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Impact of Sleep Duration on Relative Telomere Length: A Systematic Review and Meta-Analysis

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Abstract

Impact of Sleep Duration on Relative Telomere Length: A Systematic Review and Meta-Analysis

By Madison H. Bondy

Introduction: As the global population continues to get older, it is imperative that we develop a deeper understanding of the many factors that contribute to healthy aging. Evidence shows that one of these factors is sleep duration, but reports on the nature and magnitude of the relationship between sleep and aging vary across the literature. The goal of this study is to elucidate this relationship by examining how sleep duration impacts telomere length (TL), a biological indicator of aging.

Methods: A systematic search was performed to identify peer-reviewed articles published between January 1, 2000 and June 1, 2021. These studies included measures of sleep duration and associated TL data. Studies with adequate data for inclusion in a meta-analysis were assessed for risk of selection bias, information bias, and confounding. Summary estimates were calculated for each study using random effects models and heterogeneity of results was assessed. Meta-regression analyses were then employed to examine sources of heterogeneity.

Results: The literature search initially identified 1,524 studies, of which 13 met inclusion criteria for systematic review. A qualitative analysis of the articles was conducted and eight of these studies (N=14,026, mean age=50.71, 44.06% male) were ultimately included in a meta-analysis. The summary effect of all included studies for average difference in mean TL between shorter (7 hours or less) and longer (more than 7 hours) sleep durations was -0.02 (95% CI: -0.03, 0.01). Meta-regression analyses on data sorted by average study population age (less than 50 vs. 50 years or older) produced a significant effect estimate of -0.04 (95% CI: -0.07, -0.03). The effect estimate was also significant within the younger subpopulation (less than 50 years), with an average difference in mean TL between sleep categories of -0.05 (-0.07, -0.03).

Conclusions: Evidence suggests that sleep duration significantly impacts telomere length, particularly among younger populations. Future research should examine this relationship using longitudinal data, and findings would be most reliable if objective measures of sleep duration are employed.

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INTRODUCTION

Over the past several decades, the global population has undergone a substantial demographic transition as early survivorship has increased and life expectancy has expanded. Currently, 1 in 11 people in the world are over the age of 65; however, according to the United Nations (2019), by the year 2050 this statistic will change to 1 in 6 people being above the age of 65. Recognition of this trend and the consequential increase in prevalence of health issues that accompany the aging process have had a major impact on global health discourse. According to the World Health Organization, people aged 60 and older account for 23.1% of the global population suffering from non-communicable diseases (NCDs)(World Health Organization, 2008). Importantly, NCDs are now considered the most significant cause of global mortality, as they cause more than 36 million deaths each year, and their associated financial burden is estimated to reach $47 trillion by 2030 (World Economic Forum, 2011; World Health Organization, 2011). These statistics have served as a call to build on the dramatic successes for early survivorship, by mobilizing research and policy toward successful aging. For example, the National Institute on Aging has developed several strategic directions for research on aging, and a major institutional goal is to develop an understanding of the causal relationship between environmental, sociocultural, behavioral, and biological factors and consequent health disparities among older individuals (Hill, et al., 2015). This realm of research is critically important as it ultimately fosters the pursuit of health equity across the life course.

One potentially powerful influence on aging-related health outcomes is sleep. While the recommended amount of sleep does not change as adults age, the attainability of that amount of sleep is often much lower among older adults (Avidan, 2014). Additionally, sleep disturbances have significant impacts on both mental and physical health among aging populations (Reid et al., 2006). Consequently, risk of mortality has been shown to increase among older adults with sleep disturbances who are otherwise healthy (Dew et al., 2003).

The connection between sleep disturbance and aging is biologically plausible because sleep induces physiological repair at the molecular level, and aging results from the accumulation of molecular damage (Carroll & Prather, 2021). Therefore, one way to examine the association between sleep and aging would be through an indicator of cellular damage. This investigation will use telomere length (TL) as the chosen indicator, given its validity as a marker of physiological, aging-related processes (Bernadotte et al., 2016).

Telomeres are DNA-protein structures found at both ends of each chromosome, and serve to protect the genome from nucleolytic degradation, unnecessary recombination, repair, and interchromosomal fusion (Shammas, 2011). The process of DNA replication produces both a leading strand and a lagging strand. For the leading strand, the process is relatively simple. DNA polymerase moves in the 5′ to 3′ direction, adding bases that complement the template, thus, producing a complete complementary strand. The lagging strand, on the other hand, requires a backstitching mechanism because DNA polymerases can only extend DNA from a 3′ hydroxyl group.

Thus, RNA primers, which serve as sources of 3′ hydroxyl groups, are placed intermittently along the lagging strand template. DNA polymerase then extends the primers by adding complementary bases in the 5′ to 3′ direction to create a series of fragments (Okazaki fragments) that complement the lagging strand template. The lagging strand, however, does not reach the end. In theory, a final RNA primer could be placed at the end of the lagging strand, providing a 3′ hydroxyl group to signal DNA polymerase; however, that primer would eventually be removed, leaving no available 3′ hydroxyl group for DNA polymerase to extend. This creates a lagging strand that is incomplete (missing bases at the end). Because the end of the chromosome is left un-replicated, each replication cycle will produce an increasingly shorter chromosome. This dilemma, termed the "End Replication Problem," is the principal mechanism of telomere erosion. Put simply, the more erosion that occurs, the shorter the telomere, and the greater chance of the host cell entering apoptosis (cell death).

Telomere length is an indicator of physiological weathering that is associated with an array of adverse health outcomes, such as cardiovascular disease, and a general increase in all-cause mortality (Cawthon et al., 2003; Rode et al., 2015; Serrano & Andrés, 2004; Wang et al, 2018). Telomere length is known to be modified by a number of environmental factors, most notably experiences of psychosocial stress (Epel & Prather, 2018; Quinlan et al., 2014); however, these stressful experiences also have posited links to diminished sleep quality and quantity (Van Reeth et al., 2000). Accordingly, telomere length is an especially useful biomarker of aging, and will be used as such to explore the relationship between sleep and aging, overall.

While sleep is typically examined in terms of quality and/or quantity, this review only includes studies of sleep duration, or "the total amount of sleep obtained either during the nocturnal sleep episode or across the 24-h period" (Kline, 2013). This decision was based simply on the fact that measures of quality are inherently more prone to subjectivity than measures of quantity.

The link between sleep and aging has been published on for nearly a decade; however, the claims presented across publications have been notably inconsistent. Consequently, this investigation aims to synthesize existing findings on the relationship between sleep and aging, with the hope of providing an unbiased foundation for future research. To accomplish this goal, the authors chose to conduct a systematic review and meta-analysis of sleep duration and telomere length.

METHODS

Literature Search

A systematic review of the literature was conducted using PubMed (US National Library of Medicine), EMBASE (Elsevier B.V.) and Web of Science (Thomson Reuters) databases to locate articles published within the last 21 years (between January 1st, 2000 and June 1st, 2021). Search terms included "sleep" and "telomere" or "telomerase" or "biological aging" or "cellular senescence" or "epigenetic clock" or "DNA methylation" or "oxidative damage" in all fields and with associated Medical Subject Headings (MeSH terms). Additional searches were conducted by manually reviewing references

from eligible articles, relevant systematic reviews and meta-analyses, and through discussions with subject matter experts.

Two investigators (MB and KW) independently screened all titles and abstracts to determine whether articles were eligible for inclusion in the systematic review and subsequent meta-analysis. In cases of discordance of opinion, the two authors met to discuss the discrepancy and achieve consensus

Inclusion & Exclusion Criteria

The inclusion criteria for this systematic review required that studies examine the association between sleep duration and biological aging, indicated by relative telomere length. Further criteria required that studies were reported in English, and were published between January 1st, 2000 and June 1st, 2021.

The exclusion criteria for this systematic review were as follows: studies performed in animals, studies in which participants had sleep apnea, insomnia, or any other reported sleep disorder/condition, studies in which participants were less than 18 years of age, articles with incomplete information, systematic reviews, and meta-analyses.

Data Extraction

The study selection process yielded 1,524 references, of which 1,511 were excluded after abstract and full-text review (Figure 1).

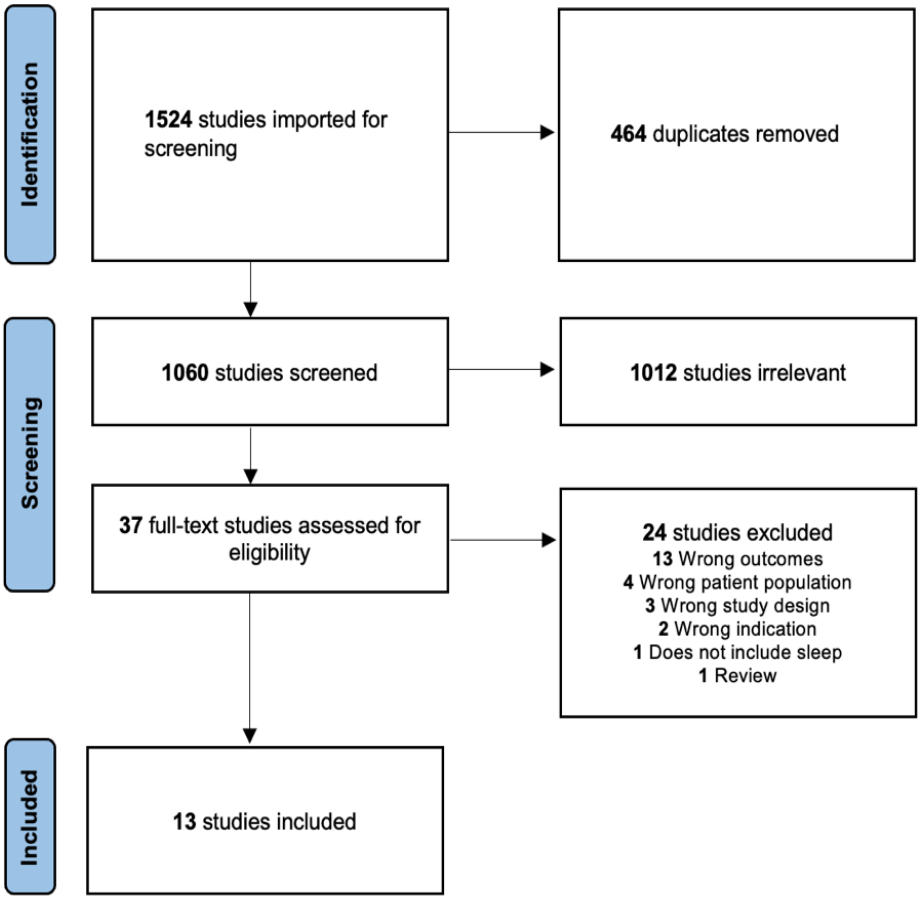

Figure 1. Process of study selection for systematic review.

Original articles were retrieved to extract the following study characteristics: primary author, date of publication, title, sample size, population description, sleep duration (measurement information and data), and relative telomere length (measurement information and data). This yielded 13 studies for the systematic review presented below. Of those 13 studies, eight were included in the subsequent meta-

analysis, based on availability/obtainability of requisite data. In cases where additional data from a study was needed to be included in the meta-analysis, authors were contacted to obtain that information.

In the case of the 2012 study published by Jackowska et al., the male and female samples were treated as separate studies in the meta-analysis due to restrictions in data availability, which increased the number of studies included in the systematic review to 14 and the number of studies included in the meta-analysis to nine. To determine the data breakdown by sex for each sleep duration category, we applied the 47.5/52.5 male/female distribution from the overall study population. This tactic is justified because sleep duration is unrelated to sex, and we can therefore assume independence.

Bias Assessment

Once publications were identified for meta-analysis inclusion, a set of grading criteria was applied to evaluate risks of biases. The grading criteria consisted of three items: risk of selection bias, risk of information bias, and risk of confounding. Each study was assigned a point value ranging from zero to three for each category, with "0" indicating the lowest risk of bias, and "3" indicating the highest. These scores ultimately serve as an important way to qualify the results of the meta-analysis.

Meta-Analysis

After assessment of biases, summary estimates were calculated for each of the nine studies using random effects models. These summary estimates were accompanied

by 95% confidence intervals (CIs), as well as measures of heterogeneity. Heterogeneity of results across studies was assessed by calculating the Q statistic and its corresponding p-value, along with the I^2 statistic. Sources of heterogeneity were then examined through a series of stratified analyses and meta-regressions. The independent variables in these stratified and meta-regression analyses included: actigraphy-based sleep assessment, questionnaire-based sleep assessment, study population location, study population health, and average study population age.

RESULTS

Systematic Review

Characteristics of the 14 publications included in the review are summarized in Table 1. Sample sizes ranged from 74 to 12,178 participants (median of 711), and ten study populations were predominantly female, with four studies having entirely female samples. Six of the studies were conducted in the United States and the remaining eight were based internationally. Mean participant age across the 12 studies in which it was reported ranged from 40.6 to 64 years (median of 46.7).

Study	Country	N	Male (%)	Mean Age (y)	Mean TL (SD) for ≤7 hours Sleep	Mean TL (SD) for >7 hours Sleep
Ammala et al., 2021	Finland	8,028	52.5	53	1.04 (0.21)	1.06 (0.21)
Cribbet et al., 2014	US	154	57.8	60.1	–	–
Jackowska et al., 2012 FEMALE	UK	228	0	64	1.00 (0.07)	0.98 (0.08)
Jackowska et al., 2012 MALE	UK	206	100	62.5	0.99 (0.08)	1.00 (0.07)
Lee et al., 2014	US	283	74	44.9	0.95 (0.31)	1.04 (0.32)
Liang et al., 2011	US	4,117	0	–	–	–
Nguyen et al., 2020	Australia	1,070	13	44.1	0.87 (0.44)	0.81 (0.37)
Prather et al., 2011	US	263	0	57.5	0.94 (0.11)	0.94 (0.15)
Prather et al., 2015	US	87	18.4	48	1.2 (0.24)	1.27 (0.23)
Révész et al., 2016	Netherlands	2,936	33.6	41.8	1.05 (0.29)	1.12 (0.31)
Tempaku et al., 2018	Brazil	925	44.1	40.6	1.36 (0.23)	1.39 (0.23)
Wynchank et al., 2019	Netherlands	2936	33.6	41.8	–	–
Zgheib et al., 2018	Lebanon	497	35.8	45.4	–	–
Zhao et al., 2017	US	12,178	20.4	–	–	–

Table 1. Baseline characteristics of studies of sleep duration and telomere length (TL).

Looking at the results of this systematic review, sleep duration was found to have a significant association with mean relative telomere length (RTL) in five of the nine studies with adequate data. A study was deemed to have adequate data if we were able to determine RTL for the two identified sleep duration categories (7 hours or less vs. more than 7 hours of sleep on average each night).

The first of these studies, by Lee et al. (2014), measured sleep duration via actigraphy, which is significantly more objective than methods employed by most of the

other studies in this review. On the other hand, the sample size was relatively small (N = 283), and all participants were severely immunocompromised due to a positive human immunodeficiency virus (HIV) diagnosis. Considering the established link between the immune system and biological aging and, more specifically, the relationship between HIV infection and accelerated telomere shortening (Zanet et al., 2014), these results should be interpreted cautiously.

The next study that reported an association between TL and sleep duration was led by Prather (2015), but it is important to note that this association only held true in particular cell populations. Additionally, sleep was measured via daily activity diary, and the sample was not only small (N = 87), but also consisted solely of medically obese participants.

Révész et al. (2016) also reported a significant relationship between TL and sleep duration, but only among participants with average daily sleep duration greater than nine hours. While the sample size for this study was very large (N = 2,936), sleep duration was self-reported, which introduces risk of information bias.

Tempaku et al. (2018) also published an association between TL and sleep duration, but only among participants in their longest sleep duration category (greater than eight hours per night, on average). The sample size for this study was relatively large (N = 925), but sleep duration was self-reported, and TL was dichotomized as "short" (bottom 10th percentile) and "non-short" (top 90th percentile). Self-reported sleep is subject to skepticism for the same reasons as with other studies in this

systematic review, and dichotomizing TL, a continuous variable, is concerning in that doing so can lead to decreased statistical power and misleading effect sizes.

Finally, the last study in this review that showed an association between TL and sleep duration was the 2012 Jackowska et al. study (male subsample). Two factors to consider for this purported relationship are the relatively small sample size (N = 206) and the sleep duration measurement method. Participants in this study were simply asked how many hours of sleep they have on an average weeknight. This introduces not only recall bias, but perhaps social-desirability bias as well.

Contrary to the significant findings described above, several studies in this systematic review published results that suggest an insignificant relationship between sleep duration and TL. Ammala et al. (2021) was one of these studies and had a very large sample size (N = 8,028), but sleep was self-reported and then dichotomized, which is problematic for reasons mentioned above. Additionally, 189 people were excluded from analysis for reporting an average sleep duration greater than 10 hours per night. This is particularly problematic given that other studies (i.e., Révész et al., 2016 and Tempaku et al., 2018) found that any statistically significant association between sleep duration and TL was limited to those with longer average daily sleep duration.

The next study that reported no significant relationship between sleep duration and TL was conducted by Nguyen et al. (2020) and not only had a large sample size (N = 1,070), but also evaluated sleep duration via actigraphy – a much more objective measure of sleep than self-report.

Prather et al., (2011) also found no significant relationship between sleep duration and TL, but sleep duration was measured by simply asking participants how much they sleep each night, which introduces biases mentioned above. Additionally, the study sample was limited to women aged 49 to 66 years, and therefore was not representative of the general population.

Finally, the last study in this review that failed to report a significant association between TL and sleep duration was the 2012 Jackowska et al. study (female subsample). Two factors to consider here are the smaller sample size (N = 228) and the fact that, once again, sleep duration was measured by asking participants how many hours of sleep they get on an average weeknight.

Bias Assessment

Risk of bias in the publications included in the meta-analysis was evaluated using the following rating system:

Rating	Selection Bias	Information Bias	Confounding
0 pts	Greater than 80% participation	Sleep quantity measured via actigraphy	Controlled for age and at least 2 other factors
1 pt	60% - 80% participation	Sleep quantity measured via questionnaire	Controlled for age and 1 other factor
2 pts	Up to 60% participation	Sleep quantity measured via participant diary	Controlled for age
3 pts	Non-responses not reported	Sleep quantity measured via self-report	Crude analysis; no adjustments

Table 2. Rating system for assessing the risk of bias in studies included in this meta-analysis.

	Rating			
Study	**Selection Bias**	**Information Bias**	**Confounding**	**Total**
Lee et al., 2014	0	0	0	**0**
Ammala et al., 2021	0	1	1	**2**
Nguyen et al., 2020	0	0	0	**0**
Prather et al., 2011	0	1	0	**1**
Prather et al., 2015	2	1	0	**3**
Révész et al., 2016	0	3	0	**3**
Jackowska et al., 2012	0	3	0	**3**
Tempaku et al., 2018	0	0	3	**3**

Table 3. Bias assessment ratings for studies included in meta-analysis.

Meta-Analysis

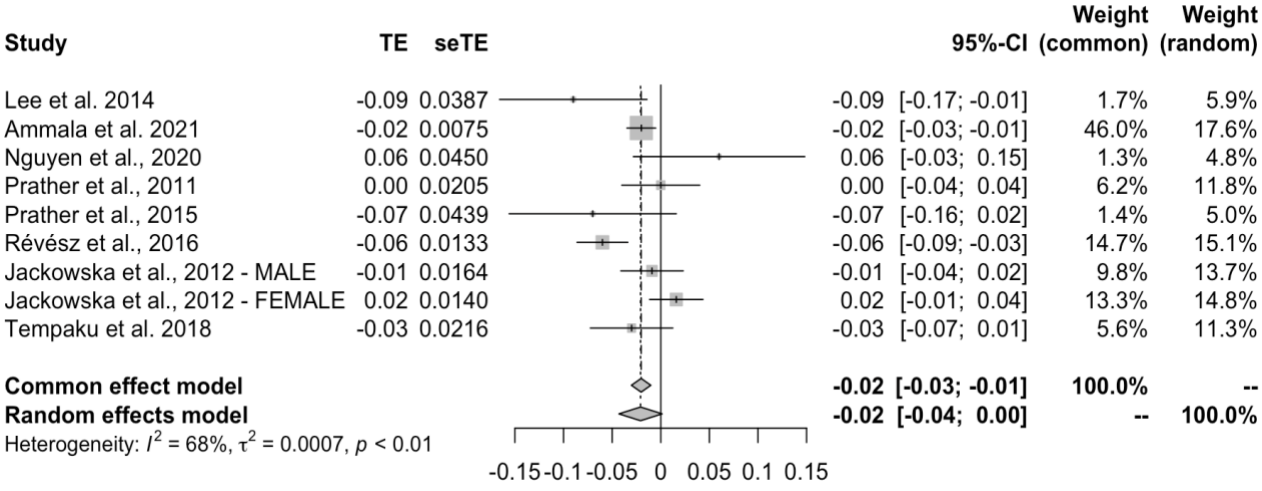

Figure 2. Forest plot presenting the meta-analysis based on estimates for the effect of sleep duration on relative telomere length. Abbreviations: CI: confidence interval, I-squared: statistical index of heterogeneity, p: p-value.

As stated above, this meta-analysis was conducted using data from nine of the 14 publications included in the systematic review. Overall, the mean RTL is 0.02 units shorter among those who typically get 7 hours of sleep or less compared to those who typically get more than 7 hours of sleep. It is, however, important to note that heterogeneity (as indicated by I^2) is substantial at 68%. This means that 68% of the variation across studies is due to heterogeneity, rather than chance.

Investigation of this heterogeneity involved subgroup analyses by methods of sleep duration measurement, as well as location, overall health condition, and average age of study populations. The results of each of these analyses are presented in Table 4 (below).

	Parameter	**Estimate**	**95% CI**
Actigraphy-based sleep assessment	*Used*	*-0.0262*	*-0.0837, 0.0313*
	Not used	*-0.0200*	*-0.0302, 0.0098*
	Meta-regression	*-0.0021*	*-0.0759, 0.0717*
Questionnaire-based sleep assessment	*Used*	*-0.0193*	*-0.0296, -0.0090*
	Not used	*-0.0397*	*-0.0875, 0.0080*
	Meta-regression	*0.0203*	*-0.0418, 0.0823*
Study Population Location	*US*	*-0.0270*	*-0.0598, 0.0058*
	Outside the US	*-0.0195*	*-0.0300, -0.0090*
	Meta-regression	*-0.0259*	*-0.0832, 0.0315*
Study Population Health	*Normal Health*	*-0.0195*	*-0.0300, -0.0090*
	With Health Issues	*-0.0270*	*-0.0598, 0.0058*
	Meta-regression	*-0.0259*	*-0.0315, 0.0832*
Average Study Population Age	*Less Than 50 years*	*-0.0496*	*-0.0698, -0.0295**
	50 years and older	*-0.0105*	*-0.0221, 0.0010*
	Meta-regression	*-0.0409*	*-0.0734, -0.0084**

Table 4. Meta-analysis results by subgroups.

The results above indicate that using actigraphy, perhaps the most objective sleep measurement method, to quantify participants' average nightly sleep duration did

not appear to influence the results of the meta-analysis. The same can be said for using questionnaires, a more subjective sleep measurement method, to quantify participants' average nightly sleep duration. Study population location also failed to significantly influence the results of the meta-analysis, as did the overall presence of health problems among the study population. To evaluate the latter, any study populations reporting significant health problems, such as obesity (Prather et al., 2015) or HIV (Lee et al., 2014), were excluded from the "normal health" category.

While the aforementioned subgroup analyses did not produce significant results, one final analysis, looking at the effect of average study population age on the relationship between sleep duration and RTL, did result in a significant finding. The average difference in mean RTL between those who typically get 7 hours of sleep or less and those who typically get more than 7 hours of sleep was -0.0409 (Table 4). This effect estimate is significant, meaning that the magnitude of the differences in mean RTL between the two sleep duration categories is impacted by study population age. In other words, study population age appears to have influenced the results of the meta-analysis. It is also worth noting that, particularly among study populations with average participant age below 50 years, the average difference in mean RTL between those who typically get 7 hours of sleep or less and those who typically get more than 7 hours of sleep is also significant at -0.0496. This indicates that the impact of sleep on RTL is likely greater among younger populations, which is interesting to consider against different narratives presented throughout the sleep and aging literature.

DISCUSSION

This systematic review revealed inconsistencies across published relationships between sleep duration and relative telomere length. Lack of consensus throughout the literature was further investigated via meta-analysis, which ultimately revealed a weak relationship between sleep duration and RTL. However, as previously mentioned, subsequent subgroup analyses did reveal a significant association between sleep duration and RTL among study populations with an average participant age below 50 years. This finding, that the impact of sleep on RTL may be greater among younger populations, is important to explore because research into age as a modifier of the relationship between sleep and RTL is quite limited.

There has been a long-standing consensus in the literature that the rate of telomere attrition decreases with chronological age (Frenck et al., 1998). Considering this, we can assume that most influences that emerge later in life are less likely to have a substantial impact on telomere length. This line of thinking is obviously supported by the aforementioned results of this meta-analysis; however, in order to ensure that future research efforts are robust, it is important to consider the plausibility of alternative findings.

The concept of developmental origins of health and disease (DOHaD) suggests that influences in early life are more impactful on biology than factors that manifest later in life (Gluckman and Hanson, 2006); however, the average ages of the populations included in this meta-analysis, even the younger populations, are all categorized as "post-reproductive." According to DOHaD, during the post-reproductive period, behavior and environment actually have increasingly potent effects on an individual's physiology due to the decline in plasticity that accompanies aging (Hanson and Gluckman, 2014). A decrease in plasticity means individuals are less equipped to counteract risks and their resilience to lifestyle challenges is blunted over time. In other words, insufficient sleep might actually be more detrimental later in life, rather than earlier, as the aforementioned finding suggests. Of course, without participants who are younger than "post-reproductive" age, it is not entirely appropriate to apply the DOHaD framework to this relationship between sleep duration and telomere length.

Another approach to consider is that aging is influenced by an accumulation of physiological damage over time. This view of aging suggests that, as an individual ages, damage accumulates and resiliency factors are increasingly unable to counteract that accumulation (Ferucci et al., 2019). Considering this perspective, one would expect older individuals to be less equipped to deal with issues, such as insufficient sleep, compared to younger individuals, which contradicts the results of this meta-analysis.

Regardless of the analytical framework being applied, how the relationship between sleep quality and TL varies with age cannot be reliably discerned without longitudinal data. With measurements of sleep quality and telomere length across

several time points, spanning multiple phases of the life course, it would be much easier to determine the true relationship between the variables.

Another limitation that should be addressed is that the studies incorporated in this review/meta-analysis primarily take place in WEIRD (Western, Educated, Industrialized, Rich, and Democratic) (Henrich et al., 2010). This attention is arguably misallocated, in that it produces a skewed understanding of health processes by overlooking the majority world in diverse, non-Western contexts. Also, it is important to consider these questions in varied contexts because researchers can information about not only variation in sleep, but also about any other potential stressors that might be present, as well as any resources for coping and resiliency.

CONCLUSIONS

This systematic review aimed to elucidate the relationship between sleep and aging by examining evidence linking sleep duration and a biological marker of aging, RTL. After a survey of relevant literature yielded largely mixed findings, a series of stratified analyses and meta-regressions revealed that average population age likely has an impact on the relationship between sleep duration and RTL. More specifically, the data suggest that the impacts of variation in sleep duration are more impactful on biological aging among younger populations.

While more information is needed to evaluate the validity of this finding, it is nonetheless important because it speaks to the significance of investigating this

relationship between sleep and aging and, accordingly, the potential need for early intervention to promote healthy aging trajectories.

Future research into this relationship between sleep and aging should be at least somewhat longitudinal in nature, incorporate multiple socioeconomic and behavioral factors, aim for objectivity in measures of sleep, and take place in a variety of study populations.

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