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Effects of Stress Coping Mechanisms on Telomere length: A literature review.

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Effects of Stress Coping Mechanisms on Telomere Length: A Literature Review

by

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Dedication

This publication is dedicated to my daughter Ellisyn Ross, always aim for the sky.

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Effects of Stress Coping Mechanisms on Telomere Length: A Literature Review

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Abstract: Studies of telomeres in humans are inconsistently related to exposure to stressors but strongly related to cell life cycle and cell senescence. Cell level stressors are related to reductions in telomere length as well as some social stressors showing moderate associations with telomere length. However, very little data has been produced in the arena of stress reducing coping mechanisms and their effects on telomere length. No systematic review of these coping mechanism effects on stress has been previously published. The goal of this review is to collect, assess, and review the English language human studies dealing with stress coping mechanisms and telomere length.

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

UTMB	University of Texas Medical Branch
GSBS	Graduate School of Biomedical Science
MPH	Masters of Public Health

Chapter 1 Introduction

TELOMERES

The end caps of chromosomes are repeating sequences of nucleic acids that buffer errors in cell replication and shortening - these end caps are called telomeres (1). Telomere shortening is thought to herald the end of a cell's ability to replicate. This end of replication is called senescence, and if a majority of an organism's cells or one organ system's cells reach senescence with no replacement, then the organism dies. Telomere shortening is the genetic cause of the majority of the effects of aging (1). Some evidence suggests that as our telomeres shorten we age and our health declines. Poorer health in older ages may be due to acquired illnesses and injuries, or simply due to different organ systems entering senescence and experiencing a decline in function. Some studies suggest that a healthy human loses telomere length at a reduced rate compared to a stressed or ill person. People who are chronically ill or under chronic stress often appear to be older than others of the same chronologic age because they have experienced accelerated aging at a genetic and cellular level (2,3). Understanding the effects of stress on telomere length as it relates to health and aging is a vital next step in many areas of health and medicine focusing on chronic illness and aging.

STRESS

At a cellular level, it is well known that high cellular stress environments are associated with early telomere shortening, senescence, and cell death (1,2,3). The classic laboratory examples of these states include highly oxidative environments or high levels

of free radicals (4,5). These biomarker cellular studies showed a need for studies of what happens when an entire organism is under stress. Many of these studies provided evidence that systemic stressors to an organism is associated with telomere shortening. The studies that are of interest in the current review are the ones that showed telomere shortening due to behavior or situations that can be potentially altered, such as interventions including psychosocial, dietary, or addiction. No study has shown that any single individual will die earlier due to shorter telomeres. However some of the limited number of studies at the population level show that there is correlative data to suggest that populations with longer telomeres on average may also have may also have a longer average life expectancy (6,7,8). There are many things that are not currently known in the studies of connecting telomere length to stress and future health; however, one key component that has been overlooked thus far is coping (9). The effect of coping mechanisms and interventions to lower stress and their effects on telomere length are woefully understudied as will be discussed in this review.

CHAPTER 2 BACKGROUND

SPECIFIC AIMS

Empirical studies demonstrate that cellular stressors, such as oxidative stress and high free radical environment, shorten telomere length and induce early cell senescence causing premature cellular death (4, 5). However, there is inconsistent research on how strong the connection is between exposure to stress, stressors, and telomere length in human studies. There is even less research on an important component of the stressor-biomarker relationship in humans – coping. Thus, the goal of this capstone is to provide a review of the literature focusing on the connection between coping mechanisms and telomere length in human studies.

SIGNIFICANCE

Telomeres

Telomeres are specialized nucleotides found at the distal ends of chromosomes. In humans, telomeres are thousands of repeating sequences of TAGGG (1). The repetition of TAGGG in humans and analogous sequences in other organisms allow for the protection of the chromosomal terminus from deleterious effects during replication including chromosome shortening and aberrant replication allowing the continued replication of cells. This is important because without the ability to repair or prevent mutations or damage to our DNA, we would die much more quickly. Different cell lines show different effects of replication depending on the length of the terminus telomere length. Cell lines with intact telomere chains are resilient to replication errors and allow

for appropriate organism growth and function. Generally, people who are genetically older and have shorter telomeres are younger in age "genetically" compared to people who are younger with longer telomeres. This is vital to future health research to understand what we can do to promote healthier and more resilient chromosomes and understand if this provides longer lived and healthier human populations (1, 10, 11).

Stress

Stress is a broad term with very applicable specific definitions. A general well accepted definition of stress is a physical, chemical, or emotional factor that causes bodily or mental tension and may be a factor in disease causation. The basic biologic empirically testable definitions include exogenous and endogenous cellular stress. More general acute and chronic stresses on organisms can be associated with more measurable empiric cellular stresses. This literature review will provide evidence from human studies that examine the connection between exposure to some aspect of psychosocial stress, telomere length, and coping.

Stress and Telomere Length

Oxidative stress can shorten the time a cell can maintain an integral telomere chain (1). In stable conditions, cells in high oxidative stress environments have exponentially shorter telomeres than those in low oxygen environments (1). The cell lines with shortened telomeres can participate in fewer cell replications and enter cellular senescence more quickly (6). Some studies have shown a positive correlation with psychosocial stressors while some have shown none (3,4,5,6,7,8,9).

Preservation of telomere length and lack of psychosocial stressors are correlatively linked and provide a basis for this review. Telomere preservation is one proposed aspect of a person's ability to maintain health while aging in that telomeres function of cell replication protection could lead to a cell lines ability to replicate accurately over the course of more cycles. As we move into the future of medicine, protective preventive measures and lifestyle changes are becoming the focus of effective care. Research shows that early incremental behavioral interventions on chronic illnesses such as diabetes and hypertension can have a greater long term effect than heroic medication and surgical interventions later in the disease process (8). Low psychosocial stress is related to lower all-cause mortality and better mental health outcomes in the general population - thus, the focus of this review is to examine data looking at interventions that reduce psychosocial stress and potentially increase telomere length.

Telomere Length and Coping

Shortening of telomere length and the resulting cellular senescence are synonymous with the end of a cell line, organ, organism, or person's ability to replicate genetic material accurately. If human somatic cell lines cannot replicate, then the human cannot participate in cellular turnover and systemic renewal (2, 3). In biological terms, cellular senescence at an organism level would cause the death of the organism as existing cells stop functioning and cannot be replaced.

The factors that increase telomere length include low oxidative stress and low free radical states. It is proposed that human coping mechanisms at a psychosocial level could

lower inflammation and lower stress hormone states – all implicated pathways in more stable cellular environments and in longer and healthier lifespans for individuals (7, 8, 9).

TELOMERE LENGTH AND AGING

The empirical data provided by cell and nucleic acid studies show that specific cellular and molecular environments shorten telomere length and cause early death of any organism (4, 5). The proposed mechanism of psychosocial stress to a person's cellular stress and early death is proposed but not proven. This literature review will review existing knowledge on systemic stress coping mechanisms to preserved telomere length and, thus, provide a basis for an avenue of study in the area of longer and healthier lives.

VARIOUS TELOMERE EFFECTS

Telomeres can be shortened quickly in high stress environments such as poisoning, radiation, or lack of oxygen. If an environment becomes too toxic, then telomere shortening does not matter as direct genetic and cellular damage kill the person long before telomere senescence (12, 13). Also, short term low stress environments allow for effective and genetic cellular repair and likely do not affect overall person's health in the long term (1). Given these parameters, we will focus on the chronic human psychosocial stress coping mechanisms have on telomere length in this literature review.

POSSIBLE USES FOR TELOMERE AND STRESS RESEARCH

Telomeres are a determinant of how we age but also an indicator of the aging process. Stress has been linked as a mitigatable factor with some interventions. By looking into how different types of psychosocial stress coping affect telomere length, research can better understand the effects of stress and coping on aging and identify potential interventions. An example of theoretical future potential public health research on telomere length with possible stress mitigation techniques and healthy living policies

put into practice. These possible interventions could include mediation and physical education.

In summary, this review will focus on coping mechanisms for psychosocial stress on telomere length. Telomere length is a marker for an organism's overall ability to accurately participate in replication and continue living. Psychosocial stressors are potentially related to premature reductions in telomere length and in poor health outcomes. What is even less well known is if any of the current psychosocial stress coping mechanisms mitigate the shortening of telomeres. This information will allow application of public health policy to the issue of chronic psychosocial stressors at a population level.

CHAPTER 3 METHODS

The review inclusion criteria included English language, peer reviewed journal publications including the search terms stress, coping, and telomere length. The publications included original research articles, study design, and commentary about peer reviewed research. Five databases were searched for the terms stress, coping, and telomeres. The databases used were Pubmed, Ovid, CINAHL, Cochrane Library, and Web of Science. The data collection phase produced 62 publications. After applying inclusion criteria of modern English language studies involving telomere length, stress, and coping mechanisms, eleven articles were determined to meet the criteria and provide original data or insight appropriate for this review.

For each article, the insights, strengths, weaknesses, and proposed next steps were recorded. For research articles, the study design, sample size, population, study length, gender, telomere evaluation method, and correlation findings were assembled. For non-research articles, the source, original contribution to the discussion, or original path forward were evaluated.

The quality for each study was assessed with four different factors. Study sample size was the first consideration for quality as it speaks to the statistical impact of the studies. Second, the study design was evaluated, with randomized controlled trials given the greatest consideration, followed in order by longitudinal or semi longitudinal studies,

cross sectional studies, research design papers, and finally response articles in peer reviewed journals. Third, the population source was evaluated to determine generalizability of results. Fourth, study length and/or post study follow up was documented.

CHAPTER 4 RESULTS

Eleven articles are included in this review. The studies covered a variety of human populations including: veterans, victims of abuse, religious people, depressed patients, obese patients, men and women of varying social support, cancer patients, and people dealing with addictive substances. The results section will present the articles with a brief summary and short discussion of their strengths and weaknesses.

LONGITUDINAL STUDIES

Qigong is an ancient form of mindfulness exercises. One longitudinal study of a female cohort in China, who suffered from domestic violence, with a sample size of 240 demonstrated that qigong, an intervention based in meditation, breathing, and exercise was associated with an increase in the activity of telomerase and a decrease in the level?? of pro-inflammatory markers (14, 15). This study has the highest impact due to longitudinal design, and the results strongly support preservation of telomere length. This study of Chinese women is powerful but could be of greater value if it provided longer and more comprehensive follow-up of a larger study population with a broader geographic scope and both sexes.

A similar study with a more modern version of mindfulness is also included in this review. This study examined mindfulness-based interventions for people dealing with the stress of living with cancer. The intervention was set up as 8 week, 2.5 hour weekly sessions including meditation, yoga, and living in the present for the experiment groups and no mindfulness intervention in the control groups in the MINDSET and

I-CAN trials (N=381). The difference between the experiment and control groups demonstrated across the board telomere length preservation when controlling for other factors (21). Similar to the Chinese study, modern methods of mindfulness produced positive preservation of telomere length by decreased shortening.

Another similar study focused on a specific version of mindfulness referred to as cognitive behavioral therapy. A longitudinal study of United States Veterans demonstrated reduced telomere length with increased levels of hostility (20). However, an intervention of cognitive behavioral therapy applied appropriately by trained professionals provided a promising mechanism of telomere preservation (20). Mindfulness exercises all have shown an increase in positive mood and outlook. Given this fact, two studies proposed that increase mood and outlook would allow for telomere preservation (23, 24). This proposal is supported by a study that demonstrated that negative mood and negative outlook are associated with reduced telomere length (23, 24).

CROSS-SECTIONAL STUDIES

Multiple cross sectional studies are included in this review. The power of cross sectional studies lies in large sample sizes but all cross sectional studies lack follow-up and suffer from selection bias. The cross sectional studies reviewed here generally show a preservation of telomere length, with a few being neutral, null, or negative. Below, the cross sectional studies will briefly be discussed in terms of their contribution to this review. First, one cross sectional study dealing with quality social interactions and depression on telomere length in Sweden demonstrated statistically increased telomere length in men and no statistically significant increase in women (16). In another study,

self-reported religious affiliation was associated with increased telomere length. However, another study of one county in the United States using the same measures of religious support as defined by quality of social interactions did not correlate with longer telomere length (17). Both a commentary and response to this study pointed out that a longitudinal study of more individuals is the next step in study design (18,19).

Depression is associated with shorter telomeres (16). A cross sectional study of 954 participants demonstrated preservation of telomere length in depression with specific coping mechanisms. The coping mechanisms that demonstrated longer telomere length include high quality sleep, stronger social connections, lower emotional suppression, and increased exercise. The findings of increased social connections and improved mindfulness preserving telomere length are largely concordant with prior studies as described above.

MULTIFACTORIAL STUDIES

Finally, multiple studies have evaluated the outcomes of reduction of psychosocial stress by a multitude of coping strategies, focusing on any means of reduction of psychosocial stress instead of one path to reduction. In general, outcomes that demonstrated telomere preservation include reduced BMI and exercise. Social interactions showed indeterminate outcomes, some positive and some with no effect (21,22,23,24). Lastly low sleep and cigarette use correlated with reduced telomere length (22).

CHAPTER 5 DISCUSSION

SUMMARY

As expected from prior studies, the review demonstrated moderate evidence between coping mechanisms, reducing psychosocial stress, and reduced shortening or preservation of telomere length. The majority of the studies demonstrated that a version of mindfulness or meditation and exercise coping mechanisms had protective effects on telomere length in subjects under stress (14, 15, 20, 21, 22, 23, 24) . Social support did not show as consistent results. As a coping mechanism, social support demonstrated inconsistent results with telomere length in two studies, was indeterminate for women in another study while being beneficial to men, and showed general benefit in one study (16, 17, 20, 22). Another coping mechanism, higher levels of self-reported religiosity, demonstrated a correlation to longer telomere length (17, 18, 19). Unhealthy psychosocial stress coping mechanisms generally correlated to shorter telomeres including smoking, poor sleep, hostility, and negative mood.

WEAKNESSES

The field of stress, coping, and telomere length has a significant lack of long term, large samples or randomized controlled studies. The majority of the current discussion is driven by cross sectional studies with limited follow up and small to modest study sample size. Some coping mechanisms cannot be randomized such as religiosity but others could be the subject of multicenter clinical trials to answer significant current limitations including lack of clear pathways in which stress, coping, and telomere length are related.

STRENGTHS

A large portion of the human population has experienced or will experience chronic stress of some variety. It has been well demonstrated in some studies that a correlation between psychosocial stress and reduced telomere length may exist, but no causational studies are presently available. In the future quality data concerning telomere length preservation and coping may have a significant impact on human health.

FUTURE STEPS

One of the jobs of public health is to take scientific data and apply it to the populations we serve. There are many public health interventions dealing with areas of chronic genetic and cellular damage that shorten people's lives. Some examples include smoking, alcohol abuse, pollution, and radiation exposure. While it is a widely held view that populations with longer telomere lengths are healthier with longer lives, there is still much research to be conducted to connect specific stressors and coping mechanisms with long term health outcomes. As evidence grows for the connection of telomere length to systemic psychosocial stress, there will continue to be two vital steps to demonstrate. First, how do we stop psychosocial stress from reducing telomere length; and second, which psychosocial stress coping mechanisms preserve telomere length and provide a longer and healthier life? These are key questions that continue to be an important part of telomere and public health research.

Multiple small longitudinal and/or cross sectional studies reviewed here demonstrate that coping mechanisms are associated with longer telomeres in specific

populations. In this paper, we have reviewed these articles and the research behind them. One of the main points of this review is that mindfulness is a promising positive coping mechanism in multiple populations across multiple countries. However, in all aspects of psychosocial stress coping, the next step in this discussion is to take the results of the currently available studies and pursue large rigorous trials to provide an evidence base for implementing psychosocial stress relief coping mechanisms.

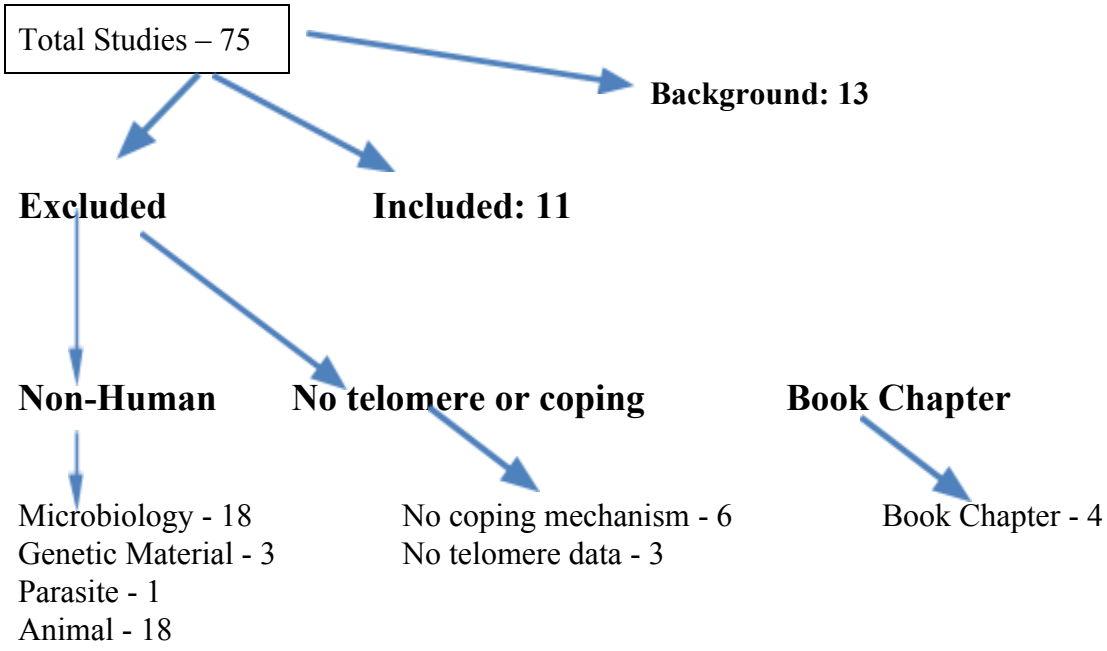
Appendix A Tables

Table 1: Results Table

		Remaining Studies
Total studies:	75	
Background References:	13	62
Microbiology exclusion:	18	43
Animal study exclusion:	18	25
No coping exclusion:	6	22
Book chapter exclusion:	4	18
No telomere exclusion:	3	15
Genetics exclusion	3	12
Parasite exclusion:	1	11
Accepted Studies:	11	0

Appendix B

FIGURE 1: Studies included in Review



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Vita

Jillian R Ross was born in 1981 in New Mexico. She is the first member of her family to achieve a Bachelors of Science degree. Her degree was awarded by Sul Ross State University summa cum laude in 2008. Jillian is the first member of her family to pursue any form of advanced degree. She is currently a student at UTMB in Galveston, TX. She is expected to graduate in Summer 2018 with an MPH degree.

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