

# Psychiatric Disorders, Morbidity, and Mortality: Tracing Mechanistic Pathways to Accelerated Aging

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## ABSTRACT

A meta-analysis published in this issue of *Psychosomatic Medicine* provides convincing evidence that certain psychiatric populations have shorter telomeres than nonpsychiatric controls, in accord with the strong evidence linking psychiatric disorders with premature mortality. After addressing the clinical significance of shorter telomeres, this editorial describes mechanistic pathways that lead to telomere shortening. Additionally, two other novel methods for measuring biological markers of accelerated aging are briefly discussed: DNA methylation and cellular senescence based on p16<sup>INK4a</sup>. These innovative approaches could be used to confirm and extend our understanding of psychiatric patients' increased health and mortality risks.

**Key words:** psychiatric disorder, telomere, mortality, DNA methylation, p16<sup>INK4a</sup>, inflammatory response.

Psychiatric patients have a greater risk for premature all-cause mortality than the general population. Epidemiological studies show that the life expectancy for all major psychiatric diagnoses is reduced by 7 to 24 years (1). Indeed, psychiatric illness takes a toll as great as or greater than the 8- to 10-year difference exacted by heavy smoking (1).

Highlighting one potential mechanistic pathway to premature mortality, the excellent meta-analysis from Darrow et al (2) provides convincing evidence that certain psychiatric populations have shorter telomeres than nonpsychiatric controls. Other recent meta-analyses have only addressed depression and telomere length, but these authors show that the effects are broader; depressive disorders, anxiety disorders, and posttraumatic stress disorder (PTSD, one of the anxiety disorders), had relatively larger effect sizes than psychotic and bipolar disorders. Psychiatric patients are more likely to have poorer health behaviors including smoking, poor diets, sedentary lifestyles, and greater alcohol/drug use compared to nonpsychiatric populations; but the differences in telomere length persist even after adjusting for these factors (2). Accordingly, Darrow et al suggest that the differences may be mediated by accelerated cellular aging.

In this commentary, we first address the clinical significance of shorter telomeres, and then we explore mechanistic pathways that lead to telomere shortening. We end by

highlighting two other novel biological markers of accelerated aging that could be used to confirm and extend our understanding of psychiatric patients' increased health and mortality risks.

## TELOMERES AND HEALTH

Telomeres have clinical significance for health: a growing literature has linked shorter telomeres with a range of negative outcomes from poor health behaviors to mortality (3). Although telomeres typically shorten over the lifespan, chronological age accounts for less than 10% of the variance in human telomere length (3). Accordingly, telomeres predict mortality and aging-related disease incidence independent of chronological age. For example, in a sample of people ages 60 or older, the mortality rate from infectious disease was more than 8 times higher among those with shorter telomeres than those with longer telomeres, and heart disease deaths occurred more than 3 times as often in the former than the latter (4). Even after adjusting for age and other key risk factors including body mass index, substance use, physical activity, blood pressure, and cholesterol levels, telomere shortening predicted all-cause mortality in a Danish population-wide study (5). Likewise, telomere shortening has been associated with the occurrence of many common age-related morbidities including dysregulated immune function, cancers, diabetes, and multiple aspects of cardiovascular disease (3,6).

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Conversely, reductions in inflammation and/or oxidative stress may affect telomere length. In a randomized controlled trial, 4 months of omega-3 supplementation significantly reduced both inflammation and oxidative stress and simultaneously lengthened leukocyte telomeres (7). Other researchers have also shown that telomeres can grow under certain conditions (8–12).

In addition to explaining the route from psychiatric disorders to mortality, telomere shortening may also exacerbate the vulnerability of psychiatric patients to premature death. For example, although depressive symptoms were associated with increased mortality and a shorter disease-free survival time among bladder cancer patients at diagnosis, patients who had both higher depressive symptoms and short telomeres had a 4-fold increased mortality risk (13).

### MECHANISTIC PATHWAYS TO TELOMERE SHORTENING

Telomeres can be maintained or lengthened by telomerase, an intracellular enzyme that adds telomeric DNA to shortened telomeres (3). Telomere length is also regulated in part by exposure to proinflammatory cytokines and oxidative stress (3,14,15). Inflammation triggers T-cell proliferation, one known cause of telomere shortening (3). Oxidative stress promotes telomere erosion during cellular replication, and thus, leukocyte telomere shortening reflects the joint burden of inflammation and oxidative stress. Inflammation and oxidative stress are both heightened in anxiety and depressive disorders (16,17).

Many psychiatric disorders have shared genetic underpinnings (2). Comparing across the individual diagnoses that were most strongly associated with telomere shortening in the analysis by Darrow et al (1)—the anxiety disorders (including PTSD) and depressive disorders—reveals a common phenomenology: an exaggerated inflammatory reactivity to stressors. The ability to minimize inflammatory responses to stressful encounters influences the burden that stressors place on an individual. Larger, more frequent, or more persistent stress-related changes in inflammation would have negative consequences for health, including a greater inflammatory impact on telomeres.

Prior depression may sensitize individuals such that they become more responsive to subsequent stressors and have a greater risk for future depressive symptoms (18,19). Depression and anxiety can play a sensitizing role in the promotion of stress-related inflammatory responses as well (20–22). Early life stress is associated with shorter telomeres, and early adversity also amplifies inflammatory responsiveness (22,23).

Psychiatric illness is complex, and inflammation may only contribute to increased morbidity and mortality in subpopulations. For example, approximately a third of depressed patients have inflammatory values that are

noticeably higher than most nondepressed comparison subjects (16). Thus, inflammation clearly plays an important role in substantial subpopulations and undoubtedly contributes to telomere shortening in those subgroups, but other pathways also contribute to the excess psychiatric-related morbidity and mortality. Below, we briefly describe 2 other promising markers that have strong relationships with chronological age; these markers provide additional avenues for understanding the heightened morbidity and mortality associated with psychiatric illness.

### DNA METHYLATION (DNAm)

Epigenetic changes in DNA methylation (DNAm) can give rise to heritable changes in gene expression (24). Indeed, DNAm can change across the lifespan, providing a molecular mechanism through which social and behavioral factors are translated into health outcomes (24). For example, the differences in DNA methylation in identical twins rise with age, a phenomenon termed *epigenetic drift* (25). The development of 2 DNAm age algorithms that are reliably related to chronological age has provided new tools to investigate questions related to accelerated aging (26,27). DNA methylation age correlates highly with chronological age ( $r \geq 0.96$  for both algorithms); Hannum's algorithm is based on blood samples, whereas Horvath has shown the replicability of his algorithm across cell types, tissues, and organs (26,28). Although both the Hannum and Horvath DNAm age algorithms show strong relationships with chronological age, they have only 6 overlapping loci and 11 overlapping genes (26,27,29).

DNA methylation age predicts accelerated age-related decline and early mortality. Individuals with higher levels of epigenetic aging relative to their actual age had a higher mortality risk (30). Data from a large population-based cohort of German older adults linked epigenetic aging acceleration with frailty (31). Other researchers showed that greater age acceleration was associated with poorer cognition, lung function, and grip strength measures (30).

Stressors can provoke persistent changes in DNA methylation (32,33). For example, cumulative lifetime stress in an urban African American cohort predicted accelerated epigenetic aging (34). In a longitudinal study of deployed military personnel, traumatic stress was associated with accelerated epigenetic aging (35). Lifetime PTSD severity was associated with accelerated DNAm age estimates compared to chronological age; furthermore, advanced DNAm age in this cohort was also linked with neural changes and had indirect relationships with working memory performance (29). Moreover, early life social stressors like low socioeconomic status can predispose individuals to develop greater proinflammatory responses to biological and behavioral stimuli, reflecting epigenetic DNAm influences on stress reactivity and proinflammatory cytokine production (36).

**CELLULAR SENEESCENCE: p16<sup>INK4a</sup>**

The expression of p16<sup>INK4a</sup> in peripheral blood T cells provides another human aging biomarker. Increasing exponentially with chronological age, p16<sup>INK4a</sup> expression rises nearly 10-fold over 60 years in humans; in contrast, telomere length decreases less than 2-fold over the same interval (37). A key effector of cell senescence and a cell cycle inhibitor that controls stem cell dynamics, p16<sup>INK4a</sup> actively influences aging (38). Greater p16<sup>INK4a</sup> expression is associated with higher IL-6, smoking and smoking history, and sedentary behavior (37). In genetic mouse models, p16<sup>INK4a</sup> inactivation has attenuated cellular senescence and slowed premature aging (38).

In conclusion, understanding the increased morbidity and mortality in psychiatric populations is important. Aging reduces telomere length, alters DNA methylation patterns, and heightens p16<sup>INK4a</sup>. A broader analysis of the key pathways through which psychiatric illness accelerates biological aging and age-related diseases is an important future direction that may help identify new avenues for intervention.

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