

# Exploring the link between depression and accelerated cellular aging: telomeres hold the key

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**Abstract:** Accumulating evidence suggests that telomeres may be a marker for biological aging and telomere length may be affected by multifactorial influences, including cumulative exposure to depression. Associations with telomere length have been reported for major depressive disorder, lifetime duration of depression, higher depression severity, and history of depression. The exact underlying mechanisms for these associations have yet to be fully elucidated; however, oxidative stress, chronic inflammation, dysregulated hypothalamus-pituitary-adrenal axis, and altered cortisol levels may be important biochemical mediators. These mediators could also be influenced by psychological stress, unhealthy lifestyle behaviors, or other potential factors, such as childhood abuse, post-traumatic stress disorder, and anxiety that are commonly associated with depression. As such, stress reduction and lifestyle interventions that may affect the telomere maintenance system should be considered for individuals with depression.

**Keywords:** depression, telomere length, biomarkers, cellular ageing

## Telomerase activity, telomere length, and aging

Telomeres are specialized nucleoprotein structures located at the end of eukaryotic chromosomes, which consist of double-stranded tandem DNA repeats and a multitude of associated proteins. They play a critical role in controlling cell proliferation and maintenance of chromosomal stability.<sup>1</sup> However, telomeric DNA repeats can be lost during every cell division, therefore, telomeres progressively shorten and ultimately leads to replicative senescence and subsequent cell death.<sup>2,3</sup> Nevertheless, telomere shortening can be counteracted by telomerase, a ribonucleoprotein enzyme, which contains an essential RNA component (telomerase RNA component) that serves as a template and as a catalytic subunit of telomerase (telomerase reverse transcriptase) that is required for the synthesis of new telomeric DNA repeats to be added to the end of chromosomes.<sup>4</sup>

Telomerase is expressed at high levels in cells of the germinal line, stem cells, and some leukocytes but repressed in most somatic cells beyond the early stages of fetal development.<sup>5,6</sup> In proliferating cells lacking telomerase, telomeres progressively shorten during every mitotic division, and this progressive telomere loss eventually leads to critically shorter telomeres, which triggers a DNA damage response that results in chromosomal end-to-end fusions or cell arrest and apoptosis, which the cell population as a whole eventually undergoes senescence.

Telomeres naturally lose approximately 30–150 bp with each cell division<sup>3</sup> and its length is highly variable among individuals at the same age and to a large extent genetically determined, with heritability estimates ranging from 40% to 80%.<sup>7</sup> There are

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no sex differences in telomere length at birth, but thereafter, males tend to have shorter telomeres than females.<sup>8,9</sup> Short telomeres can lead to chromosomal instability, which can increase the rates of genetic mutations and chromosome abnormalities.<sup>10</sup> This loss of cell viability associated with telomere shortening is thought to contribute to the onset of degenerative diseases that occur during human aging.<sup>11</sup>

Telomere length has been associated with aging and several age-related diseases. For example, several signs of geriatric syndrome, such as delayed recall and verbal fluency,<sup>12</sup> lower grip strength,<sup>13</sup> and age-related diseases, including cardiovascular disease,<sup>14</sup> type 2 diabetes,<sup>15</sup> neurological disease,<sup>16</sup> as well as cancer<sup>17</sup> are characterized by the presence of short telomeres, probably reflecting the past proliferative history to apoptosis and senescence and suggesting that it might be an indicator for the underlying mechanisms that bring about aging.

Indeed, telomere length is not merely a biomarker of age-related diseases, but also a potential determinant of lifespan. Animal studies demonstrated that telomere shortening and lower telomerase activity are causes of metabolic and mitochondrial damage,<sup>18</sup> and that telomerase reactivation reversed tissue degeneration.<sup>19</sup> In human, inverse association between the telomere length and risk of death from heart disease or infections has been observed.<sup>20</sup> A sample of elderly Swedish twins confirmed these findings by demonstrating that shorter telomere length was related to a higher risk of mortality, independent of early familial environment, and genetic factors.<sup>21</sup> Similar results were reported from the elderly Danish twin cohort, where the co-twin with the shorter telomeres died earlier than their counterparts, further suggesting that telomere length might directly contribute to longevity.<sup>22</sup> However, other studies did not confirm this finding.<sup>23–25</sup>

Recently, the concept of frailty, as an indicator of biological age as opposed to chronological age was developed. It is characterized by the loss of physiologic reserves and increased vulnerability to functional impairment and age-related diseases.<sup>26–28</sup> Recent literature has suggested inflammatory processes as an underlying mechanism for frailty.<sup>29,30</sup> Therefore, telomere shortening may also be associated with frailty. In support of this idea, the association between telomere length and frailty has been studied in a sample of Chinese men and women aged 65 years and above. Although women were frailer than men, they had a longer telomere length. In men only, frailty index was positively associated with mortality. However, there was no association between telomere length and frailty index in either sex.<sup>31</sup> Other studies also

found no correlation between telomere length and frailty index.<sup>32,33</sup>

## Associations between depression and telomere length

While many age-related diseases such as cardiovascular disease,<sup>14</sup> type 2 diabetes,<sup>15</sup> neurological disease,<sup>16</sup> and cancer<sup>17</sup> have been associated with a shorter telomere length, an emerging literature implicates depression, highly prevalent in older adults, as a potential pathway toward accelerated aging. Prior work has identified relations of depression to age-related diseases such as diabetes,<sup>34</sup> metabolic disorders,<sup>35</sup> coronary heart disease,<sup>36</sup> cognitive impairments/dementia,<sup>37</sup> and cancer.<sup>38</sup> In addition, depression could also be a risk factor for mortality in aging.<sup>39</sup> Although the biological mechanisms mediating these associations remain unclear, accelerated biological aging is a potential mechanism of such increased risk, and this process is thought to occur at the level of telomeres.

Over the past few years, a number of studies have measured the mean telomere length from individuals with major depressive disorder (MDD), and have found evidence for accelerated telomere shortening in the disease. Simon et al<sup>40</sup> found that individuals with either major depression or bipolar disorder had shorter telomere length as compared to age-matched controls after adjustments for age, sex, and a lifetime smoking history, with an overall mean difference of 660 bp, corresponding to approximately 10 years of accelerated aging in those with mood disorders, assuming an average yearly attrition of 59 bp.<sup>41</sup> In a sample of Taiwanese patients, those with major depression had significantly shorter telomere length compared to community controls after controlling for age and sex.<sup>42</sup> The association between major depression and shortened telomeres were further replicated in other samples of patients with MDD.<sup>43–45</sup> Recently, in a large sample of 11,647 women, recurrent major depression was associated with shorter telomere length.<sup>46</sup> In addition, the chronicity of depression has been observed to be inversely associated with telomere length. In a previous study where only marginal association between current major depression disorder and telomere length was found, a significant inverse relationship was observed between total cumulative lifetime duration of depression and telomere length, with the mean difference of 281 bp, reflecting approximately 7 years of accelerated aging in those with cumulative lifetime depression.<sup>47</sup> This suggests that telomere shortening may progress with longer exposure to depression. This is

supported by the study of Elvsashagen et al<sup>48</sup> who evaluated the correlation between lifetime depressive episodes and telomere length in patients with bipolar II disorder as compared with healthy age, sex, and education-matched controls; where there was a positive correlation between lifetime number of depressive episodes and the percentage of short telomeres. In the Netherlands Study of Depression and Anxiety, Verhoeven et al extended these findings by showing that both higher depression severity and longer symptom duration in the past 4 years were associated with shorter telomere length.<sup>49</sup> Similarly, another study demonstrated that a history of depression was also associated with shortened telomeres, independent of the severity of depressive symptoms.<sup>50</sup> Finally, in a recent meta-analysis using data from 25 studies found a significant but small association between depression and shorter telomere length.<sup>51</sup>

Although there appears to be a significant association between depression and shorter telomeres, some studies reported mixed results. In a sample of older patients with coronary heart disease, MDD was associated with shorter telomere length after adjustment for age and sex, but this association was attenuated after further adjustment for body mass index, smoking, diabetes, left ventricular ejection fraction, statin use, antidepressant use, physical activity, and anxiety. Furthermore, the baseline MDD was not predictive of a 5-year change in telomere.<sup>52</sup> Malan et al<sup>53</sup> evaluated the relationship between telomere length and the development of MDD in women who were the victims of rape and found no significant associations of relative telomere length with pre-existing MDD or the development of MDD after a 3-month follow-up. Other studies have also failed to demonstrate any significant association between MDD and telomere length (Table 1).<sup>54,55</sup>

Apart from MDD, several studies have examined depressive symptoms and the risk of developing depression in the context of telomere shortening, but the results have been mixed. In the West of Scotland Twenty-07 Study, depressive symptoms were longitudinally associated with shorter telomere length in younger adults, but not in the middle- or older-aged groups.<sup>56</sup> Gotlib et al<sup>57</sup> found that children at familial risk of developing depression had significantly shorter telomere length than did their low-risk counterparts. However, another study found no association between depressive symptoms and telomere length in a cohort of older patients with chronic heart failure, although there was a negative relationship between perceived mental health and telomere length.<sup>58</sup> Furthermore, depressive symptoms were

neither cross-sectionally nor longitudinally associated with telomere length in a sample of older men aged 70 years and over.<sup>59</sup> Collectively, there may be a link between depression and shorter telomeres; however, the data was still inconclusive.

## Potential mechanisms mediating the relationship between depression and telomere shortening

The exact mechanisms that may underlie the association between depression and accelerated telomere shortening have yet to be fully elucidated, but oxidative stress and chronic inflammation are two important biochemical pathways that are dysregulated in depressed individuals, and may contribute to the depressed state itself and to accelerated aging. Epidemiological studies have reported associations of depression with increased oxidative stress<sup>60-63</sup> and inflammatory markers such as C-reactive protein and pro-inflammatory cytokines.<sup>64,65</sup> A meta-analysis further demonstrated that not only were inflammatory markers positively associated with depression; there was also a dose-response relationship between them, in which an increased inflammatory state was associated with increased depressive mood.<sup>66</sup> Oxidative stress has a negative effect on telomere length maintenance, both through the inhibition of telomerase activity<sup>67</sup> and direct erosion of telomeric DNA.<sup>68</sup> Conversely, antioxidants prolong telomerase activity and decelerate telomere shortening.<sup>69</sup> Chronic inflammation enhances turnover of leukocyte, which may reduce telomerase activity and telomere length. For example, an inverse association has been observed between C-reactive protein and telomere length in a sample of older adults.<sup>70</sup> Pro-inflammatory cytokines have also been shown to regulate telomerase activity in cultured cells,<sup>71</sup> which may influence telomere length.

However, oxidative stress and chronic inflammation are not the only potential mediators involved in the accelerated telomere shortening in depressed individuals, other pathways such as dysregulated hypothalamus-pituitary-adrenal (HPA) axis and the altered neuroendocrine stress response may play a role as well.<sup>72,73</sup> Increasing evidence for hyperactivity of the HPA axis as indicated by increased cortisol secretion among depressed individuals has been reported,<sup>74</sup> whereas higher cortisol levels have been associated with reduced telomerase activity<sup>75</sup> and shorter telomere length.<sup>76</sup> Higher cortisol levels may also exacerbate oxidative stress and pro-inflammatory cytokines release.<sup>77</sup> However, a recent study demonstrated that hypocortisolemia was associated with shorter telomere length.<sup>44</sup> Indeed,

**Table I** Studies of depression/depressive symptoms and telomeres

Reference	Design	Sample	Sample size Full sample (patient/control)	F (%)	Age (year) Full sample (patient/control)	Telomere length Full sample (patient/control)
40	Cross-sectional	MDD + BPD and control	88 (44/44)	45	50.8 (51.1/50.5)	7.31 (6.98/7.64) kb
42	Cross-sectional	MDD and control	664 (253/411)	59	(44.5/45.3)	(8.17/9.13) kb
43	Cross-sectional	MDD and control	74 (54/20)	57	49.1	(7.20/7.55) kb
44	Cross-sectional	MDD and control	542 (91/451)	52	(60.4/58.9)	(5.26/5.54) kb
45	Cross-sectional	MDD and control	57 (9/48)	–	18–64	(87.9/101.2) (Telomere content)
46	Cross-sectional	MD and control	11,647 (5,864/5,783)	100	(30–60/40–60)	–
47	Cross-sectional	MDD and control	Total sample: 35 (18/17) Sub-sample: 27 (10/17) (In the sub-sample 10 Individuals had greater lifetime duration of major depression)	66	(36.8/36.6)	Total sample: (5.1/5.1) kb Sub-sample: (4.8/5.1) kb
48	Cross-sectional	BD-II and control	56 (28/28)	68	34.8 (34.8/34.8)	–
49	Cross-sectional	Current + remitted MDD and control	2,407 (current MDD 1,095 + remitted MDD 802/510)	66.8	(Current MDD 40.7, remitted MDD 43.5/40.5)	(Current MDD 5.6, remitted MDD 5.5/5.5) kb
50	Cross-sectional	A history of unipolar depression and control	94 (44/50)	100	(53.1–53.8/51.1)	–
52	Longitudinal	MDD with stable coronary heart disease and control	Baseline: 952 (206/746) 5 year follow-up: 608 (127/481)	Baseline: 18.6	Baseline: (61.7/68.1)	Baseline: (0.86/0.89) kb
53	Longitudinal	Rape survivors with and without MDD	Baseline: 63 (23/40) 3 m follow-up: 63 (31/32)	100	22.3	–
54	Cross-sectional	Current late-life depression and never-depressed	483 (355/128)	65	70.5	(5.039/5.048) kb
55	Cross-sectional	MDD and control	332 (166/166)	54	41.3 (41.3/41.3)	(9.1/8.9) kb
56	Longitudinal	General population	1,063 (337 aged 37, 441 aged 57, 285 aged 76)	Baseline: 55	Baseline: 55.7	Baseline: 0.8 kb
57	Cross-sectional	Girls had mothers with no current or past Axis I disorder and girls had mothers with a history of recurrent episodes of depression	97 (50/47)	100	12.0/12.0	–
58	Cross-sectional	Patients with chronic heart failure	890 (299/536) (No in the sub-groups may not sum up to the total)	39	73	0.69 T/S ratio
59	Longitudinal	Elderly men in general population	Baseline: 171 Follow-up: 75	0	Baseline: 78 Follow-up: 84	Baseline: 5.0 kb Follow-up: 4.8 kb

Mean difference	P-value	Adjustment	Key results
660 bp	0.002	Age, sex, smoking, and mood disorder	MDD was associated with shorter telomere length
960 bp	<0.001	Sex, age, Apo E2, and MAOA promoter polymorphism	MDD was associated with shorter telomere length
350 bp	0.007	Nil	MDD was associated with shorter telomere length
277 bp	0.001	Age and sex	MDD was associated with shorter telomere length
–	0.002	–	MDD group had a significantly decreased mean telomere content compared with control subjects
–	–	–	MD was associated with shorter mean telomere length (OR: 0.85, 95% CI: 0.81–0.89)
Total sample: 40 bp	Total sample: 0.66	Total sample: age and sex	Chronic courses of MD had significantly shorter telomeres than control subjects
Sub-sample: 281 bp	Sub-sample: 0.05	Sub-sample: age, sex, lifetime, and current tobacco use and BMI	
552 bp	0.08	–	BD-II was associated with an increased load of short telomeres
–	Current MDD vs control: 0.027 Remitted MDD vs control: 0.036	Age, sex, education, BMI, smoking, alcohol use, physical activity and somatic disease	MDD was associated with shorter telomere length
–	<0.01	Age	Individuals with a history of depression showed significantly shorter telomeres
Baseline: 0.03 kb	Cross-sectional: 0.06 Longitudinal: compared with control subjects, those with MDD at baseline were less likely to experience telomere shortening and more likely to experience telomere lengthening after adjustment ( $P=0.40$ )	Age, sex, diabetes, BMI, smoking, left ventricular ejection fraction, statin use, physical inactivity, antidepressant use and anxiety	MDD was not predictive of 5-year change in telomere length after adjustment for covariates and baseline telomere length
–	Baseline: 0.21 3 m follow-up: 0.93	–	No significant associations were observed between telomere length and the development of MDD at either baseline or after 3 months
0.009 kb	0.82	Age, sex, years of education, number of cigarette years, alcohol use, physical activity, BMI, and number of chronic disease	Late-life depression was not associated telomere length
0.2 kb	0.65–0.91	–	MDD was not associated with telomere length
–	Baseline: 0.012–0.013 (in the youngest 37-year-old cohort only)	Sex, social class, assay plate, and medication use	Average depression symptoms and their change over time were negatively associated with telomere length, but on in the youngest cohort (37 years)
–	<0.001	Age, tanner stage, and child Depression Inventory	Girls of depressed mother (high risk group) had shorter telomere length than their low-risk peers
–	0.51	–	Depressive symptoms were not associated with telomere length
–	Baseline: 0.37–0.78 Follow-up: 0.96	Age, living arrangement, smoking status, alcohol consumption, physical activity, chronic disease, and BMI	Depressive symptoms were not associated with telomere length in both cross-sectional and longitudinal analyses

**Abbreviations:** BMI, body mass index; vs, versus; OR, odds ratio; CI, confidence interval; MDD, major depressive disorder; BPD, borderline personality disorder; MD, major depression; MAOA, monoamine oxidase A, Apo E2, apolipoprotein E2; BD-II, Bipolar II disorder

lower cortisol levels have also been reported among older depressed individuals, particularly among those with physical frailty,<sup>78</sup> suggesting that physical frailty may exhaust the stress response potentially resulting in hypoactivity of the HPA axis, or lower cortisol levels.<sup>78,79</sup> Therefore, further research is necessary to examine the underlying pathway that accounts for both hyperactivity and hypoactivity of the HPA axis with depression, and their associations with telomere shortening (Figure 1).

## Psychological stress and unhealthy lifestyle behaviors as potential moderators

Psychological stress, the most significant predictor of depression<sup>80</sup> and unhealthy lifestyle behaviors that are more common among the depressed, including smoking,<sup>81</sup> alcohol intake,<sup>82</sup> unhealthy diet,<sup>83</sup> physical inactivity,<sup>84</sup> and poor sleeping quality<sup>85</sup> have been implicated in contributing to alterations in the biochemical mediators as discussed in the previous section, resulting in telomere shortening and cellular aging (Figure 1).

## Psychological stress

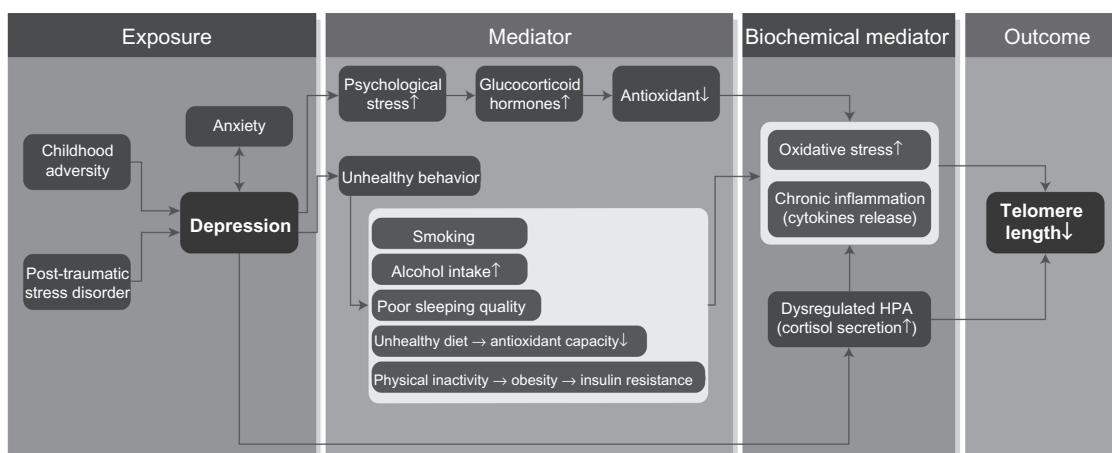
Numerous studies have shown that cumulative exposure to the chronic stress of depression had a central role in telomere length. The first evidence that psychological stress may impact telomere maintenance came from a study which described shorter telomere length in mothers of chronically ill children.<sup>86</sup> Similar findings were reported by Parks et al,<sup>87</sup> who reported significantly shorter telomere length in older women with higher levels of perceived stress and stress hormone. The mechanisms by which psychological stress impacts the body at the cellular level are unknown,

but studies have reported that stress is associated with the release of glucocorticoid hormones, which have been shown to reduce the levels of antioxidant, and may, therefore, cause increased oxidative damage to DNA<sup>88</sup> and accelerated telomere shortening.<sup>68</sup>

## Unhealthy lifestyle behaviors

Smoking was associated with an increased oxidative stress as well as with inflammatory response,<sup>89</sup> both of which can induce DNA damage and may expedite telomere shortening.<sup>68,90</sup> Telomeres in smokers have been shown to be significantly shorter than those in the never- or ex-smokers categories of the same age group.<sup>91</sup> There was also a dose-effect relationship between the cumulative long-life exposure to tobacco smoking and telomere length.<sup>92</sup> In addition, active smoking has been associated with accelerated telomere shortening.<sup>93</sup>

Similarly, heavy alcohol consumption was associated with increased oxidative stress and inflammation,<sup>94</sup> and both processes may enhance telomere shortening. However, evidence from population-based studies on the relation between alcohol intake and telomere length has been limited and inconsistent. Previous studies have noted that alcohol abusers had significantly shorter telomere length compared with controls.<sup>95,96</sup> However, other studies, that examined the relationship between alcohol intake and telomere length have found no<sup>25,97</sup> or marginal associations.<sup>98</sup> In a recent longitudinal sample of 4,576 general population individuals, alcohol intake was not associated with telomere length either cross-sectionally or longitudinally.<sup>99,100</sup> Discrepant findings may have resulted from differences in the patterns of alcohol intake. A meta-analysis suggested that heavy, irregular drinking could modify the favorable effect of alcohol intake on the risk of coronary heart disease.<sup>101</sup>



**Figure 1** Schematic model of pathways linking depression and telomere shortening. **Note:** The relationships are possibly interrelated and bidirectional.



Associations between dietary factors and telomere length have also been examined previously. A number of studies have reported eating processed meats,<sup>102,103</sup> and food high in polyunsaturated fats<sup>99</sup> or saturated fatty acids<sup>104</sup> were associated with shorter telomere length, whereas high intake of vegetables and fruits,<sup>105</sup> omega-3 fatty acids,<sup>106</sup> fiber,<sup>99,107</sup> vitamins,<sup>99,108–112</sup> or Chinese green tea<sup>113</sup> were related to longer telomere length. These observations have led to a belief that the association between depression and telomere length may be moderated in part by dietary factors. The mechanisms by which dietary factors impact the body at the cellular level are unknown, but antioxidant capacity may play a role. Diet rich in antioxidants may maintain the telomeres, via the modulation of oxidative stress and inflammatory reactions.<sup>114</sup> Micronutrients like vitamin C, E, folic acid, and marine omega 3 fatty acids are associated with anti-oxidative function, and thereby may be associated with long telomeres due to their anti-oxidative properties.<sup>115</sup> In a recent study on children and adolescent populations, higher dietary total antioxidants has also been associated with longer telomere length.<sup>116</sup> Red meat, refined grains, and sugar-sweetened soft drinks, however, may be associated with oxidative stress and inflammation,<sup>117–119</sup> which could impact cellular aging.

Increasing evidence also suggests that physical inactivity has an adverse effect on telomeres,<sup>120,121</sup> whereas increasing physical activity has been associated with longer telomere length.<sup>121</sup> The mechanisms by which physical activity impacts the body at the cellular level have not yet been fully elucidated. One possibility is that physical activity acts via reduction of obesity and prevention of insulin resistance. This could have favorable effects on telomere length,<sup>122</sup> possibly through the modulation of oxidative stress and inflammatory responses.<sup>123</sup> Furthermore, physical activity may help to buffer the effects of chronic stress on telomere length.<sup>124</sup>

Disrupted sleep quality has also been associated with shorter telomere length.<sup>125–127</sup> The biological mechanisms underlying the association between sleep quality and telomere attribution remain to be elucidated. Indeed, disrupted sleep quality has been associated with elevated pro-inflammatory cytokine production,<sup>126</sup> cortisol secretion,<sup>128</sup> and enhanced autonomic activation,<sup>129</sup> which may contribute to telomere shortening.

## Other potential moderators

A growing body of literature suggests that childhood adversity, post-traumatic stress disorder, and anxiety may have considerable impacts on cellular aging. Both childhood adversity and post-traumatic stress disorder have been suggested to

be predisposing factors to the development of depression and anxiety,<sup>130,131</sup> which often coexist with each other,<sup>132</sup> suggesting that these factors may moderate the association between depression and telomere shortening, possibly by influencing the biochemical mediators as discussed in the previous section (Figure 1).

## Childhood adversity

Several studies have reported an association between childhood adversity and levels of pro-inflammatory cytokines<sup>133</sup> and cortisol levels,<sup>134</sup> as well as telomere length in adulthood<sup>135–138</sup> and in older adults,<sup>133,139</sup> suggesting that childhood adversity has an impact on aging at the cellular level, although another study did not find an association.<sup>140</sup> Recent studies also suggested that childhood adversity might even accelerate telomere shortening during childhood. Drury et al<sup>141</sup> found that greater exposure to institutional care correlated with reduced buccal cell telomere length in children aged 6–10 years. In a prospective longitudinal study, children who experienced two or more kinds of violence exposure showed significantly more telomere erosion over 5 years, even after adjusting for confounders.<sup>142</sup> Therefore, there is some evidence of a relationship between childhood adversity and telomere length.

## Post-traumatic stress disorder

Accumulating evidence indicates that individuals with post-traumatic stress disorder, a trauma-related disorder that may develop after exposure to one or more traumatic events,<sup>143</sup> may be susceptible to accelerated telomere shortening,<sup>137,144</sup> as indicated by the shortened telomere length. The authors of the later study suggested this effect was largely determined by the presence of substantial adverse childhood events.<sup>137</sup> Among military personnel, middle-aged war veterans with current post-traumatic stress disorder had a shorter telomere length compared with age-matched healthy controls.<sup>145</sup> This finding was replicated by Zhang et al<sup>146</sup> in a sample of army special operations personnel. However, one study evaluated male soldiers with post-traumatic stress disorder and found that the development of post-traumatic stress disorder symptoms was associated with telomere lengthening.<sup>147</sup> Therefore, the association between post-traumatic stress disorder and telomere length lacks consistent support from the literature.

## Anxiety

Preliminary evidence has also suggested an association between anxiety and shorter telomere length. In one study

of individuals with various anxiety-type disorders, only older individuals (48–87 years old) showed shortened telomere length compared with age-matched controls, suggesting that more chronic exposure to the disorder was required for the telomere shortening to be observed.<sup>136</sup> In another study on phobic individuals, only those with more severe symptoms showed telomere shortening.<sup>148</sup> In contrast, Surtees et al<sup>138</sup> did not observe significant differences in telomere length in the presence of either a 12-month or a lifetime generalized anxiety disorder among 4,441 women (aged 41–80 years). These discrepant findings may be due to different ascertainment methods of diagnoses and reflecting different samples' characteristics. Therefore, findings remain inconclusive regarding telomere shortening in anxiety disorder.

## Conclusion and prospects for interventions

Telomere length is a robust indicator of “biological age” and may represent a biomarker for assessing an individual's cumulative exposure to depression. A growing body of research demonstrates that individuals diagnosed with MDD have shortened telomere length, which may underlie the association between depression and increased rate of age-related diseases. The potential biochemical pathways by which depression affects telomere length have been discussed, including oxidative and inflammatory stress, alternations in the HPA axis, and cortisol levels. These biochemical mediators could be influenced by several potential moderators associated with depression, including psychological stress and unhealthy lifestyle behaviors. However, these mechanisms remained to be clarified. Furthermore, the associations of telomere length with childhood abuse, post-traumatic stress disorder, and anxiety that are also potential moderators of depression have also been reviewed.

Accepting the pathophysiological role of the biochemical mediators and moderators described above in the relationship between depression and telomere length, interventions that may affect the telomere maintenance system should be considered. A number of stress reduction and lifestyle interventions have shown to favorably impact telomere length or telomerase activity. For example, stress reduction and meditations may reduce cognitive stress and stress arousal and increase positive states of mind and hormonal factors, which could, in turn, promote telomere maintenance.<sup>149</sup> Exercise may also confer health benefits by enhancing immune and metabolic regulation, preventing insulin resistance as well as buffering the deleterious effects of stress, which could have favorable effects on telomere length.<sup>124</sup> A 3-month

intervention with lifestyle changes including a plant-based diet, moderate exercise, stress management, and social support has been associated with increased telomerase activity.<sup>150</sup> Similarly, a combination of healthy behaviors, defined by low-risk healthy lifestyle factors for chronic disease, was also associated with longer telomeres in community and clinical samples.<sup>98,151</sup> Therefore, further studies should examine whether these interventions may be suitable for individuals with depression, resulting not only in a reversal of depressive symptoms but also in decelerating telomere shortening, reversing cellular aging, and reducing the risk of age-related diseases.

## Disclosure

The authors report no conflicts of interest in this work.

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