female schizophrenia patients.<sup>62</sup> This apparent sex-dependent parallel could be considered to support a hypothesized association between psychosis and telomeric degeneration. As described above, the case control study, Wolkowitz et al (2017), was unable to find a general association between LTL and schizophrenia, attributing LTL shortening to differences in gender instead.<sup>50</sup> Interestingly, the study does find significantly shorter LTL in women with schizophrenia compared to female controls. This highlights the potential confounding effect of sex within this population and emphasizes the need for future studies to control for sex-related differences.

#### **4. Other Subject-Level Variables**

In addition to age and sex, there are several other subject-level variables that could play a potentially confounding role in the assessment of LTL in schizophrenia patients. Healthy life style factors, such as diet and exercise, have been implicated.<sup>63</sup> High body mass index, circulating glucose levels, and abdominal fat are associated with shortened telomeres, whereas intake of antioxidants, vitamins, and less processed meat are linked to longer telomeres.<sup>14,64</sup> Numerous studies have found associations between moderate to severe physical exercise and longer LTL.<sup>7</sup> Chronic poor sleep quality has also been found to be predictive of shortened LTL in certain subpopulations.<sup>7,14</sup> Small but significant associations between certain aspects of socioeconomic status, particularly educational attainment, and LTL have also been reported.<sup>7</sup> The significance of these lifestyle factors on LTL is still largely unknown. The high prevalence of these factors in schizophrenia patients, however, suggests that they should receive consideration nonetheless.

#### **5. Substance Use and Tobacco**

In addition to an increased prevalence of unhealthy behavior, individuals with schizophrenia are at increased risk for developing substance abuse disorders.<sup>65</sup> This proposes additional potential confounding effects on telomere length in this patient population. For instance, alcohol abuse has been found to lead to earlier onset of aging-related diseases, and one study reports TL to be nearly halved in alcohol abusers compared to controls.<sup>66</sup> There seems to be a strong negative correlation between TL and

the number of drink units consumed per day. Similarly, studies report significantly shorter LTL in drug abusers than healthy controls, suggesting an association between LTL attrition and drug addiction.<sup>67</sup> Given the known oxidative damage caused by smoking, it is often assumed that tobacco consumption should also be associated with LTL degeneration.<sup>14</sup> Published results are however largely contradictory, and a recent, large-scale (n = 4,576) 10-year-follow-up study reports no significant correlation between LTL and tobacco consumption, body weight, physical activity, or alcohol consumption.<sup>68</sup> This development puts into questions the associations between LTL and lifestyle factors reported by several cross-sectional studies. However, until a clear association is either established or disproven, future investigations should continue to control for these potentially confounding covariates.

## **6. Genetics & Paternal Age**

LTL at birth has been found to be a major determinant throughout the lifespan.<sup>69</sup> Telomere length is therefore in part genetically programmed, and according to a major meta-analysis, TL heritability is estimated to be approximately 70%.<sup>9,70</sup> The confounding effect of inherited differences between individuals is likely the hardest to control for in any study. However, as patient genotyping becomes less costly and more accessible in future years, investigators should make an effort to assess the potential impact of inherited polymorphisms on LTL.

Another inheritable determinant of LTL has been shown to be advanced paternal age at the time of conception.<sup>69,71</sup> Various studies have illustrated that LTL is longer on average in offspring of older fathers.<sup>69</sup> The root causes of this effect are still unknown.

Interestingly, it has been observed that TL is longer in the sperm of older as opposed to younger men. This observation is contradictory to the normal age-dependent telomere shortening in proliferative somatic cells and may contribute to the advanced paternal age effect on offspring LTL. Given the widespread awareness of increased risk of genetic abnormalities and de novo mutations caused by advanced parental age, the idea that advanced paternal age may actually lengthen offspring LTL, thereby providing a plausible protective effect against aging-related disorders, has largely been considered to be enigmatic.<sup>71</sup> Due to the possibility of advanced paternal age attenuating measurements of telomeric degeneration in schizophrenia patients, this phenomenon plays an important potential confounding effect on the studies analyzed in this discussion. The authors of Nieratschker et al (2013) acknowledge this in discussing the plausibility of their findings of increased LTL in schizophrenia patients to be attributed to advanced paternal age, not the disorder itself.<sup>52</sup> Unfortunately, data on paternal age was unavailable to them and they could not test this claim.

Interestingly, advanced paternal age is not just associated with longer LTL in offspring, it has also been implicated in raising the risk of schizophrenia.<sup>72,73</sup> This finding is typically explained by the observation that advanced paternal age is strongly associated with an increase in de novo point mutations.<sup>72,74</sup> These point mutations may, in part, contribute to

the etiology of schizophrenia. This increased risk of schizophrenia has been more strongly reported in male than female subjects. Similarly, Malaspina et al (2014) cites longer LTL in its male schizophrenia patients with older fathers, as opposed to shortened LTL in female counterparts.<sup>47</sup> This has given rise to the hypothesis that advanced paternal age induces a unique phenotype of schizophrenia that coincidentally is associated with longer LTL. This theoretical unique phenotype is apparently more common in men. In a letter to the editors of *Schizophrenia Research*, the research team behind Malaspina et al (2014) responds to the unexpected findings of Nieratschker et al (2013) by analyzing their own outliers in order to identify demographic, cognitive, and symptom profiles associated with elongated leukocyte telomere length (eLTL) in schizophrenia patients.<sup>75</sup> This small pilot cohort of outliers reveals the same gender-specific trends on LTL observed by the effect of advanced paternal age, implying that the LTL observed in this sample is a unique phenotype associated with specific risk factors of psychosis and not to be generally associated with a schizophrenia diagnosis. Reports of either general or gender-specific LTL elongating effects of advanced paternal aging therefore reveal another important potential confounding effect, one that has typically not been controlled for in past studies.

## **7. Comorbid Medical Conditions**

As alluded to earlier, roughly a third of schizophrenia patients are afflicted with metabolic syndrome.<sup>22</sup> Rates of metabolic syndrome vary broadly among the general population due to genetic and geographical differences. However, schizophrenia patients



are considered to be at high risk compared to the general population, even after controlling for these variables. Notably, the syndrome remains prevalent in over 20% of non-medicated patients, illustrating that these systemic pathologies are not merely the

#### Five major features of the Metabolic Syndrome

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##### Obesity

- Excess total body fat
- Central fat distribution/Upper body obesity
- Increased visceral fat

##### Insulin resistance/Hyperinsulinaemia

##### Dyslipidaemia

- Hypertriglyceridaemia
- Decreased HDL cholesterol
- Increased LDL cholesterol

##### Impaired Glucose Tolerance/Type 2 Diabetes

##### Hypertension

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<b>Table 2: Major Features of Metabolic Syndrome</b>
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Adapted from <i>Mitchell et al. (2013)</i> <sup>22</sup>
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side effect of antipsychotic therapeutics. Rather these symptoms reflect serious comorbidities that decrease an individual's life expectancy and have even been found to negatively impact clinical wellbeing.<sup>24,26</sup> Some of the common disorders grouped under this syndrome, such as type 2 diabetes mellitus and cardiovascular disease, can be classified as chronic inflammatory disorders and therefore enact a potentially confounding effect on telomeric attrition in these patients.<sup>14</sup> The idea that comorbid medical illnesses may somehow be linked to telomeric degeneration and pathological aging is supported by the observation of greater incidences of metabolic syndrome in chronic schizophrenia in comparison to first-episode schizophrenia. Additionally, one should take into account a potential mortality bias, as subjects with the most severe medical conditions (and most severe cellular aging) are likely to die at a younger age and therefore become excluded from analyses, skewing the results. Despite these varied,

related potential confounding factors, medical comorbidities have not consistently been controlled for in past studies, especially within control groups.

## **8. Comorbid Psychiatric Conditions**

The significant prevalence of accelerated LTL degeneration in nearly every major psychiatric disorder has been discussed above. Perhaps most important in its potentially confounding role on LTL studies in schizophrenia is depression.<sup>9</sup> LTL shortening has been found to be significantly associated with MDD in case-control trials, and there have even been findings of significant links between LTL attrition and depressive symptom severity or chronicity.<sup>9,10</sup> The coincidence of psychotic and depressive symptoms is incredibly high.<sup>76</sup> The idea of parsing out any potential effect on LTL exerted by symptoms of depression within patients with psychotic disorders therefore seems nearly impossible. With several publications citing a unique model of pathological aging in schizophrenia, investigators can be reassured that the observed associations are not entirely influenced by comorbid mood diagnoses or depressive symptoms.<sup>32,33</sup> Ratings on the severity of depressive symptoms should however be collected in future studies in an attempt to control for this potentially confounding effect.

## **9. Chronic Stress & History of Trauma**

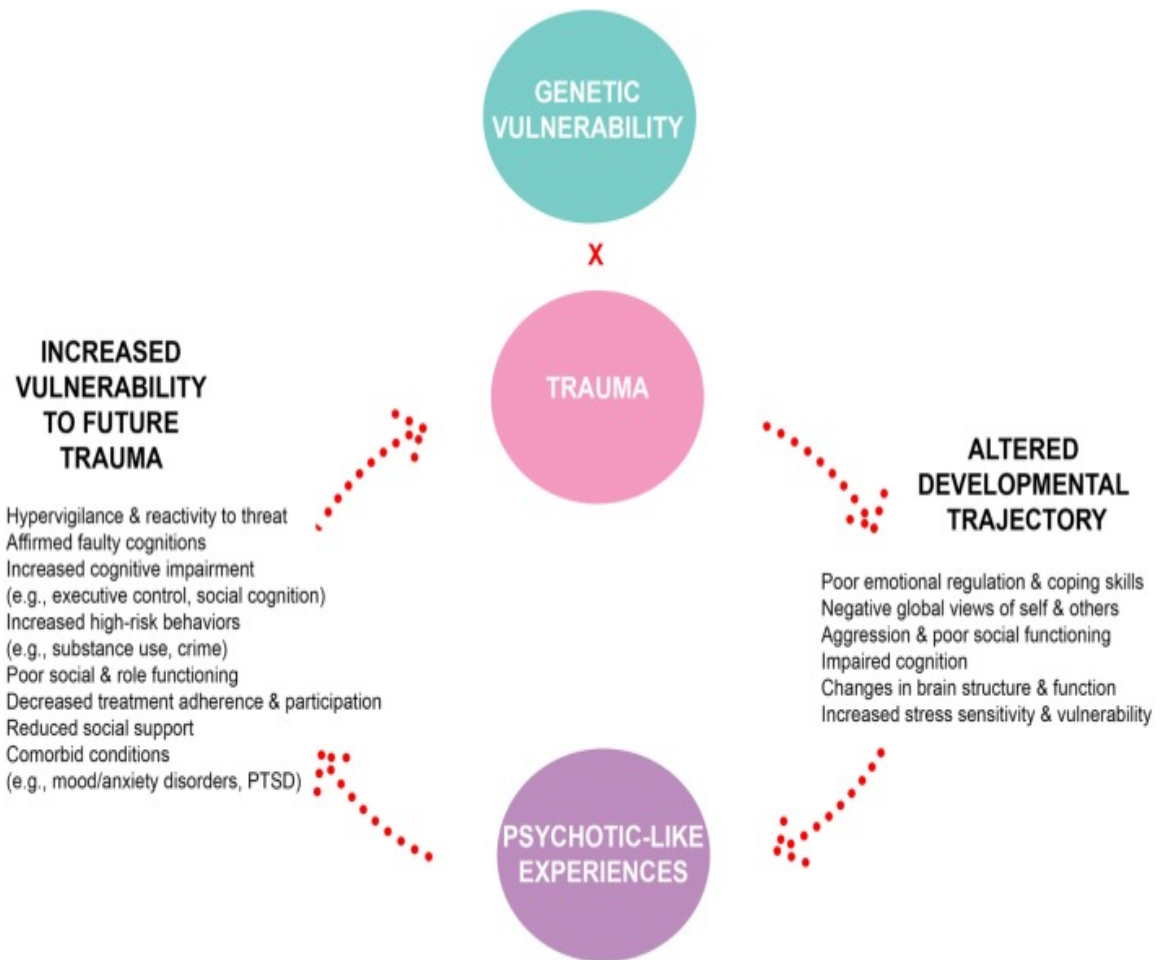
In an attempt to explore alternative mechanisms of telomeric attrition, Lindqvist et al (2015) summarizes several studies on the effect of stress hormones (cortisol and catecholamines) on LTL shortening. While there is no report of a clear link between LTL

and resting cortisol levels, there are somewhat consistent findings of an inverse relationship between LTL and cortisol release in response to psychological stressors.<sup>9</sup> It is therefore easy to see why psychological stress and trauma could have a confounding effect on any observed increase in telomere degeneration within psychiatric patient populations. This effect would be especially pronounced in schizophrenia, due a high incidence of stress and trauma in these patients. Many large-scale population-based studies provide persuasive evidence of a dose-response association between childhood trauma and psychosis that is indicative of a causal relationship.<sup>77</sup> Similarly, 80% of UHR youth endorse a lifetime history of childhood trauma or victimization, features that have been shown to be highly predictive of psychosis onset.<sup>78</sup> It appears that these early incidences of psychological trauma set individuals up for vulnerability to stress-related psychiatric conditions and telomeric degeneration.<sup>63</sup>

The effect of psychological stressors on LTL has been outlined in numerous publications. Epel et al (2004) reports that women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared to low stress women.<sup>79</sup> Price et al (2013) supports this proposed relationship with findings of an association between shorter LTL and sustained adulthood psychosocial stress of various types.<sup>80</sup> The review also suggests an emerging trend of a dose-dependent relationship between early-life stress or adverse life events and pathological telomere degeneration observed in adulthood. This trend has been replicated in MDD and anxiety disorder patient populations, suggesting a plausible effect in

schizophrenia as well.<sup>81,82</sup> Findings by Deng et al (2016) of decreased telomerase activity as a result of chronic stress are in agreement with the previous trends discussed.<sup>83</sup>

Some studies are attributing a greater impact of early-childhood trauma on telomere attrition than just heightened susceptibility to stress-related pathologies. Tyrka et al (2010), for instance, reports that participants with a history of maltreatment had significantly shorter LTL than those who did not.<sup>84</sup> Subscale analyses show both physical and emotional neglect to be linked to TL. The findings of Kiecolt-Glaser et al (2011) show multiple childhood adversities to be related to both heightened inflammatory cytokines and telomeric shortening.<sup>85</sup> This implies a direct link between childhood adversity and pathological aging. In conclusion, the elevated prevalence of chronic stress and childhood trauma in this patient population, in addition to the strong causative implications of stress and trauma on telomeric degeneration amount to yet another important confounding covariate [Figure 7]. Ratings of childhood adversity and history of stressful life events should be collected in future studies in order to control for this effect.



**Figure 7 – The Cycle of Trauma and Psychotic-Like Experiences**

A large body of evidence supports a causal relationship between trauma and psychosis. This figure expands on this by elucidating how a trauma-induced altered developmental trajectory can lead to psychotic-like experiences.

Trauma also plays an important, potentially causative role in heightened telomeric degeneration. It remains to be determined if advanced LTL attrition and psychosis are independent comorbidities or if telomeric aging is a part of the depicted “altered developmental trajectory.”

Figure adapted from *Mayo et al. (2017)*<sup>78</sup>

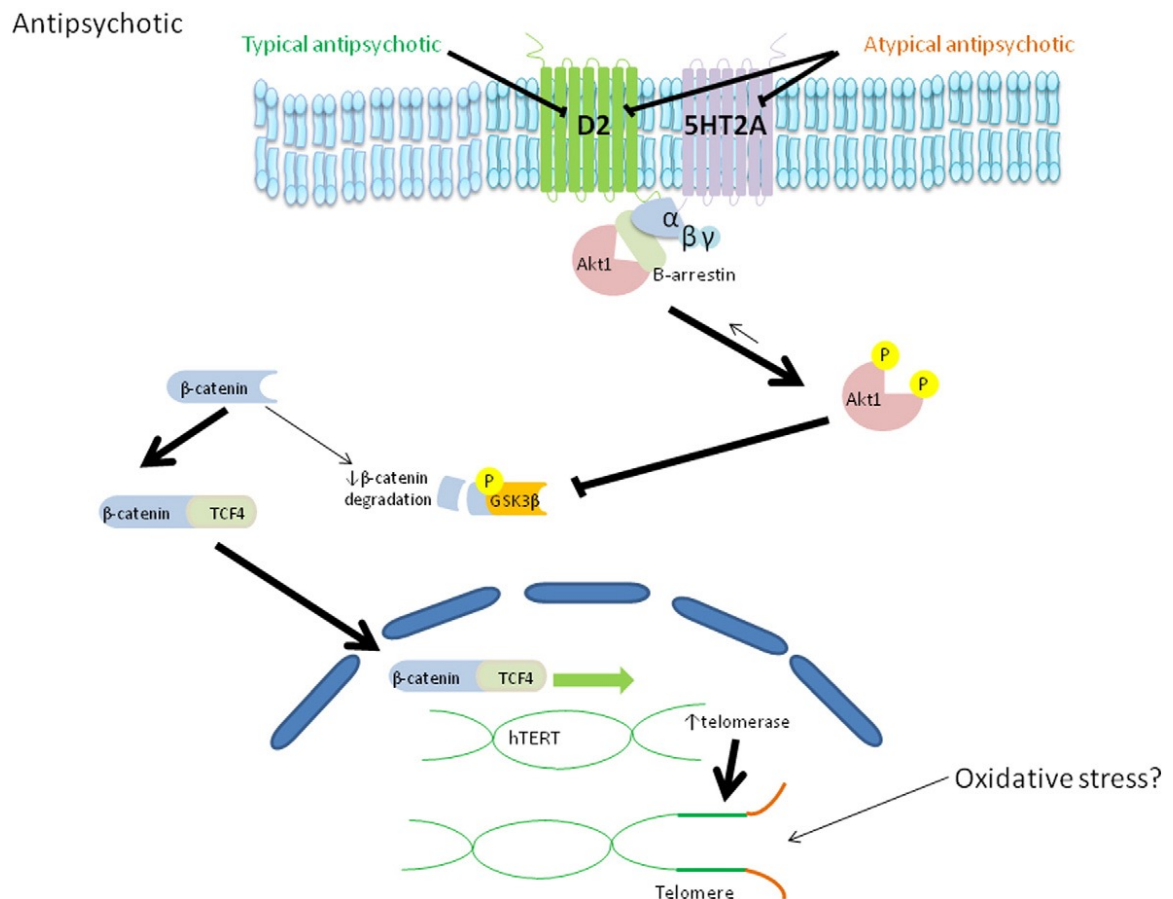
## **10. Psychotropic Medication**

The most common association between antipsychotic medication and symptoms of accelerated aging in schizophrenia is the knowledge that many therapeutics cause serious metabolic side effects.<sup>19</sup> This discussion has presented multiple lines of evidence in support of metabolic syndrome being linked to pathological aging and telomeric degeneration, thus not solely being the result of medication side effects. However, the fact that antipsychotic medication does produce some of these seemingly aging-related metabolic symptoms implies that medication could have a confounding effect on measures of accelerated aging, including LTL, in schizophrenia patients. For instance, one study that failed to find a conclusive relationship between LTL and schizophrenia, Monroy-Jaramillo et al (2017), did however reveal significant telomere erosion in a group of subjects taking the atypical antipsychotic olanzapine, known for its high risk of causing metabolic issues.<sup>51</sup> These findings suggest certain antipsychotic medication may have a modulating effect on LTL in schizophrenia patients. Since the patients taking olanzapine were not any more overweight and did not yet display advanced metabolic symptoms, it is unclear whether the observed decrease in TL is a result of metabolic disturbances caused by the medication or whether it is simply an independent covariate. Medication-induced telomere shortening is therefore plausible, but needs further investigation.

A more heavily studied inquiry is whether psychotropic medication has a protective effect against DNA damage and could therefore be attenuating measurements of LTL

attrition. One review reports that most currently used antidepressants are able to prevent or reverse neurotoxin-induced DNA damage, which suggests that this effect plays an important role in the relief of depressive symptoms.<sup>17</sup> Savolainen et al (2012) expands on this by testing the effect of antidepressants and psychotropic medication on LTL in a large cohort of hospitalized patients.<sup>86</sup> Patients hospitalized for psychiatric reasons who were taking either class of medications displayed significantly longer LTL than patients without a history of mental disorders. Psychiatric patients not taking antidepressant or psychotropic medications did not differ significantly in telomere length with the control group. Based on these results alone, TL seems to be exclusively associated with medication status, not any particular diagnosis. Nieratschker et al (2013) references this study in attempting to explain its unexpected findings of elongated LTL in schizophrenia patients, entertaining the idea that LTL is more associated with medications than pathology in this patient population as well.<sup>52</sup> Martinsson et al (2013) reports similar findings in bipolar disorder, with long-term lithium treatment being strongly associated with longer LTL.<sup>87</sup> These results have important implications in the study of LTL in schizophrenia, as adjunctive treatment with lithium is not uncommon this patient population.<sup>88</sup> Interestingly, longer telomeres were also linked to the therapeutic efficacy of the drug. The better the response to lithium, the longer LTL was exhibited by individual patients. The authors hypothesize that the induction of telomerase is involved in lithium responsiveness, a concept that is replicated and expanded upon by Bersani et al (2015). This review raises the possibility that telomerase and other targets modulated by psychotropic medication mutually interact with and influence each other in order to bring

about the therapeutic effect in the treatment of all psychiatric disorders<sup>89</sup> [Figure 7]. In ascribing such as ubiquitous role to telomerase, the authors emphasize the importance of the study of telomere biology in psychiatry.



**Figure 8 – Impact of Antipsychotics on Telomerase Activity**

Interaction of typical and atypical antipsychotics with D2 and D2/5HT2A receptors respectively enhances the inhibition of the AKT1/GSK3B pathway. This is hypothesized to lead to increased telomerase activity and consequent telomere elongation.<sup>54</sup>

Adapted from *Polho et al (2015)*



The potential confounding role of psychotropic medication in modifying LTL in psychosis patients is substantial, but has not always been feasible to control in previous studies. It is unclear how much exposure to medication is required for a significant effect to take place, as Li et al (2015) did not find a measurable effect of risperidone treatment after 8 weeks.<sup>49</sup> Longer periods of time may be required in order for an measurable effect to take place. Future studies should control for medication nonetheless.

Not a single study discussed above was able to control for all of these vast potentially confounding covariates. Given the overall contradictory nature of the currently available data, one can plausibly assume that outside confounding factors were at play. Future studies should employ a longitudinal study design and monitor as many of these factors as possible in order to arrive at a more conclusive relationship between LTL and psychosis.

## **FUTURE DIRECTIONS**

The current state of the literature strongly suggests a significant relationship between schizophrenia and pathological accelerated aging. Cumulative evidence for increased incidence of inflammatory states, oxidative stress, and telomeric degeneration in psychosis patients compared to healthy controls collectively supports this relationship. However, current findings are limited to associations and plausible connections; neither causality nor chronicity has been established for any of these features observed in accordance with psychosis. The first major question that remains to be answered is whether some unexplored aspect of schizophrenia causes an acceleration in cellular aging or whether underlying phenomena, such as inflammation and oxidative stress, predispose individuals to both conditions.<sup>6</sup> The answer may not even be mutually exclusive. Knowledge of the causality of this relationship could potentially revolutionize the field of psychopharmacology. It would either encourage closer monitoring and treating of aging-related metabolic dysregulation in schizophrenia patients or conventionalize the treatment of early psychotic symptoms with adjunctive anti-inflammatory and antioxidant medications. A second important remaining inquiry is whether accelerated telomeric attrition is a feature of disease duration and/or severity or whether telomere shortening antedates the onset of psychosis and could therefore act as a viable predictive biomarker.<sup>9</sup> One study has cited significantly greater LTL degeneration in chronic schizophrenia patients compared to early cases, and another found a linear trend of neuroanatomical degenerative aging starting in prodromal patients and ending in chronically ill

individuals.<sup>41,33</sup> These results do support a relationship between LTL and disease duration/severity, however require further replication.

Despite the lack of a conclusive causal relationship, the large variety of factors linking schizophrenia and accelerated telomeric degeneration implies that their relationship is more than just a biologically unrelated correlation. A more likely explanation for their coincidence is that an early neurodevelopmental insult predisposes an indiscriminate subset of psychosis patients to augmented telomeric attrition. Such insults could include a genetic defect, early exposure to psychological stress and trauma, or a combination of factors. These proposed neurodevelopmental insults would likely not be unique to schizophrenia, as studies in most psychiatric disorders have yielded significant correlations with telomere shortening. However, some investigations indicate that pathological aging in schizophrenia could be differentially accelerated.<sup>32,33</sup> This observation suggests that independent factors that are commonly associated with schizophrenia, such as chronic stress, antipsychotic medication, substance/tobacco use, and metabolic comorbidities could be amplifying the hypothesized predisposed telomeric degeneration. Seeing as these factors vary in individual patients, one can extrapolate a plausible explanation for the significant variation in LTL observed within the published literature. Ultimately, increased telomeric attrition could plausibly produce chronic inflammatory states and oxidative stress within schizophrenia patients, which would in turn contribute to aging-related symptoms and potential structural brain changes. The model outlined above is purely speculative, and future investigation is required in order

to gain a definitive understanding of the relationship between LTL and schizophrenia. Though dysfunctional telomere biology is not unique to psychosis, the possibility that telomeric degeneration affects disease outcome and could be differentially related to schizophrenia warrants investigation.

There simply is not enough published data on recent-onset or UHR patients to make inferences about the potential ability of LTL to serve as a predictive biomarker. Current trends are promising as it appears that LTL degeneration, even if less severe than in chronic schizophrenia, is significantly measurable in early psychosis cases. Early detection and intervention are so crucial in the improvement of prognoses in psychosis cases that future investigations into the feasibility of LTL as a diagnostic biomarker are worthwhile. Longitudinal studies that control for age, sex, family history, substance use, and comorbid medical conditions will be instrumental in elucidating a definitive relationship between LTL and the course of psychotic disorders. Some studies should additionally focus on antipsychotic-naïve subjects, individuals with no significant history of trauma or stressful life events, and patients without depressive symptoms.

With telomeric degeneration becoming implicated in a growing number of disorders and medical fields, another important future direction for research in general is determining how reversible this deterioration is. Several psychological and behavioral intervention studies in non-psychiatric populations have found a positive effect of intensive lifestyle modification, healthier eating habits, and meditative stress reduction on PBMC basal

telomerase activity and LTL.<sup>9,63</sup> Especially physical exercise has been receiving a lot of attention for its putative therapeutic effect on telomere length. In a mouse model of schizophrenia, physical exercise was shown to increase adult neurogenesis and telomerase activity in addition to improving behavioral deficits.<sup>90</sup> This result has been replicated to an extent in human studies, as noted by a review summarizing the alleviation of health deficits, symptoms, and biomarkers in schizophrenia spectrum disorders by physical exercise.<sup>91</sup> Not as much effort has been devoted to finding pharmacological reversal methods of telomere degeneration. Approaches to reactivate telomerase by chemical means in various patient populations have been successful; however, seeing as increased uncontrolled telomerase activity is known to be carcinogenic, these have not been the most popular treatment route.<sup>14</sup> With an increasing number of psychotropic medications displaying the potential of lengthening telomeres, the reversal of telomere attrition in psychiatric populations seems promising. Studies have shown that finite periods of TL lengthening have the potential to slow down or alter LTL degeneration trajectories.<sup>92</sup> With further investigations, the reversal of aberrant telomere shortening could become a feasible treatment route for patients with psychotic disorders and provide promising impacts on individual prognoses.

## LIST OF JOURNAL ABBREVIATIONS

AJP	American Journal of Psychiatry
Am. J. Med. Genet.	American Journal of Medical Genetics
Arch Gen Psychiatry	Archives of General Psychiatry
Can J Psychiatry	The Canadian Journal of Psychiatry
Cancer Prev Res	Cancer Prevention Research
J Psychopharmacol	Journal of Psychopharmacology
Mol Psychiatry	Molecular Psychiatry
Neurotox Res	Neurotoxicity Research
Pediatr Research	Pediatric Research
Pharmacoepidem. Drug Safe.	Pharmacoepidemiology and Drug Safety
Psychiatry Clin Neurosci	Psychiatry and Clinical Neurosciences
Schizophr Bul	Schizophrenia Bulletin

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## CURRICULUM VITAE

