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Shorter telomeres among individuals with physical disability: The moderating role of perceived stress

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Abstract

Objectives: Evidence suggests that individuals with physical disability may suffer from psychological distress and accelerated cellular aging, manifested by shortened telomere length (TL), compared with healthy individuals. Studies indicate that high levels of perceived stress and depression may increase the physiological susceptibility and thus, may contribute to a short TL. However, the moderating role of perceived stress and depression within the relationship between physical disability and TL remains unknown. **Methods:** The participants consisted of 119 male subjects (mean age 54.36 years, range 35−70). Of them, 30 were able-bodied and 86 had a physical disability: 34 were due to Poliomyelitis (polio) and 55 were due to spinal cord injury (SCI). Blood samples for TL analysis were collected; the participants completed questionnaires and underwent disability evaluation. **Results:** Participants with disability had a shorter TL as well as elevated levels of perceived stress and depression compared with able-bodied controls. Both the perceived stress and depression were correlated with a shorter TL. Nonetheless, perceived stress, rather than depression, moderated the relationship between disability and TL; among participants with higher perceived stress levels, in particular, individuals with physical disability had a shorter TL than the able-bodied controls. **Discussion:** The present findings suggest that individuals with physical disability and who exhibit high levels of perceived stress may be particularly vulnerable for accelerated cellular aging, suggesting that perceived stress can be used as a valuable target for intervention.

Keywords: Poliomyelitis, spinal cord injury, perceived stress, depression, premature ageing, telomere length.

Introduction

Natural aging involves a gradual decline in physical and mental functioning, and a higher risk of diseases and disabilities (Ferrucci et al., 2020). Although normative, these processes proceed at varied paces and exhibit diverse manifestations among individuals; they are determined by different factors including genetic predispositions, personal circumstances, and social and medical sources of influence (WHO, 2018). Research indicates that chronic physical disability may also explain heterogeneity in the aging process and that individuals who suffer from physical disability due to a spinal cord injury (SCI) or Poliomyelitis (polio) may also suffer from accelerated aging.

Longitudinal studies have shown that SCI is associated with premature aging, manifested by an accelerated deterioration in several body systems such as the cardiovascular, endocrine, immune, and respiratory systems (Jensen et al., 2013; Li et al, 2020). Furthermore, the clinical complications following SCI can lead to immune system frailty (Hitzig et al., 2011). Although research on accelerated aging has been scarce among survivors of polio, some findings point to the delayed effects of the disease even many decades after recovery (Chu & Lam, 2019). These include complications that are typically age related, such as arthritis and osteoporosis, which similarly to SCI, tend to appear chronologically earlier among this population, implying an accelerated aging process (Chu & Lam, 2019). This apparent accelerated aging process among individuals with SCI or polio may also take place at a cellular level, manifested by the telomere length.

Cellular telomeres are specific DNA–protein structures located at the ends of each chromosome. Their unique structure protects the integrity of the DNA by preventing deterioration and faulty recombination; it serves as a central mechanism for regulating cellular life span (Liu et al., 2019). Every cell division brings about a shortening in telomere length (TL); thus, TL serves as a biomarker of cellular senescence (Liu et al., 2019). Accordingly, evidence has indicated a link between shorter telomeres and age-related conditions such as arthritis, hypertension, and cardiovascular illness, as well as early mortality (e.g., Arbeev et al., 2020).

Studies on individuals with SCI have shown that the severity of SCI was associated with TL, and that the clinical characteristics of SCI, such as bladder dysfunction or problems with mobility were associated with a shorter TL (Monroe et al., 2019). To the best of our knowledge, however, no study has explored TL among individuals with polio, who may exhibit similar health-related problems. Furthermore, within the relationships between SCI/polio and TL, the role of psychological distress, which often occurs in these conditions, has not been investigated.

Living with a physical disability may entail an ongoing struggle to maintain psychological and biological equilibrium, a process that may involve elevated perceived stress and depression (O’Donnell et al., 2005; Kariuki et al., 2011). Evidence indicates that perceived stress and depression often co-occur in the context of coping with disabilities (Slavich & Irwin, 2014) and may predict each other (Beck, 1967). Individuals with physical disability such as SCI or polio may not only face multiple challenges in their day-to-day life—they may also appraise them as demanding and beyond their ability to cope, a phenomenon known as perceived stress (Lazarus & Folkman, 1994; Lequerica et al., 2010). This experience, in turn, may adversely affect individuals' capacity to cope with a disability (Jang et al., 2004; Kobasa et al., 1982) and may contribute to depression symptoms.

Studies among individuals with SCI show a higher probability of mental distress, with clinical levels of depression being the most common psychological outcome (Saunders, Krause, & Focht, 2012). Similarly, a robust association has been found between paralytic poliomyelitis and depression (Pierni & Stuifbergen, 2010). For both populations, the presence of depression may increase the risk for accelerated cellular aging. Research among various populations, including individuals with chronic illnesses or disabilities (Wolkowitz et al., 2011), has consistently reported relationships between depression and a short TL. Although less consistent, studies that explored TL with regard to stress have suggested that elevated perceived stress may also be associated with a shortened TL (Epel et al., 2004; Rentscher, Carroll., & Mitchell, 2020).

Nevertheless, the moderating role of perceived stress and depression within the relationships between physical disability and TL remains unclear. Specifically, whether elevated perceived stress and depression symptoms intensify the negative implications of physical disability on TL, remains to be investigated. Elevated perceived stress or depression may take a physiological toll (Wolkowitz et al., 2011), which could engender higher vulnerability to the adverse effects of physical disability on accelerated cellular aging. According to this reasoning, individuals with polio or SCI, and who also suffer from elevated perceived stress or depression, may experience allostatic overload (Slavich & Urwin, 2013), which may drive several biochemical processes, such as higher levels of inflammation and oxidative stress (Epel & Prather, 2018), and thus may amplify the detrimental effects of physical disability on cellular erosion. The current study explored these suppositions for the first time. In light of the literature reviewed above, we hypothesize the following hypotheses 1) participants with physical disability due to SCI or polio will have shorter TL compared to able-bodied controls, and 2) perceived stress and depression will moderate the relationship between physical disability and TL – while overall participants with physical disability will have shorter TL compared with able-bodied controls, this difference will be greater under conditions of elevated perceived stress or depression.

Methods

Participants

A total of 119 participants (mean age 54.36 years, range 35−70) took part in the current study. Among them, 30 were able-bodied and 89 had a physical disability: 34 due to polio and 55 due to SCI. The sample included only males, given the known differences in TL as well as in the telomere attrition rate between genders (Ghimire et al 2019). Inclusion criteria for all the participants were as follows: 1) good health and lack of substantial medical conditions other than SCI or polio (or a history of such conditions) according to individual reports, which were randomly confirmed by cross checking medical records and 2) intact cognition and the ability to comprehend and complete questionnaires. Able-bodied individuals were recruited from the employee population at [masked for review]. Participants who had a physical disability were recruited from the outpatient clinics of the Department of Neurological Rehabilitation, [masked for review] or from [masked for review]. Recruitment was done by ads and flyers that were available at the rehabilitation centers. Individuals who agreed to participate in the study were contacted for further explanations and upon their agreement, they signed a consent form and were invited for data collection. The present study was approved by the Helsinki Committee of [masked for review] and the Institutional Review Board of [masked for review].

Procedures

The study was cross sectional. An enrolment ratio of 3:1 for the disability group and the able-bodied group, respectively, was chosen based on the expected homogeneity among able-bodied participants vs. participants with a physical disability in regards to the study variables. According to sample size calculations a total sample of 90 participants was sufficient for the moderation analyses, assuming medium-sized effects, with 0.80 power and 0.05 probability of Type I error. However, considering that the disability group consisted of two subpopulations, the total sample size was increased by 30%.

Each participant was invited to a single testing session. Prior to data collection, each participant signed a consent form after receiving a full explanation of the study's goals and protocols. Afterwards, the participants were interviewed by the physicians using a structured questionnaire and completed self-reported questionnaires (in a random order). In addition, venous blood was sampled from each participant in the same testing session, in order to analyze TL.

Measures

Telomere Length. Terminal Restriction Fragment (TRF), representing TL, was measured by Southern blotting with a DIG-labeled probe according to the manual provided in the TeloTAGGG Telomere Length Assay (Roche, Mannheim, Germany). A detailed protocol is presented at the supplemented materials and methods.

Perceived Stress Scale (PSS). Perceived stress was measured via PSS (Cohen et al., 1983). This scale assesses individual's stress during the last month and indicates the frequency of feelings and thoughts that occur in stressful situations such as irritation, lack of control over a situation, lack of the ability to cope with demands, and more. The scale consists of 14 items: half of them describe negative experiences and the other half describes positive coping. Participants rated their responses on a 5-point

Likert-type scale ranging from "0" (never) to 4 (very often). After the seven positive items were reversed, the final score was obtained by averaging all 14 items. In this study, Cronbach alpha was .93.

Depression symptoms. Depression symptoms were measured via the Beck Depression Inventory (BDI; Beck, 1967). This inventory includes 21 items in which each item is rated on a scale from 0 to 4. A total score is computed by summing the items. The BDI shows high internal consistency, with a Cronbach's internal reliability of $\alpha = .86$ and $\alpha = .81$ for psychiatric and non-psychiatric populations, respectively (Beck, Steer, & Carbin, 1988). In this study, Cronbach alpha was .94.

Background Variables. Data on demographics, including chronological age, years of education, occupational status, and marital status were obtained through questionnaires. Participants reported their weight and were asked if they perform physical exercise on a regular basis (yes/no). The functional assessment of the participants was carried out using the Functional Independence Measure (FIM; Keith et al., 1987), which was completed by a trained rehabilitation nurse. The grading of the 18 items, which comprise the six domains of function (self-care, sphincter control, transfers, locomotion, communication, and social cognition) range from "requiring total assistance = 1" to "completely independent=7". In addition to the sum score of all the items combined, a FIM score ≥ 90 was used to indicate a mildly impaired functional state requiring only minor assistance (Luk et al., 2006). In this study, Cronbach alpha was .96.

Analytic Strategy

Data were analyzed using IBM SPSS Statistics 25 and the PROCESS computational macro. Continuous variables are presented as the means and standard deviations and the categorical variables as medians and interquartile range.

Dichotomous variables are presented as percentages. *F*-tests or *Chi Square* tests were conducted to determine the differences in the study's variables between study groups.

Given that research has indicated that occupational status was linked with depression; that age and weight were associated with shorter TL (e.g., Mundstock et al., 2015); and as found in our previous study on the same dataset (Lahav et al., 2021) that physical exercise was associated with longer TL, these factors served as a covariate in the present analysis.

To assess the differences in TL between participants with a physical disability of polio or SCI and able-bodied participants, after adjusting for age, occupational status, weight, and physical exercise, a One-way Analysis of Covariance (ANCOVA) was conducted. To examine the relationships between depression and perceived stress, on the one hand, and TL on the other, after adjusting for age, occupational status, weight, and physical exercise, two linear regression models were conducted. These models included the covariates in the first step and depression or perceived stress in the second step of the model.

To assess the moderating role of perceived stress and depression, in the relationship between physical disability and TL, two hierarchical regression analyses were conducted for perceived stress and depression, respectively. The analysis included five blocks: The first block consisted of chronological age. The second block consisted of physical disability. The third block consisted of occupational status, weight and physical exercise. The fourth block consisted of perceived stress or depression symptoms. The fifth block consisted of the interactions between physical disability, on the one hand, and perceived stress or depression symptoms, on the other hand. All the variable scores were standardized. Next, significant interactions were probed using the PROCESS computational macro (Hayes, 2012).

Results

Background characteristics, depression, perceived stress, and the study group

For the entire sample, the average levels of perceived health and depression were 22.88±10.97 and 27.84±8.54 respectively and ranged between 1 and 43 and between 21 and 52, respectively. The average level of FIM score was 91.66±21.87 and ranged between 50 and 126.

Table 1 presents the background characteristics as well as the levels of depression and perceived stress among participants with polio, participants with SCI, and able-bodied participants. As can be seen, the participants with polio were somewhat older than those with SCI and the able-bodied controls. Participants with SCI had more years of education than the other two groups. There were also differences in the prevalence of employment and physical exercise between the three groups. Able-bodied participants had the highest frequency of employment, followed by participants with polio and participants with SCI. A greater proportion of participants with polio engaged in physical exercise, compared with that of participants with SCI and the able-bodied participants.

As expected, a significantly smaller proportion of participants with polio or SCI had a FIM score $\geq$ 90 compared with the able-bodied participants, indicating that the majority of the polio group required assistance; there was no difference between the SCI and polio groups. Similarly, the levels of depression and perceived stress were significantly higher among the SCI and polio groups, compared with the able-bodied participants; the SCI and polio groups were similar to each other.

TL Descriptive information

The maximum value of TL for the entire sample was 10.1 kilo base pairs (kb) and the minimum was 3.20, with a mean of 6.24±1.66. Descriptive information for TL was examined using a histogram, skewness and kurtosis values, as well as by a critical assessment of any outliers for possible exclusion from the analyses or for making required adjustments. Telomere length was checked using recommended skew values of less than 2 and kurtosis values of less than 7. Skew values between 2 and 3 and kurtosis values less than 10 were considered as moderately non-normal (Curran, West, & Finch, 1996). Telomere length was in the recommended acceptable range for skewness (0.40) and kurtosis (−0.70), with no outliers.

Physical disability and TL

The results of the ANCOVA test, which explored the differences in TL between participants with a physical disability and able-bodied participants, revealed a significant difference between the study groups, after adjusting for age, occupational status, weight, and physical exercise (F (2, 112) = 26.75, p<.001). Post-hoc analyses, which compared the three groups, indicated that the able-bodied participants had longer telomeres than both the participants with polio, and those with SCI (see Figure 1). However, no difference was found between participants with polio, and those with SCI in TL.

Perceived stress, depression, and telomere length

The results of the regression analysis indicated significant negative relationships between perceived stress and TL (β = −.74, p<.001, 95% CI [-.93, -.66]) as well as between depression and TL (β = −.52, p<.001, 95% CI [-.72, -.40]), after adjusting for age, occupational status, weight, and physical exercise. This indicates that elevated perceived stress and depression symptoms were associated with shorter telomeres, beyond the effect of age, occupational status, weight, and physical exercise. A supplementary analysis indicated significant relationships between perceived stress and depression (r=.59, p<.001).

Physical disability and telomere length – the moderating roles of depression and perceived stress

Two hierarchical regression models were conducted to assess the moderating role of perceived stress and depression, regarding the relationships between physical disability and TL. Given that no differences in telomere length were found between participants with polio and those with SCI, physical disability was treated as a dummy variable. The absence of physical disability was coded 0 and its presence was coded as 1.

The hierarchical regression exploring the moderating role of depression explained 53.7% of the variance of telomere length, $F(7,111) = 18.38$, $p < .001$ (see Table 2). The model revealed significant effects for chronological age only, and the interaction between physical disability and depression was non-significant (p =.91). The hierarchical regression exploring the moderating role of perceived stress explained 67.5% of the variance of telomere length, $F(7,111) = 33.00$, $p < .001$ (see Table 3). The model revealed significant effects for chronological age, physical disability, and perceived stress. A physical disability of polio or SCI, a higher age and elevated levels of perceived stress were associated with shorter telomeres. The interaction between physical disability and the perceived stress was significant. The supplementary analysis indicated that this interaction remains significant after removing all covariates from the model (p =.03).

The significant interaction between physical disability and the perceived stress was probed using the PROCESS (Model 1) computational macro (Hayes, 2012) by computing the conditional effects at 1 SD below and 1 SD above the mean of the moderator, i.e., the levels of perceived stress. Results indicated that the relationships between physical disability and TL were governed by the levels of perceived stress.

Whereas among participants with lower perceived stress levels there was shorter TL in individuals with physical disability compared with able-bodied controls (β = -.25, *p* =.012), among participants with higher perceived stress this difference was significantly greater (β = -.98, *p* = .00; see Figure 2).

Supplementary analyses exploring the role of perceived stress and depression, regarding the relationships between physical disability and TL, while utilizing the FIM score as an indicator for physical disability, revealed similar trends: The interaction between physical disability and depression was non-significant (*p* =.11), but then again, the interaction between physical disability and perceived stress was significant (β = -.23, *p* =.003). Probing this interaction indicated that whereas among participants with lower perceived stress levels there was shorter TL in individuals with physical disability compared with able-bodied controls (β = -.16, *p* = .05), among participants with higher perceived stress this difference was significantly greater (β = -.67, *p* = .00).

Discussion

The present study investigated the role of perceived stress and depression in TL, among participants with physical disability (SCI or paralytic polio) compared with able-bodied controls. Participants with a disability had a shorter TL as well as elevated levels of perceived stress and depression compared with able-bodied controls; no differences were found between the SCI and polio subgroups. Interestingly, although both perceived stress and depression were associated with TL, the final model indicated that the contribution of perceived stress in explaining TL was greater than that of depression. Furthermore, perceived stress rather than depression moderated the relationship between disability and TL. To the best of our knowledge, these findings are novel; next we will elaborate on their possible interpretations.

The shorter TL among participants with SCI compared with controls confirms previous reports on an age-adjusted association between the severity of SCI and a shorter telomere length; those with severe injury had a shorter TL (Monroe et al., 2019). Our finding is in agreement with reports on the accelerated deterioration of various body-systems (Sun et al., 2016) and age-related complications (Jensen et al., 2013) among participants with SCI. To the best of our knowledge, this is the first report on shortened TL among participants with polio, indicating that as in SCI, this type of disability is also associated with cellular senescence. Other neurological conditions leading to disability, such as multiple sclerosis, have also been associated with a shorter TL (e.g., Guan et al., 2015).

Generally, TL exhibits a linear decline from the mid-50s to the mid-70s age groups, by about 8% (e.g., Ghimire, Hill, Sy, & Rodriguez, 2019). Here we show that TL was reduced among the SCI and polio groups by about 30%, compared with able-bodied controls, despite adjusting for age, which is quite substantial. Furthermore, the TL of the participants in the SCI and polio groups resembles that of older individuals (mean age 77.5 years) whose TL was analyzed by members of our group (Uziel et al., 2018). We thus can conclude that SCI and polio are associated with a significant accelerated aging on a cellular level.

The similar TL among the SCI and polio groups may result from the similar disability status of the groups. Despite the polio group having a somewhat higher FIM sum score than the SCI group (83 vs. 78, respectively), this difference is not clinically significant. Furthermore, among both groups, a similar percentage of participants had a FIM score > 90 (20.6 vs 12.7%, respectively), the cut off for mild impairment, suggesting that they possess a similar functional disability status. Interestingly, TL was similar among participants with SCI and polio despite the fact that the polio group had experienced a disability from childhood, whereas those with SCI acquired it in adulthood (from the age of 18 years and above). Perhaps TL has a floor effect, namely, that it has a minimal length per age in pathological conditions, and the duration of disability had no additional effect on TL over the presence of the disability. The similar TL among these groups may also suggest that the disability itself, rather than the underlying cause of disability (either a traumatic injury or an illness, respectively) has a greater impact on accelerated ageing.

Several biological factors may underlie a shorter TL among participants with SCI and polio; these include oxidative stress and systemic inflammation (Gavia-García et al., 2021; Jensen et al., 2013; Sun et al., 2016), hypertension (Tellechea & Pirola, 2017) or increased body mass index (Atowoju, Adegoke, & Babalola, 2015), conditions that may be more frequent among participants with physical disability. However, in a recent study among participants with SCI, TL was neither associated with the aforementioned conditions nor with other biological indices (Monroe et al., 2019). In addition, in the present study, the two groups did not differ in their weight. Reduced physical activity subsequent to mobility restrictions may also explain cellular senescence among participants with physical disability, since it has been found to be associated with TL (Puterman et al., 2010). However, in the present study, participants with disability were more active than the able-bodied controls, suggesting that this explanation is less likely. Furthermore, in the final model, neither physical activity nor weight significantly contributed to TL. Note that participants of both disability groups participate regularly in sport activities as part of their continuous outpatient rehabilitation programs. Although physical activity has been suggested to mitigate cellular senescence (Denham et al., 2016) and despite the relatively active lifestyle of the participants with physical disability, their TLs were shorter than those of the able-bodied participants. Hence, it appears that other factors may have contributed to the shorter TL found among the disability groups.

Participants with SCI or polio had elevated levels of perceived stress and depression, compared with the able-bodied participants, a finding consistent with previous reports (Kariuki et al., 2011). This finding may reflect the effects of multiple challenges, as well as struggles and losses that individuals with SCI or polio face as a result of their physical disability. Both manifestations of psychological distress may take a toll on the physiological system, and may contribute to accelerated aging. Indeed, previous research in populations other than those with physical disability has revealed that depression or perceived stress is associated with shortened TL (Schutte & Malouff, 2016) as well as with an increased rate of age-related diseases (Wolkowitz, Reus, & Mellon, 2011); the latter is another biological indicator of accelerated aging. The present findings indicate, for the first time, that elevated perceived stress was not only associated with a short TL—it also moderated the relationships between disability and TL; among participants with higher perceived stress levels in particular (as opposed to those with lower perceived stress levels), individuals with physical disability had a shorter TL than did the able-bodied controls.

The moderating role of perceived stress may be explained via the allostatic model. Exposure to acute stressors leads to an adaptive activation of the metabolic and immune systems, known as “allostasis”, which subsides after the stressors cease (Slavich & Irwin, 2014). Nevertheless, an enduring exposure to stressors may result in “allostatic overload”, i.e., excessive, dysregulated activation of these systems, which in turn, wears down the physiological system and subsequently modifies body and brain functioning (McEwen, 2013).

The allostatic model of stress has been reported to be a central mechanism underlying the deleterious influences on health among different target populations. Its effects may be accumulated throughout a lifetime, thus impacting the susceptibility of individuals with disabilities to accelerated aging (Cao et al., 2020). This mechanism is particularly relevant regarding subjective or perceived stress. Individuals with disability and who suffer from high perceived stress levels may appraise disability-related challenges and other difficulties and struggles in their lives, in a manner that is negative, threatening, and beyond their ability to cope (Galvin & Godfrey, 2001). This type of appraisal may be implicated in a cascade of biochemical changes including increased inflammation and oxidation and the release of stress hormones, which have been associated with a shorter TL (Steptoe et al., 2017). Thus, higher perceived stress levels may hamper the function of bodily systems and exacerbate the negative implications of physical disability on cellular aging.

Interestingly, depression did not moderate the association between disability and TL, despite its higher levels among the disability groups. Although depression has been associated with a shorter TL (Lahav et al., 2018; Slavich & Irwin, 2014), some studies indicate that the underlying role of stress is at the heart of allostatic dysregulation (Lex et al., 2017). It has been suggested that stressful life events set off a chain of biological responses, including inflammation, and that these, in turn, contribute to the development of depression (Slavich & Irwin, 2014). Similarly, stress and stress responses have been claimed to be involved in the development of depression (Wichers et al., 2009), placing stress as a possible precursor, not only for accelerated cellular aging, but also for depression. Thus, stress appraisals may play a prominent role in intensifying the implications of physical disability on cell senescence over depression, and perhaps they also induce a greater burden on allostasis (Monroe & Harkness, 2005).

Several limitations should be considered. First, given the gender effect on TL (Ghimire et al 2019), we enrolled only male participants, which limits the generalization of the conclusions to females. Second, the sample size is relatively small and lacked a priory group matching for age and education. Future, larger sample studies can better match the groups for background variables and consider additional biomarkers (e.g. pro- inflammatory and oxidative stress) in order to further illuminate mechanisms underlying shorter TL among people with physical disability. Third, as cell composition may vary across participants, we cannot rule out its possible influence on the reported TL. Fourth, since this is a cross sectional study, we cannot infer causality regarding the association between disability, perceived stress, and TL. Lastly, although the questionnaires assessing depression and perceived stress have relatively high validity (e.g., Beck et al 1988), they may be subject to biases related to self-reporting. It is recommended that future studies include clinical evaluations or stress biomarkers, in addition to self-reports in order to validate the stress levels.

In summary, the present findings indicate that participants with disability have a shorter TL than do the able-bodied controls, and that perceived stress, rather than depression, moderates the association between disability and TL. The findings shed light on the toll of stress among individuals with physical disability and its relationship with premature ageing. Furthermore, the findings suggest that interventions targeting subjective interpretations and perceptions related to stress may mitigate premature aging among individuals coping with SCI or polio-related disabilities. Outcome studies addressing perceived stress among non-disabled individuals seem promising (Stillwell et al., 2017) and may encourage studies on the use of similar interventions in disability cases.

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References

Arbeev, K. G., Verhulst, S., Steenstrup, T., Kark, J. D., Bagley, O., Kooperberg, C., Reiner, A. P., Hwang, S. J., Levy, D., Fitzpatrick, A. L., Christensen, K., Yashin, A. I., Aviv, A. (2020). Association of Leukocyte Telomere Length with Mortality Among Adult Participants in 3 Longitudinal Studies. *JAMA Network Open 3*, e200023–e200023. https://doi.org/10.1001/jamanetworkopen.2020.0023

Atowoju, A. A., Adegoke, B. O., & Babalola, J. F. (2015). Hypertension and obesity among paralytic poliomyelitis survivors in Nigeria. *Hong Kong Physiotherapy Journal, 33,* 21-27. https://doi.org/10.1016/j.hkpj.2014.10.002

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571. DOI: 10.1001/archpsyc.1961.01710120031004

Beck, A.T. (1967). *Depression.* Harper and Row: New York.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*, 77–100. doi:10.1016/0272-7358(88)90050-5

Cao, Y., DiPiro, N., & Krause, J. S. (2020). Association of secondary health conditions with future chronic health conditions among persons with traumatic spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *26*, 283–289. https://doi.org/10.46292/sci20-00020

Chu, E., & Lam, K. (2019). Post-poliomyelitis syndrome. *International Medical Case Reports Journal*, *12*, 261–264. https://doi.org/10.2147/IMCRJ.S219481

Cohen S, Kamarck T, & Mermelstein R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*, 385–96. https://doi.org/10.2307/2136404

Curran, P. J., West, S. G., & Finch, J. F. (1996). The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *Psychological Methods,*, *1*, 16-29. https://doi.org/10.1037/1082-989X.1.1.16

Denham J., O'Brien, B. J., & Charchar, F. J. (2016). Telomere length maintenance and cardio-metabolic disease prevention through exercise training. *Sports Medicine,* 1213-1237. doi: 10.1007/s40279-016-0482-4. PMID: 26914269.

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences*, *101*(49), 17312-17315. https://doi.org/10.1073/pnas.0407162101

Epel, E. S., & Prather, A. A. (2018). Stress, Telomeres, and Psychopathology: Toward a Deeper Understanding of a Triad of Early Aging. *Annual review of clinical psychology*, *14*, 371–397. https://doi.org/10.1146/annurev-clinpsy-032816-045054

Ferrucci, L., Gonzalez-Freire, M., Fabbri, E., Simonsick, E., Tanaka, T., Moore, Z., Salimi, S., Sierra, F., & de Cabo, R. (2020). Measuring biological aging in humans: A quest. *Aging Cell*, *19*(2), e13080. https://doi.org/10.1111/acel.13080

Galvin, L. R., & Godfrey, H. P. D. (2001). The impact of coping on emotional adjustment to spinal cord injury (SCI): Review of the literature and application of a stress appraisal and coping formulation. *Spinal Cord*, *39*(12), 615–627. https://doi.org/10.1038/sj.sc.3101221

Gavia-García, G., Rosado-Pérez, J., Arista-Ugalde, T. L., Aguiñiga-Sánchez, I., Santiago-Osorio, E., & Mendoza-Núñez, V. M. (2021). Telomere length and oxidative stress and its relation with metabolic syndrome components in the aging. *Biology, 10*(4), 253. https://doi.org/10.3390/biology10040253

Ghimire, S., Hill, C. V., Sy, F. S., & Rodriguez, R. (2019). Decline in telomere length by age and effect modification by gender, allostatic load and comorbidities in National Health and Nutrition Examination Survey (1999-2002). *PloS one, 14*(8), e0221690. https://doi.org/10.1371/journal.pone.0221690

Guan, J. Z., Guan, W. P., Maeda, T., Guoqing, X., GuangZhi, W., & Makino, N. (2015). Patients with multiple sclerosis show increased oxidative stress markers and somatic telomere length shortening. *Molecular and Cellular Biochemistry, 400*(1-2), 183–187. https://doi.org/10.1007/s11010-014-2274-1

Hayes, A. F. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling.

Hitzig, S. L., Eng, J. J., Miller, W. C., & Sakakibara, B. M. (2011). An evidence-based review of aging of the body systems following spinal cord injury. *Spinal Cord*, *49*(6), 684–701. https://doi.org/10.1038/sc.2010.178

Jang, Y., Poon, L. W., & Martin, P. (2004). Individual differences in the effects of disease and disability on depressive symptoms: the role of age and subjective health. *International Journal of Aging & Human Development*, *59*(2), 125–137. https://doi.org/10.2190/RT1W-2HD7-KG5X-K1FB

Jensen, M. P., Truitt, A. R., Schomer, K. G., Yorkston, K. M., Baylor, C., & Molton, R. (2013). Frequency and age effects of secondary health conditions in individuals with spinal cord injury: A scoping review. *Spinal Cord*, *51*(12), 882–892. https://doi.org/10.1038/sc.2013.112

Kariuki, M., Honey, A., Emerson, E., & Llewellyn, G. (2011). Mental health trajectories of young people after disability onset. *Disability and Health Journal*, *4*(2), 91–101. https://doi.org/10.1016/j.dhjo.2010.08.001

Keith, R. A., Granger, C. V., Hamilton, B. B., & Sherwin, F. S. (1987). The functional independence measure: a new tool for rehabilitation. *Advances in Clinical Rehabilitation, 1*, 6–18.

Kobasa, S. C., Maddi, S. R., & Kahn, S. (1982). Hardiness and health: a prospective study. *Journal of Personality and Social Psychology*, *42*(1), 168–177. https://doi.org/10.1037//0022-3514.42.1.168

Lahav, Y., Avidor, S., Stein, J. Y., Zhou, X., & Solomon, Z. (2018). Telomere Length and Depression Among Ex-Prisoners of War: The Role of Subjective Age. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *75*(1), 21–29. https://doi.org/10.1093/geronb/gby006

Lahav, Y., Levy, D., Ohry, A., Zeilig, G., Lahav, M., Golander, H., Guber, A. C., Uziel, O., & Defrin, R. (2021). Chronic Pain and Premature Aging - The Moderating Role of Physical Exercise. *The Journal of Pain, 22*(2), 209–218. https://doi.org/10.1016/j.jpain.2020.08.001

Lazarus, R. S., & Folkman, S. (1994). *Stress, appraisal, and coping.* New York: Springer.

Lequerica, A. H., Forchheimer, M., Albright, K. J., Tate, D. G., Duggan, C. H., & Rahman, R. O. (2010). Stress appraisal in women with spinal cord injury:

Supplementary findings through mixed methods. *International Journal of Stress Management, 17*(3), 259–275. https://doi.org/10.1037/a0019716

Lex, C., Bäzner, E., & Meyer, T. D. (2017). Does stress play a significant role in bipolar disorder? A meta-analysis. *Journal of Affective Disorders*, *208*, 298–308. https://doi.org/10.1016/j.jad.2016.08.057

Li, C., Clark, J., & Krause, J. S. (2021). Twenty-five-year cross-sequential analysis of self-reported problems: Findings from 5 cohorts from the Spinal Cord Injury Longitudinal Aging Study. *Archives of Physical Medicine and Rehabilitation, 102*(5), 888–894. https://doi.org/10.1016/j.apmr.2020.11.016

Liu, J., Wang, L., Wang, Z., & Liu, J. P. (2019). Roles of telomere biology in cell senescence, replicative and chronological ageing. *Cells*, *8*, 54. https://doi.org/10.3390/cells8010054

Luk, J. K., Cheung, R. T., Ho, S. L., & Li, L. (2006). Does age predict outcome in stroke rehabilitation? A study of 878 Chinese subjects. *Cerebrovascular Diseases, 21*(4), 229–234. https://doi.org/10.1159/000091219

McEwen B. S. (2013). The brain on stress: Toward an integrative approach to brain, body, and behavior. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science, 8*(6), 673–675. https://doi.org/10.1177/1745691613506907

Monroe, S. M., & Harkness, K. L. (2005). Life stress, the "Kindling" Hypothesis, and the recurrence of depression: Considerations from a life stress perspective. *Psychological Review, 112,* 417–445. https://doi.org/10.1037/0033-295X.112.2.417

Monroe, D. M., Goldstein, R. L., Teylan, M. A., Hart, J. E., DeVivo, I., Orr, E. H., & Garshick, E. (2019). Clinical associations with telomere length in chronic spinal cord injury. *Spinal Cord 57*, 1084–1093. https://doi.org/10.1038/s41393-019-0336-7

Mundstock, E., Sarria, E. E., Zatti, H., Mattos Louzada, F., Kich Grun, L., Herbert Jones, M., Guma, F. T., Mazzola In Memoriam, J., Epifanio, M., Stein, R. T., Barbé-Tuana, F. M., & Mattiello, R. (2015). Effect of obesity on telomere length: Systematic review and meta-analysis. *Obesity*, *23*(11), 2165–2174. https://doi.org/10.1002/oby.21183

O'Donnell, M. L., Varker, T., Holmes, A. C., Ellen, S., Wade, D., Creamer, M., Silove, D., McFarlane, A., Bryant, R. A., & Forbes, D. (2013). Disability after injury: The cumulative burden of physical and mental health. *Journal of Clinical Psychiatry*, *74*, 137–143. https://doi.org/10.4088/JCP.12m08011

Pierini, D., & Stuifbergen, A. K. (2010). Psychological resilience and depressive symptoms in older adults diagnosed with post-polio syndrome. *Rehabilitation nursing : the official journal of the Association of Rehabilitation Nurses*, *35*(4), 167–175. https://doi.org/10.1002/j.2048-7940.2010.tb00043.x

Puterman, E., Lin, J., Blackburn, E., O'Donovan, A., Adler, N., & Epel, E. (2010). The power of exercise: buffering the effect of chronic stress on telomere length. *PloS one*, *5*(5), e10837. https://doi.org/10.1371/journal.pone.0010837

Rentscher, K. E., Carroll, J. E., & Mitchell, C. (2020). Psychosocial stressors and telomere length: A current review of the science. *Annual Review of Public Health, 41*, 223–245. https://doi.org/10.1146/annurev-publhealth-040119-094239

Schutte, N. S., & Malouff, J. M. (2016). The relationship between perceived stress and telomere length: A meta-analysis. *Stress and Health*, *32*(4), 313-319. https://doi.org/10.1002/smi.2607

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin, 140*, 774–815. https://doi.org/10.1037/a0035302

Steptoe, A., Hamer, M., Lin, J., Blackburn, E. H., & Erusalimsky, J. D. (2017). The Longitudinal Relationship Between Cortisol Responses to Mental Stress and Leukocyte Telomere Attrition. *The Journal of clinical endocrinology and metabolism*, *102*(3), 962–969. https://doi.org/10.1210/jc.2016-3035

Stillwell, S. B., Vermeesch, A. L., & Scott, J. G. (2017). Interventions to reduce perceived stress among graduate Sstudents: A systematic review with implications for evidence-based practice. *Worldviews on Evidence-Based Nursing*, *14*(6), 507–513. https://doi.org/10.1111/wvn.12250

Sun, X., Jones, Z. B., Chen, X. M., Zhou, L., So, K. F., & Ren, Y. (2016). Multiple organ dysfunction and systemic inflammation after spinal cord injury: a complex relationship. *Journal of Neuroinflammation, 13*(1), 260. https://doi.org/10.1186/s12974-016-0736-y

Tellechea, M. L., & Pirola, C. J. (2017). The impact of hypertension on leukocyte telomere length: a systematic review and meta-analysis of human studies. *Journal of Human Hypertension, 31*(2), 99–105. https://doi.org/10.1038/jhh.2016.45

Uziel, O., Reshef, H., Ravid, A., Fabian, I., Halperin, D., Ram, R., Bakhanashvili, M., Nordenberg, J., & Lahav, M. (2008), Oxidative stress causes telomere damage in Fanconi anaemia cells – a possible predisposition for malignant transformation. *British Journal of Haematology, 142*, 82-93. https://doi.org/10.1111/j.1365-2141.2008.07137.x

WHO aging and health (2018). retrieved from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health, April 22, 2021

Wichers, M., Geschwind, N., Jacobs, N., Kenis, G., Peeters, F., Derom, C., Thiery, E., Delespaul, P., & van Os, J. (2009). Transition from stress sensitivity to a depressive state: longitudinal twin study. *The British Journal of Psychiatry: The Journal of Mental Science, 195*(6), 498–503. https://doi.org/10.1192/bjp.bp.108.056853

Wolkowitz, O. M., Reus, V. I., & Mellon, S. H. (2011). Of sound mind and body: depression, disease, and accelerated aging. *Dialogues in Clinical Neuroscience, 13*(1), 25. doi: 10.31887/DCNS.2011.13.1/owolkowitz

Table 1: Characteristics of the study groups (n=119)

	Participants with Poliomyelitis (a) (n = 34)	Participants with spinal cord injury (b) (n = 55)	Able-bodied participants (c) (n=30)	*F* or X^2	*Group comparison*
Age (M,SD)	59.97 (4.12)	53.13 (7.72)	50.27 (8.03)	17.01***	a>b,c
Years of education (M,SD)	12.12 (2.34)	14.91 (3.55)	12.90 (2.29)	10.20***	b>a,c
Marital status (married: n,%)	30 (88.2)	37 (67.3)	26 (86.7)	8.72	-
Occupational status (employed: n, %)	19 (55.9)	23 (41.8)	30 (100)	27.92***	-
Physical exercise (exercise: n, %)	21 (61.8)	29 (52.7)	8 (26.7)	8.51*	-
Weight (M,SD)	83.29 (14.39)	80.00 (13.81)	80.9 (15.04)	0.55	-
FIM score (> 90 :n,%)	7 (20.6)	7 (12.7)	30 (100)	68.93***	-
Depression Symptoms (M,SD)	27.71 (8.51)	31.35 (8.95)	21.57 (1.10)	15.97***	a,b>c
Perceived Stress (M,SD)	25.00 (10.05)	27.45 (9.56)	12.10 (6.24)	29.57***	a,b>c

Note: M= mean, SD= standard deviation, n= number, FIM= Functional Independence Measure. *p<0.05; ***p<0.001. The group comparisons column refers to *F*-tests only and compares the mean level of the variable in each group: a = Participants with Poliomyelitis, b=Participants with spinal cord injury; c= Able-bodied participants.

Table 2: Regression model exploring the moderating role of depression regarding the relationship between physical disability and telomere length (n=119)

		β	*R^2 change*
Block 1			
	Age	-.52***	.10
Block 2			
	Age	-.22	.33
	Physical disability	-.73***	
Block 3			
	Age	-.26*	.02
	Physical disability	-.75***	
	Occupational status	.02	
	Weight	.05	
	Physical exercise	.14	
Block 4			
	Age	-.31***	.09
	Physical Disability	-.55***	
	Occupational status	-.03	
	Weight	.03	
	Physical exercise	.04	
	Depression symptoms	-.39***	
Block 5			
	Age	-.31**	.00
	Physical Disability	-.50	
	Occupational status	-.03	
	Weight	.03	
	Physical exercise	.04	
	Depression symptoms	-.44	
	Physical Disability X Depression symptoms	.06	

Note: All study variables were standardized. *p<0.05; **p<0.01; ***p<0.001

Table 3: Regression model exploring the moderating role of perceived stress regarding the relationship between physical disability and telomere length (n=119)

		β	R^2 *change*
Block 1			
	Age	-.52***	.10
Block 2			
	Age	-.22	.33
	Physical disability	-.73***	
Block 3			
	Age	-.26*	.02
	Physical disability	-.75***	
	Occupational status	.02	
	Weight	.05	
	Physical exercise	.14	
Block 4			
	Age	-.34***	.20
	Physical Disability	-.31**	
	Occupational status	-.08	
	Weight	-.04	
	Physical exercise	-.05	
	Perceived stress	-.66***	
Block 5			
	Age	-.37***	.03
	Physical Disability	-.59***	
	Occupational status	-.10	
	Weight	-.01	
	Physical exercise	-.05	
	Perceived stress	-.47***	
	Physical Disability X Perceived stress	-.34**	

Note: All study variables were standardized. *p<0.05; **p<0.01; ***p<0.001

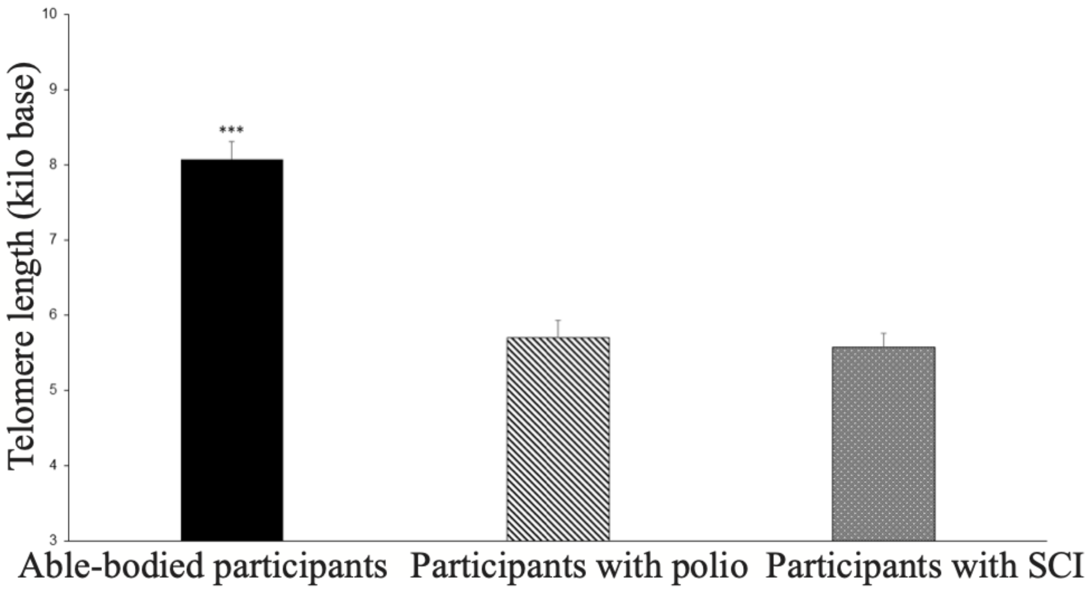

Figure 1. Difference between able-bodied participants, participants with polio, and participants with SCI in TL, adjusting for age, weight, and physical exercise (***p<0.001). Values represent the means and standard errors.

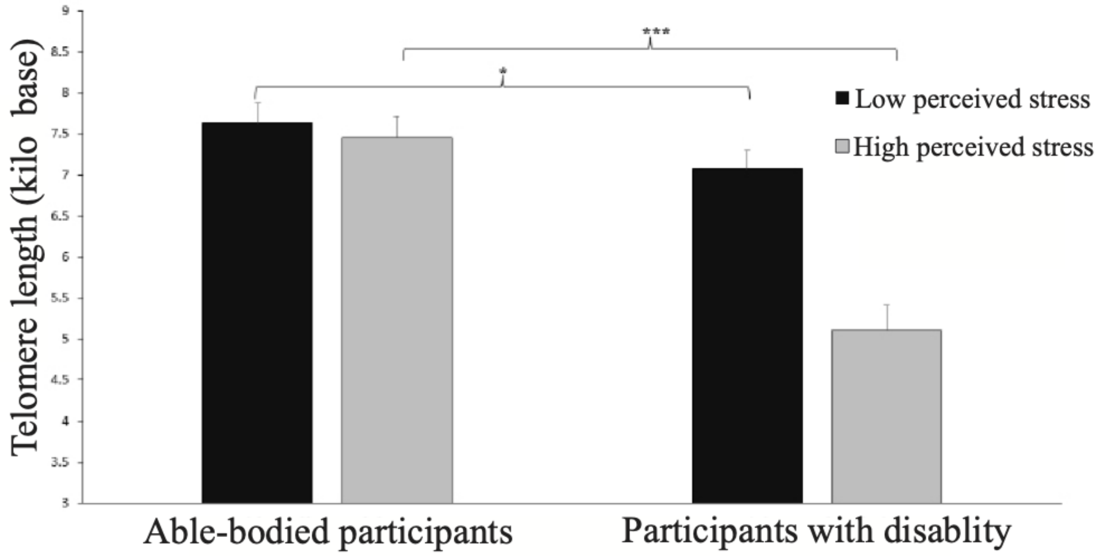

Figure 2. The moderating roles of perceived stress in the relationship between physical disability and TL (*p<0.05; ***p<0.001). Values represent the means and standard errors.