IMPACT OF LIFESTYLE, NUTRITION, AND STRESS ON TELOMERE SHORTENING, MORTALITY, AND INCIDENCE OF AGE-ASSOCIATED DISEASES IN HUMANS

by

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ABSTRACT

When human and animal cells divide, they go through the cell cycle to replicate their DNA and ensure that all new cells receive a copy of each chromosome. Most of the chromosomal DNA is replicated accurately and efficiently by large enzyme complexes called DNA polymerase delta and DNA polymerase epsilon. A problem arises, however, with DNA replication at the ends of chromosomes in regions called telomeres. Telomeres are short in comparison to the full length of a chromosome and act as protective caps at the ends to prevent degradation. The two major DNA polymerases cannot replicate the ends completely and small numbers of base-pairs are lost from the telomeres with each replication cycle. Such ends must be replicated by a specialized DNA polymerase called telomerase. Most human cells stop producing telomerase during embryonic development and the telomeres subsequently get shorter over time. The rate of telomere shortening varies among individuals and evidence suggests that people with shorter telomeres have increased vulnerability to age-associated diseases such as heart disease, cancer and other ailments. Rates of telomere shortening are influenced by several factors. These influences include nutrition, psychological factors, lifestyle/behavioral choices, plus other predetermined factors like biological sex and genetics. In the current study the medical literature related to telomere shortening and human health has been comprehensively reviewed and the results summarized.

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TABLE OF CONTENTS

Page

LIST OF FIGURES

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Page

I. INTRODUCTION

The chromosomes within human cells are long, linear polymers of DNA that have several components. These features include relatively short sections at the chromosomal DNA ends known as telomeres as well as subtelomeric regions that serve as a bridge between the telomeric repeats and the DNA (Figure 1).

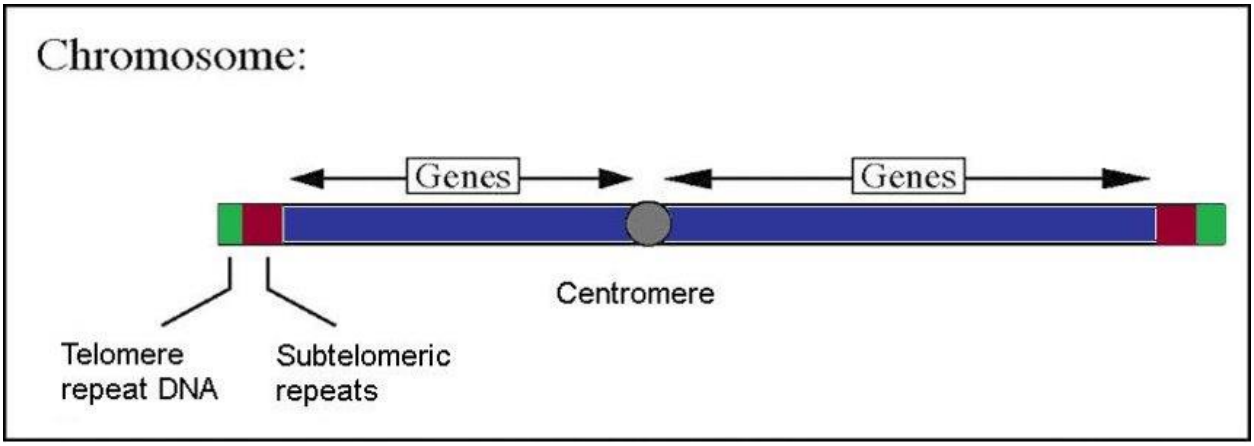

Figure 1. Diagram representing major features of human chromosomes including the telomere caps at the DNA ends.

Chromosomes contain a centromere that serves as the point of attachment of the mitotic spindle during mitosis which plays a vital role in cell division. The majority of the chromosome consists of genes that code for proteins or functional RNAs as well as some inactivated gene regions that are non-coding. The information encoded within chromosomes plays an important role in the function of various bodily processes and each gene serves a specific purpose. This information dictates the function of various cell types, regulates cell function and ultimately plays a role in cell division, a critical component of growth, reproduction, and repair in multicellular organisms. This process allows cells to duplicate their DNA and create new cells through a series of phases (G_1, S,

G_2, and M), with DNA replication specifically occurring during S phase. For all eukaryotes, and even more specifically, humans, the majority of DNA is replicated through a process involving two main DNA polymerase enzymes (polymerases delta and epsilon). These proteins, combined with a few other necessary proteins, allow the double-stranded molecule to be opened and prepped for duplication. During replication, two types of new strands emerge: the leading strand in the 5'-3' prime direction and the lagging strand in the 3'-5' prime direction. Due to limitations in the process in which DNA replicates, the lagging strand is left with gaps in the new DNA strand that are later filled in by an enzyme called ligase. The issue lies at the end, where ligase cannot fill in the remaining gap, nor can a polymerase add the rest of the DNA without a primer to work off of. Here, we find telomeres.

Telomeres contain a repeating segment of TTAGGG bound by several proteins which serve as a cap to protect the ends of the DNA strands, similar to how aglets protect the ends of a shoelace from fraying and falling apart. The manner in which telomeres protect DNA extends beyond just adding extra length to the chromosome as the lengthened ends form a loop (often referred to as a T-loop) as seen in Figure 2 (1).

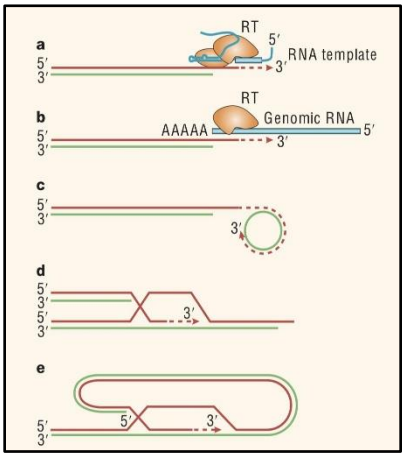

Figure 2. T-loop structure of telomere at DNA end (1).

This structure confines the very end of the strand inside of a bubble of sorts that keeps it safe from exonuclease degradation and other damage it may experience. One type of damage that telomeres will suffer is the loss of short fragments with each successive replication cycle (2-4). As referenced earlier, limitations of DNA replication leave a gap at the end of the lagging strand, and without any factors to fill that gap, it will thus be shortened. Luckily for eukaryotic organisms, a special complex called telomerase alleviates that exact problem.

Telomerase is a ribonucleoprotein complex that is responsible for the elongation of DNA caps in eukaryotes. This complex contains both a reverse transcriptase portion as well as an RNA portion that contains the necessary template to elongate the telomere (Figure 3).

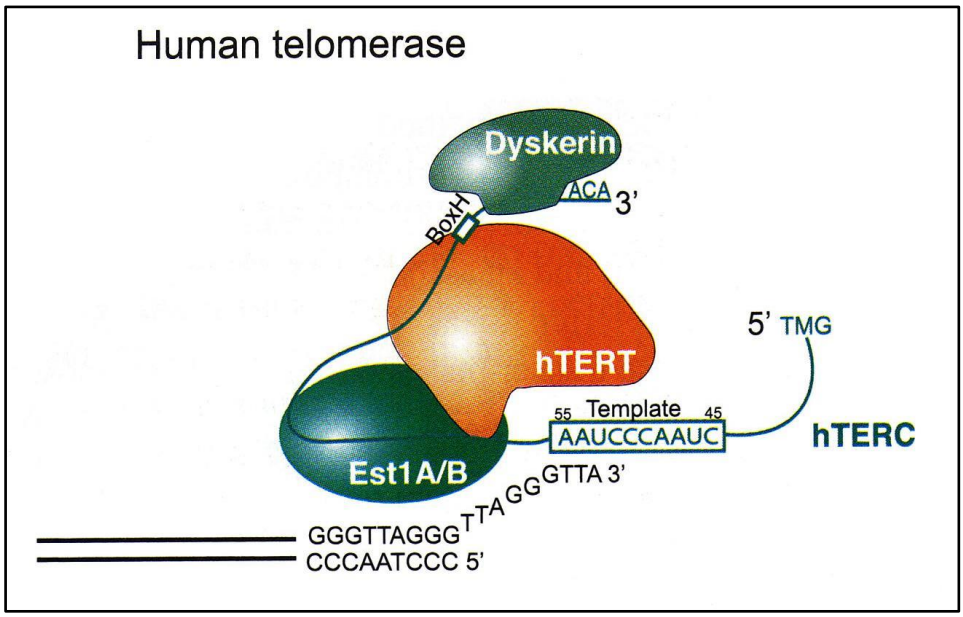

Figure 3. Human telomerase structure (5).

While telomerase is an important player in cell division, its use is short-lived, with its production being turned off in almost all normally functioning cells in the body. Unlike specific cells such as epithelial, lymphatic, and germ line cells where telomerase is constantly on to keep these important cells replicating, most other cells will lose telomerase function during development. Turning off telomerase leads to cells developing a replication limit otherwise known as the Hayflick limit. As cells lose more of their telomeres and reach a hazardously short length, they enter a state of senescence in which they are under cell arrest and can no longer replicate. At this point, these cells become marked for apoptosis where they are then broken down and recycled. While it may seem counterintuitive to turn off such an important enzyme, it is advantageous that telomerase function is halted as a constant surplus of telomerase in cells increases the likelihood that cells will reach a state of replication immortality. In the event that telomerase is turned on in cells where it was otherwise dormant, the cells have increased potential to become cancer cells. Most human cancer cells have acquired mutations in a few specific genes regulating cell growth and have also turned telomerase expression back on.

Although the inactivation of telomerase occurs for a reason, that does not negate the reality of the harmful impacts that are derived from short telomeres. It is expected and observed that as humans age, their telomeres will slowly shorten in most somatic cells. They begin at a set amount and, with no active telomerase available to lengthen them, it is inevitable that they will experience gradual attrition. However, after experimentation, it has been discovered that the rates at which one's chromosomes shorten vary from person to person. For individuals that had higher rates of telomere degradation, there was a

correlated increase in the likelihood of disease and a heightened mortality rate compared to those with longer telomeres at the same age (6-8).

It has been observed that there is considerable variation seen in telomere lengths among individuals of the same age groups. This thesis project will focus on three main areas that contribute to such differences: lifestyle choices, nutritional factors, and psychological stress; however, there are two other factors that are worth noting: biological sex and genetics.

When it comes to human aging, it is known that men age quicker than women and thus it has been speculated that such differences in rates of aging can be explained by sexual differences in telomere attrition. While there have been no studies that have found telomeres to be the main driver in these differences in aging between the sexes, it remains a common belief that telomere attrition still plays a critical role in this process. Some research has suggested that one confounding factor in the mechanism explaining the role of telomeres on aging differences could be through hormones (9). This study highlighted the ability of the steroid hormone estrogen to promote the expression of telomerase in cells and, as women have higher levels of estrogen, it implies that this ability can result in longer telomeres than in their male counterparts. One important note to make on this connection is that this is mainly seen in cancer patients and that telomerase, in normally functioning cells, does not get turned back on once it has been inactivated. However, the influence of estrogen on telomerase could play a role in the starting length of telomeres as biological women have longer telomeres at birth than biological men. This difference could also be explained by expression differences in other proteins such as dyskerin, which plays a key role in telomerase function (10). However, other studies have revealed

that the differences found in telomere lengths between men and women were not always detectable using previously published research techniques (11). Fisher and Riddle go on to propose that there is a need for more research in this area to determine a strong link to explain the differences observed in aging between the sexes.

As the field of genetics grows and develops, more connections to the underlying mechanisms behind some diseases and conditions become clear. One such instance of this is the emerging group of health conditions labeled as Telomeropathies. These are a collection of disorders and ailments that stem from telomere-related issues. Dyskeratosis congenita is one such telomeropathy as it stems from defects in any one of six genes as explained by (12). The authors explain that four of these genes are related to the telomerase complex and thus, those with this defect experience shorter-than-normal telomeres whereas the other two genes are responsible for the complex that protects the telomere ends of DNA which results in increased telomere damage (12). There are a multitude of other conditions that are associated with genetic defects relating to telomere/telomerase structure and function. With more research, more conditions will likely be linked to such defects. Although conditions such as these do greatly impact the length and function of telomeres, the focus of this study will instead be on those without such conditions in order to evaluate other factors that may impact telomere length.

II. MATERIALS AND METHODS

MATERIALS

All resources used in this thesis were searched for and obtained through the use of the Public Medline (otherwise noted as PubMed) database or through an initial search through Google Scholar followed by Full PDF access through the Texas State University database engine.

METHODS

Each focus factor analyzed in this thesis was individually searched with the respective keywords and specifications listed below.

A. Background on Telomere Shortening

All papers in this category were identified with a variation of three searches, all with the common requirement of a "Title/Abstract" specification in the Advanced search options within the PubMed software. With this designation, searches were conducted with keywords "telomere shortening", telomere and aging, "telomere length" and health, "telomere length" and aging, and telomere and lifestyle. Multiple words were placed within quotation marks in the PubMed search box when it was important to match a specific word order.

B. Telomeres and Lifestyle

A similar pattern was repeated here with searches conducted using keywords of "telomere", "telomere length" and "telomere shortening" with the keyword "lifestyle".

C. Telomeres and Nutrition

Once sufficient sources were found for the correlation between telomere structure/length and lifestyle factors, a similar search was conducted instead searching for a link with the keyword "diet".

D. Telomeres and Psychological Stress

Lastly, this process was repeated including the keywords "psychological stress". An initial search using just the keyword "stress" brought up search results that were also found with the search using the keywords "psychological stress". Since the clarification of psychological stress was more specific to what is being addressed in this section, this was the primary search term used for this focus area. Simply using the keyword "stress" resulted in publications that focused on oxidative stress and, while this research is important to understanding the mechanisms behind telomere and overall DNA damage, it was not a key factor that was observed for this thesis.

After the initial searches were conducted, the results were filtered to determine which were most relevant to the focus of this paper and to factor out any relevant results that may have been published in the far past and have since been superseded by more recent findings/publications.

This study considered many variables such as genetics, gender-association, geographical impacts, socioeconomic status, nutrition, psychology, and lifestyle and ultimately determined that the latter three were the major factors identified in past research.

III. RESULTS AND DISCUSSION

To develop a solid understanding of the current research that has been done in the area, search data collected from PubMed was plugged into graphs to allow for easy identification of when the field gained momentum as well as when specific topics gained more insight. The first three graphs below (Figures 4, 5, and 6) showcase 1991 as an important year marking the beginning of research relating to telomeres and human aging. The search terms were "telomere shortening" (Figure 4), telomere + aging (Figure 5), and "telomere length" + aging (Figure 6). The first major publication covering the mechanisms underlying telomere and telomerase function that was known at the time was authored by Nobel prize winner Carol Greider (Figure 4). At the same time, the Human Genome Project had just begun and a new wave of research regarding genetics and the human genome had taken off. This was followed by a similar increase in interest (Figures 5 and 6) in the relation between telomere length and attrition to the aging processes that occur in humans as well as other eukaryotes.

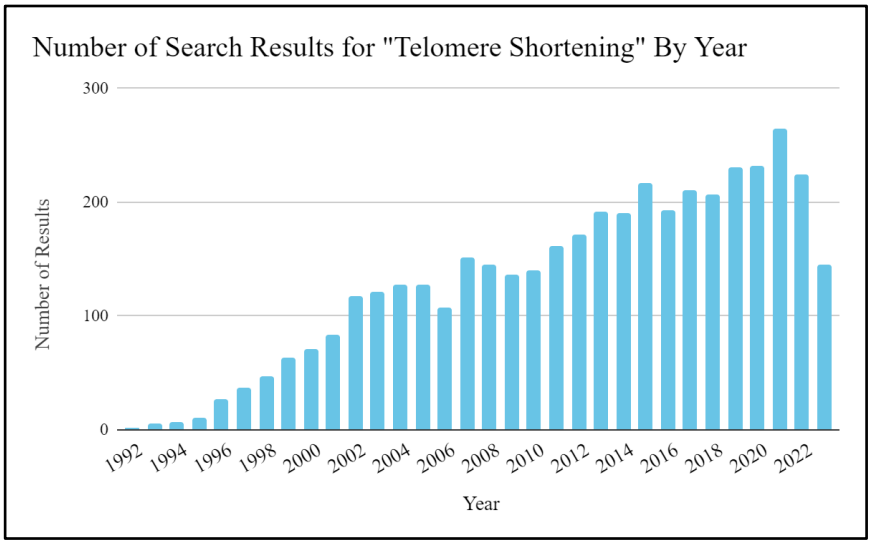

Figure 4. Search result graph for “telomere shortening” by year.

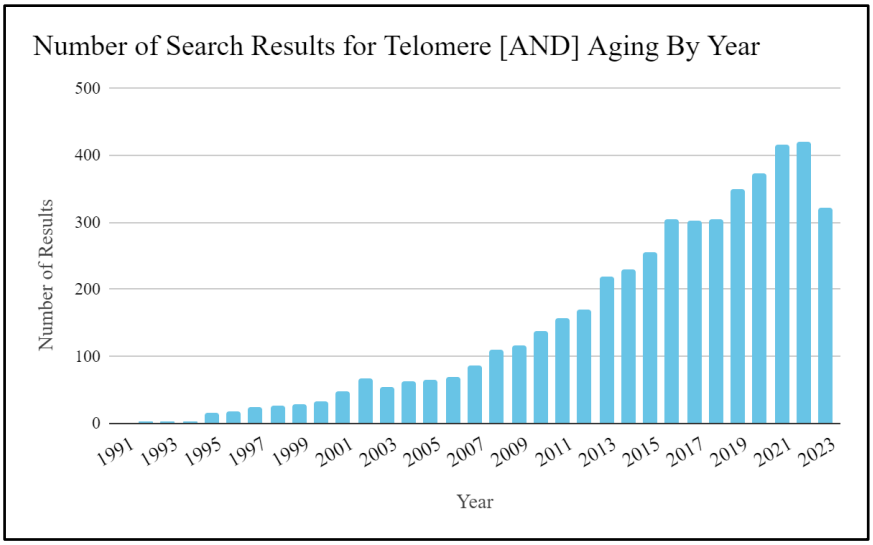

Figure 5. Search result graph for telomere + aging by year.

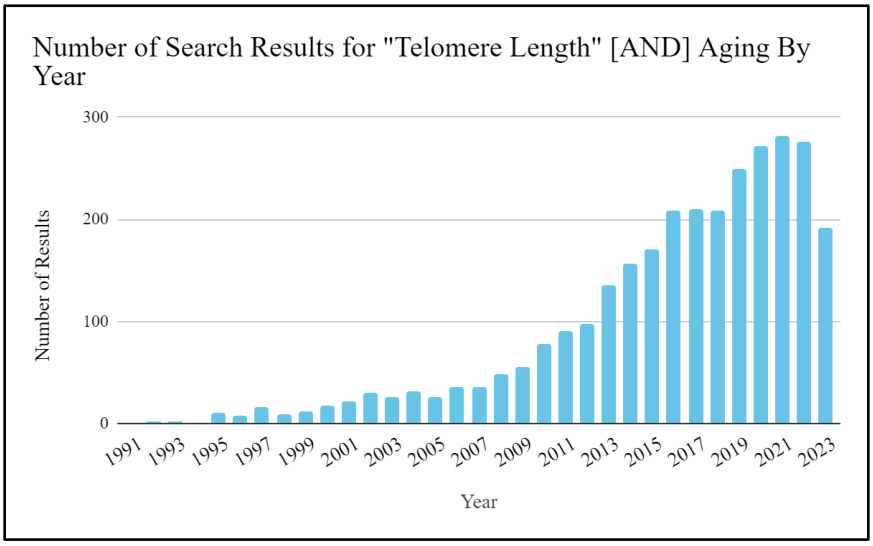

Figure 6. Search result graph for “telomere length” + aging by year.

Once a solid base of knowledge was established, it was easier for researchers to utilize that knowledge to uncover more pieces to the puzzle, and in 2003, Richard

Cawthon et al. did just that (6). Here, they had a major breakthrough and found a significant correlation between telomere lengths and human mortality rates. Cawthon et al. presented evidence that individuals with shorter telomeres compared to others of the same age were two times as likely to die and were three times as likely to succumb to heart disease (6). One important note that was mentioned at the end of the study was that while there was a correlation between telomere shortening and aging, there could be genetic and environmental factors at play that augmented the impacts of the shortening. This is a point that will be further explored at a later time in this thesis. Building off of the research that was done by Cawthon and his team, several other studies found a similar link between the degradation of telomeric repeats and an increase in mortality rates (13-15). While the research does point to an important connection between leukocyte telomere length (LTL), which is the most common cell used to study telomere lengths, other research has suggested that the correlation loses statistical significance after about 60 years of age (16). Martin-Ruiz et al. propose that these values are not reliable to form a prediction on mortality outcomes past about 60 years of age due to the high instability of telomeres past this age. At this point, it is assumed that the damage inflicted on telomeres throughout life causes them to vary in lengths and stabilities past 60 years of age, which makes it difficult to establish a reliable comparison between subjects' telomere length and their respective mortality predictions (16).

As more research revealed a link between telomeres and the process of aging, interest in how the length of telomeres corresponds with overall health began to increase, beginning in 2001, as shown in Figure 7. This wave of research demonstrated that short telomeres were an indicator of increased risk for health conditions such as heart disease,

cancer, infection, and more (17, 18). This, once again, points back to the 2003 paper by Cawthon et al. where it was determined that individuals with shorter telomeres were much more likely to suffer from illness and infection, pass from heart disease, and cancer (6, 15).

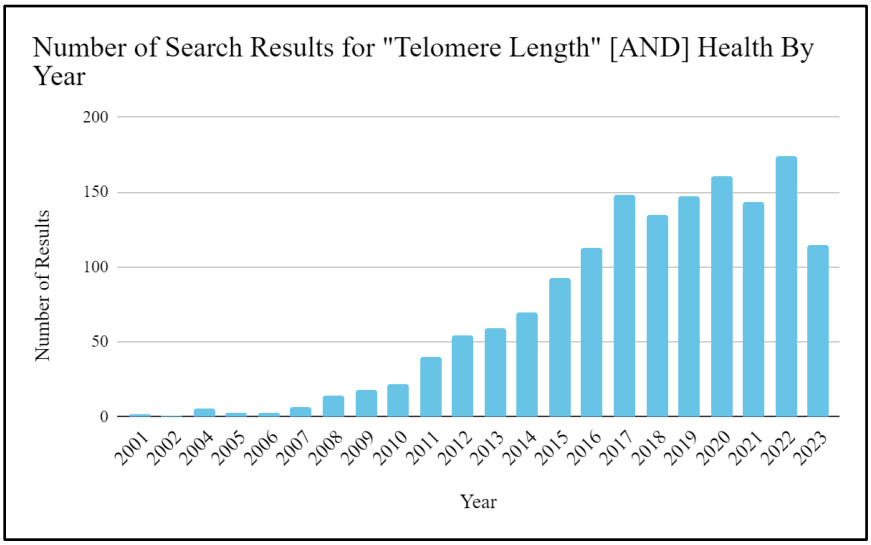

Figure 7. Search result graph for “telomere length” + health by year.

Once a clear link between health and telomere attrition rates was established, research quickly began to consider lifestyle factors that impact one’s health that could, in turn, influence the rates of telomere degradation that occurred, thus amplifying the overall consequences of such factors on health. There are not as many results for the Telomere [AND] health search as seen in Figure 8. This may be due to the restrictive nature of the search which limited results to only papers that included both words in the title and abstract. Additional research was conducted to uncover more specific research on the major factors that seem to impact telomere length - nutrition, psychological stress,

and lifestyle choices - and this yielded more focused results that were deemed relevant to this study. For the purposes of this thesis, the three factors that impact overall health outcomes will be further explored rather than focus on research that comes from simply focusing on health.

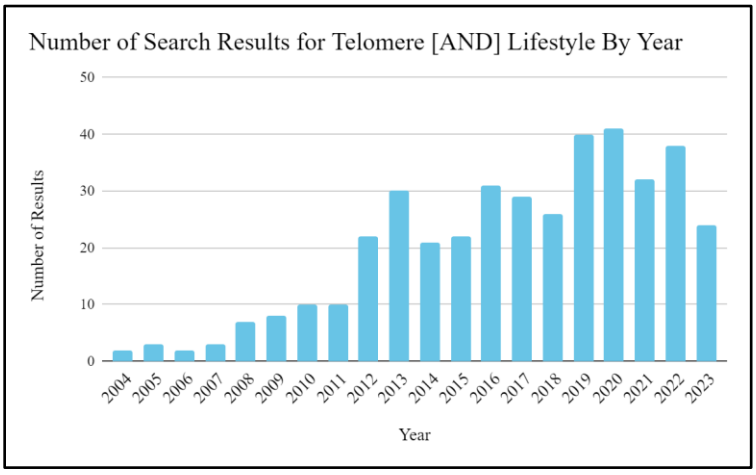

Figure 8. Search result graph for telomere + lifestyle by year.

These searches demonstrate the interest the field has taken in understanding the impacts that external lifestyle factors, like Cawthon mentioned in his 2003 paper, can have on telomere lengths. This will be further discussed but for now, the three specific searches allowed for the creation of a focus on the main factors that were being examined for links to telomere lengths. These factors of lifestyle, nutrition, and psychological stress will be examined below.

Lifestyle

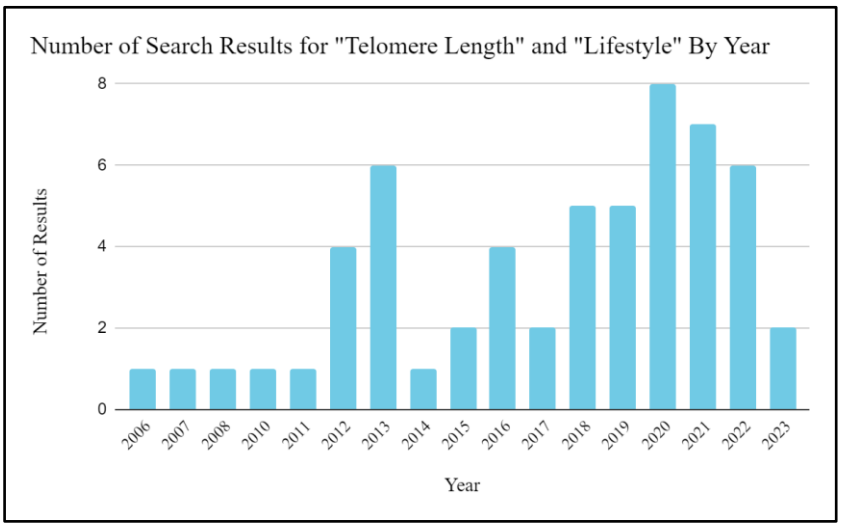

Figure 9. Search result graph for “telomere length” + lifestyle by year.

The chart from Figure 9 depicts results of searching with the keywords "telomere length" and lifestyle. It showcases the trend in publications covering the relationship between telomere length and behavior. While there generally aren’t that many, more results were found if specific lifestyle factors such as drinking, smoking, exercise habits, and more were searched for specifically rather than using a more broad search. The original search revealed these three lifestyle factors such as the choice to drink and what frequency it is used, the choice to smoke, and the rates of exercise one engages in regularly as major influences. One important note here is that any mentions of smoking in this thesis will explicitly be referring to the use of cigarettes. Due to a lack of data covering other substances or products like e-cigarettes or vapes, the impacts of the use of such products will not be considered; however, as more research emerges regarding the

health consequences associated with these substances, research regarding how they impact telomere lengths should be considered.

When it comes to smoking, a variety of sources have discovered significant links to shortened telomeres for those who have smoked compared to those who have never smoked (19-22). Müezzinler et al. did find a correlation between smoking and shortened telomeres; however, they note that they were unable to find a trend that remained consistent over time, nor did they determine there to be a significant amount of damage to the telomere length and found, on average, shortening equivalent to about 73 base pairs less for current smokers compared to those who have never smoked (21). The review conducted by Astuti et al. presented data that supports the negative impacts of smoking on telomere length, but also used data to suggest that there is a benefit to quitting. They observed, albeit weak, an inverse relationship between the years of smoking and the rates of degradation in telomeres (20). While the mechanism behind how cigarette smoking is correlated with telomere attrition has yet to be discovered, it is hypothesized that smoking introduces free radicals that may induce oxidative stress which then causes damage to chromosomes and telomeres (20). There have been conflicting results that show shorter telomeres for those that have never smoked than those that currently do, but Müezzinler et al. hypothesize that this is due to what is called the “thrifty telomere” hypothesis which essentially states that individuals are born with differing lengths of telomeres and as such, those with initially shorter telomeres may expend less resources on maintenance efforts which ultimately leads to what appears to be longer telomeres. The downside of this hypothesis comes at the end when the neglected maintenance comes back and leads to very quickly degrading telomeres due to a lack of damage control (21).

An interesting result appeared when searching for the impact of alcohol use on telomere length: unless there was an alcohol-related disorder such as addiction or a dependence on the substance, rates of alcohol consumption seem to have no statistically significant impact on telomere length (23, 24). Rather, the current research in this area seems to be generally inconclusive. The review by Maugeri et al. revealed that there seemed to be a higher correlation of telomere shortening for those who were classified as low or heavy drinkers, whereas those classified as moderate had the longest telomeres (23). Dixit et al. proposed that these results could be due to hasty conclusions based on inconclusive data (25). While it may be assumed that moderate to heavy alcohol consumption results in negative consequences to overall health, additional research would need to be conducted before a clear link between drinking and telomere attrition is established.

One last major lifestyle factor that appears to have some impact on telomere length is the amount of exercise one partakes in regularly. Multiple papers have attempted to understand the relationship that is present between exercise and telomere maintenance; however, similar to alcohol, no clear cause and effect relationship has been discovered. Some sources have concluded that regular exercise helps maintain longer telomere lengths and proposed that regular exercise can potentially be used as a method to attempt to increase telomere lengths (26-28). Despite most research in the field leaning towards exercise having an overall positive impact, there has been research to combat this. In a 2003 paper by Collins et al., leukocyte telomere length of athletes was observed and in those that presented with Fatigued Athlete Myopathic Syndrome (FAMS) and regularly engaged in heavy training, telomere lengths were significantly shorter than

those who did not show signs of FAMS (29). This research does provide an interesting insight as to how excess exercise may be detrimental to those who may be suffering from additional ailments that may exacerbate any negative impacts from heavy training; however, it focused on individuals that deviate from the average individual due to a health concern and thus the conclusion that exercise can cause more detrimental effects than positive cannot be assumed to apply to all individuals. Individuals that do not regularly engage in heavy training, but rather partake in light to moderate levels of exercise are shown to have slightly longer telomeres in older adults (26, 27). The reduction of inflammation in the body caused by body fat that can be burned during exercise and the reduction of oxidative stress experienced by DNA through the increase in antioxidant properties from skeletal muscles and the heart seem to have a positive impact on telomere maintenance.

Figure 10 highlights the main takeaways from previous research in this field. More research should be conducted to better understand the underlying mechanisms behind these relationships.

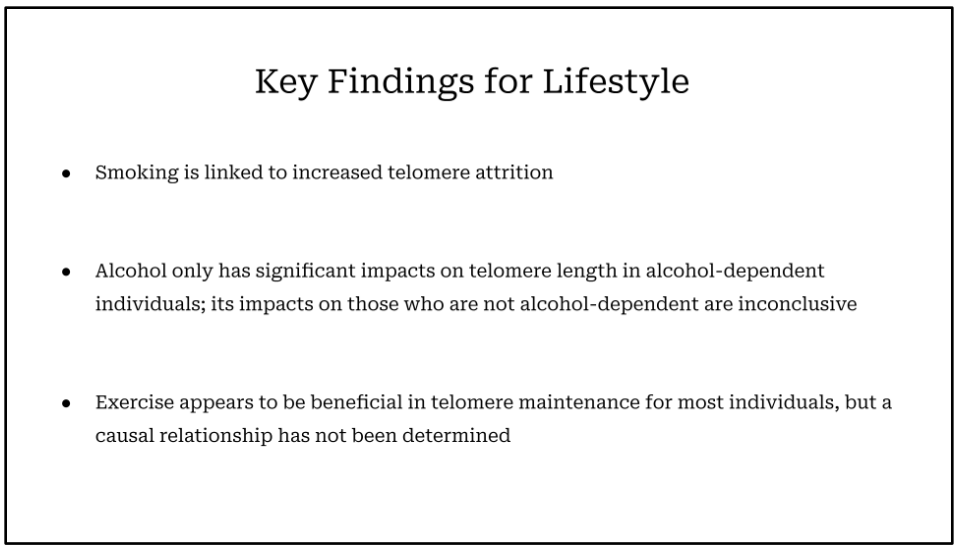

Figure 10. Main findings regarding telomere maintenance and lifestyle choices.

Nutrition

Figure 11 shows that there has been an increase in interest in how diet plays a role in telomere length and overall health outcomes that may be correlated with shortened telomeres. Although this section covers nutrition as a whole, a search relating telomere length to diet specifically resulted in the most relevant results. With the public becoming more concerned about how nutritional choices can impact their health, it makes sense that research would begin to examine the relationship that exists between diet and telomere length. Research in this field slowly but surely began to notice the relationship between these two factors and in 2011, the number of publications increased and continued to increase as more knowledge was uncovered (Figure 11).

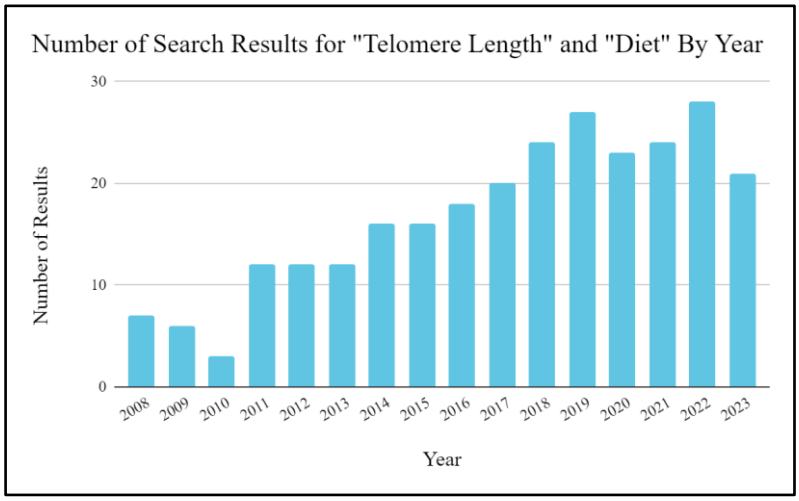

Figure 11. Search result graph for “telomere length” + nutrition by year.

Beginning in 2008, review papers began compiling what was known about the relationship between diet and TL. Nordfjäll et al. observed that obesity seemed to have

negative consequences on TL but only in women (30). This, however, did not necessarily answer the question of diet and TL as other factors are involved in obesity, and thus, more research in this field was needed. Starting in 2011, however, this area was picking up speed and the impacts of diet on TL were seen through multiple publications that found an association between the two factors (31-35). Generally, studies have shown that regular intake of fruits and vegetables in one's diet has a positive association with TL (34, 35). Valera-Gran et al. took this research one step forward and evaluated the impact that such eating habits would have on children; telomeres are longer when an individual is younger and as such, research pertaining to how factors can aggravate the rates of attrition could lead to discoveries that could help decrease excessive shortening at a young age (35). Most research conducted on specific diets such as the Mediterranean diet - which cuts out processed foods, trans fats and refined grains and sugars - proposed that further research be conducted to determine the longitudinal impact that results from adopting such a dietary change. Research by Marin et al. discovered the positive impact that this diet has on oxidative stress: it lessens the impact that such stress has on cells and cellular processes. However, they did not focus on how this reduction in oxidative stress could consequently influence attrition rates over time (36). Although such a discovery was made for oxidative stress, there still has yet to be a publication that highlights any findings for the Mediterranean diet and long-term TL, but researchers still seem to hold to the belief that such a diet could result in positive impacts on TL if not overall health.

The major observations made in previous research are highlighted in Figure 12. As with all research areas presented in this thesis, more research should be conducted to determine a clear causal relationship between various food groups, their nutritional value,

and the effect of these on telomere maintenance and length.

Figure 12: Main findings regarding nutritional choices and telomere length.

Psychological Stress

Despite the low number of publications relating psychological stress to TL compared to other factors, Figure 13 does show that there have still been some findings in this area. There were other publications found with a less restrictive search using just stress rather than psychological stress and due to their relevance, they were included; however, the most relevant search specifically looked for psychological stress as research on the impacts of oxidative stress have been deeply investigated and fills a more generic search with less pertinent results.

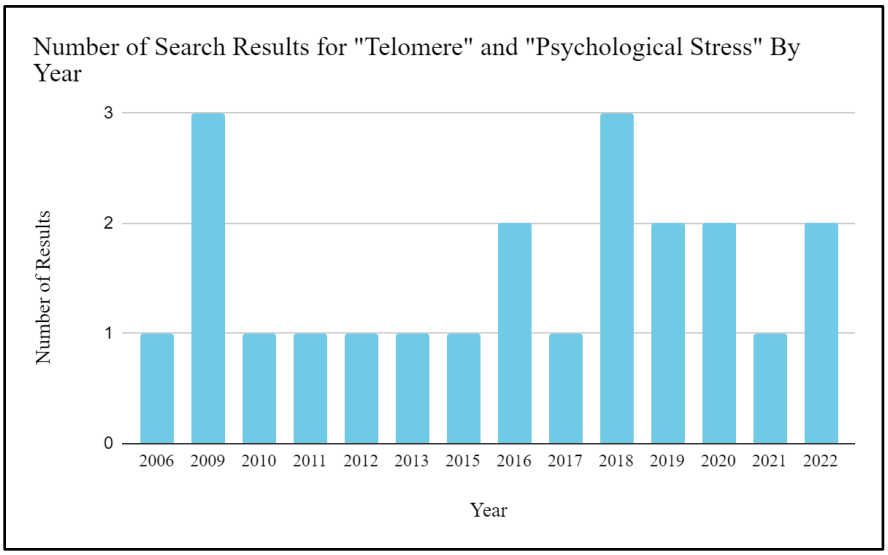

Figure 13. Search result graph for “telomere” + “psychological stress” by year.

Psychological stress (to be referred to as simply “stress” for sake of brevity) has been discovered to have a relationship with telomere shortening through multiple papers (37, 14, 38, 39, 8, 40-42). Most of the research done in this field has analyzed the

associations with mental illness such as depression. The findings have all pointed to the same conclusion that, despite not fully understanding the mechanism, mental illness and thus psychological stress is correlated with shorter telomeres (37, 8, 40). An interesting result was found in research reviewed by Deng et al., 2015 in which telomerase activity levels were observed in those with high levels of psychological stress. The results of these experiments varied, with the presence of some mental disorders being correlated with decreased levels of telomerase activity, while others such as major depressive disorder (MDD) being associated with higher telomerase activity (but still shorter telomeres in a surprising outcome). A key finding was that individuals who were involved in practices to help reduce stress such as meditation had higher rates of telomerase activity (43). Deng et al. mentioned that several authors cited in their paper propose a theory that the increased telomerase activity seen in individuals with MDD could be a response to accelerated shortening to telomeres caused by increased cortisol levels and other damage, but ultimately concluded that further research will need to be conducted in this area to determine the mechanism behind this observation (43).

While these studies primarily focus on stress in adults, there are a handful of authors that covered the consequences of stress in adolescence (39, 42) as well as the impacts of stress on fetuses in pregnant mothers (14, 38, 44). Most research on the impacts of stress on TL in childhood focused on the impacts of mental illness in youth, though that is not the only contributing factor to such stress. Research has also focused on Adverse Childhood Experiences (otherwise known as ACEs), which are characterized as traumatic experiences at an early age that lead to long term health impacts into adulthood. Investigations into the association between attrition rates and ACEs has shown that these

experiences are correlated with shorter telomere length that can be detected as early as 10 years old (45). While these findings show important consequences of stress at an early age, there has been research suggesting that there can be negative outcomes from stress even before birth as stress experienced by pregnant women can inadvertently result in shorter telomeres in their fetuses (14, 38, 44). As telomeres generally stop undergoing elongation via telomerase during development, newborns start their life with a set telomere length that under normal conditions will only shorten (with the exception of specific cells). This implies that the stress endured by pregnant women could negatively impact the starting length of their children's telomeres which could potentially lead to shorter telomeres than their peers as they age and undergo normal rates of telomere shortening.

Major conclusions resulting from past research into links between psychological stress and increased rates of telomere degradation in individuals of all ages are summarized in Figure 14. This research gives insight to the major significance of mental health issues and the negative impacts stress can have on the body beyond what has already been found and is widely discussed in both medical and social spheres. As research continues to link mental illness to negative health consequences, such research will play a key role in understanding the long-term impacts of such stress.

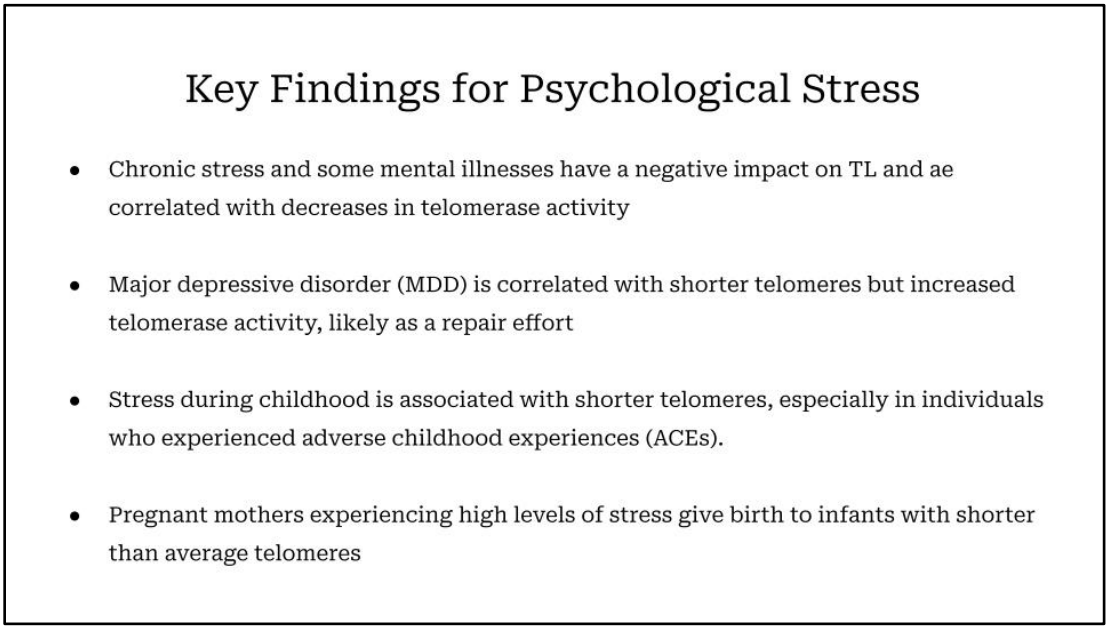

Figure 14. Leading findings between psychological stress and telomere degradation.

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