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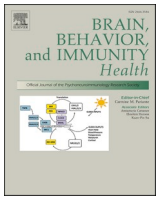

The association between sleep quality and telomere length: A systematic literature review

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ABSTRACT

Several sleep parameters present an elevated risk for processes that contribute to cellular aging. Short sleep duration, sleep apnoea, and insomnia are significantly associated with shorter telomeres, a biological marker of cellular aging. However, there has been no review or analysis of studies that have examined the association between the psychological construct of sleep quality and telomere length. The present study aimed to provide a systematic review of the association between sleep quality and telomere length. A systematic review of English articles was conducted using MEDLINE/PubMed, PsycINFO, Google Scholar, and Web of Science electronic databases, with the final search conducted on 3rd September 2021. Search terms included sleep quality, poor sleep, insomnia, sleep difficulties, sleep issue*, non-restorative sleep, telomere*, cellular aging, and immune cell telomere length. Study eligibility criteria included human participants aged 18 years or older and a reproducible methodology. Study appraisal and synthesis were completed using a systematic search in line with a PICOS approach (P = Patient, problem, or population; I = Intervention, prognostic factor, exposure; C = Comparison, control, or comparator; O = Outcomes; S = Study designs). Twenty-two studies met review inclusion criteria. Qualitative synthesis of the literature indicated insufficient evidence overall to support a significant association between sleep quality and telomere length. Limitations across studies were addressed, such as the assessment of examined constructs. Findings highlight important targets for future research, including the standardised operationalisation of the sleep quality construct and experimental study designs. Research in this area has clinical significance by identifying possible mechanisms that increase the risk for age-related disease and mortality. PROSPERO Registration No.: CRD 42021233139.

Sleep difficulties are reported by an estimated 30%–50% of the adult population worldwide (Brownlow et al., 2020). Sleep difficulties are associated with significant neuropsychological and biological issues that negatively impact key domains of human functioning. Inadequate sleep is associated with mental health deterioration and accelerated age-related decline, which in turn increases the risk for morbidity and mortality (Anderson and Bradley, 2013; Iloabuchi et al., 2020; Soldatos and Paparrigopoulos, 2005; Yaffe et al., 2014). Inadequate sleep presents an elevated risk for processes that contribute to cellular aging, including cellular damage and telomere shortening (Carroll et al., 2015; Chen et al., 2014). In particular, poor sleep quality is thought to contribute to cellular damage through negative effects on telomere length (Gulec et al., 2012).

Telomeres are repeating segments of noncoding DNA located at the end of chromosomes (Blackburn, 2000). Telomeres help to maintain the integrity of chromosomes. They cap the ends of chromosomes to protect chromosomes from various events, such as breakages and inappropriate fusion with neighbouring chromosomes (Kwon et al., 2015). Telomeres sensitively survey DNA damage. They regulate the amount of uncapping needed to protect coding DNA when cells divide, earning their label as "dynamic regulators of cellular lifespan" (Wong and Collins, 2003). Problems with the replication of the DNA-protein structures during cell division can lead to the progressive shortening of telomeres (Blackburn, 1991). When telomeres become significantly damaged or critically shortened, they begin cell senescence, and any further cell division can threaten the integrity of the coding DNA. Telomeres that are incompletely replicated during each cell division become shorter with advancing age (Armanios, 2013). Accordingly, telomere length is considered a biomarker of aging (Blackburn, 2000). Telomere length is measured using standard laboratory procedures in clinical and population-based studies. Relative telomere length is commonly measured from peripheral blood leukocytes using quantitative

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Polymerase Chain Reaction (qPCR) and Southern Blot procedures. Aside from cell division, other factors thought to accelerate telomere attrition include genetic and environmental influences, such as inflammation and exposure to oxidative stress (Barnes et al., 2019; Brydon et al., 2012).

Sleep is an essential restorative physiological process (Zisapel, 2007). The human body is in a state of synthesis during sleep. Sleep helps restore the body's nervous, immune, muscular, and skeletal systems. This restorative process is crucial for cognitive functions, such as emotional regulation and memory, and overall health and well-being (Gottlieb and Bhatt, 2019). Sleep quality is a complex psychological construct that characterises several sleep-related domains, including sleep latency, sleep maintenance, and sleep efficiency (Ohayon et al., 2017). Sleep quality is also an aspect of human functioning that appears to deteriorate with increasing age (Bixler, 2009; Mazzotti et al., 2012). Notably, the observed reduction in sleep quality with increasing age appears analogous with telomere attrition across the lifespan (Cawthon et al., 2003; Epel et al., 2004).

Sleep quality has been assessed using various approaches in clinical research, including subjective measures of the sleep experience (e.g., feeling rested upon waking). Common self-report measures used to assess sleep quality include the General Sleep Disturbance Scale (GSDS; Lee, 2007), Jenkins Sleep Problems Scale (JSPS; Jenkins et al., 1988), and Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI is considered the gold-standard measure of global sleep quality and sleep patterns in research and clinical settings (Mollayeva et al., 2016). The PSQI provides an assessment of global sleep quality based on the retrospective appraisal of seven sleep domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime functioning impairment. The sleep experience across the previous month is self-rated, and higher composite PSQI global scores indicate poorer overall sleep quality. The PSQI has good overall internal reliability ($\alpha = .83$) and excellent discriminant validity, differentiating "poor" sleep from "good" sleep in clinical and non-clinical samples (Mollayeva et al., 2016). Another approach used to assess sleep quality is a single item metric that screens for general sleep problems. This dichotomised approach to sleep quality appraisal (i.e., sleep is rated as "good" or "poor") correlates well with more comprehensive self-reported measures of sleep quality (Hughes et al., 2018). Sleep quality is also measured using inferences from objective sleep measures obtained through polysomnography (i.e., sleep onset latency, waking after sleep onset, total sleep time), which are corresponded with subjective sleep measures, such as sleep diaries (Buysse et al., 2006).

A burgeoning body of clinical research has identified significant associations between telomere length and sleep-related constructs. A recent meta-analysis comprising 2639 participants across eight studies found significant associations between shortened telomere length and obstructive sleep apnoea (OSA; Huang et al., 2018). Several studies have reported links between chronic poor sleep quality and an increased risk for age-related disease and early mortality (Colten and Altevogt, 2006; Ensrud et al., 2012; Li et al., 2018; Ohayon et al., 2017; Parthasarathy et al., 2015), and there is evidence that inflammation pathways are involved (Irwin et al., 2016; Motivala, 2011). Collectively, this research highlights telomere shortening as a plausible biological mechanism through which poor sleep quality may increase the risk for age-related disease. However, to date, there has been no review or analysis of studies involving human adults that have examined the relationship between sleep quality and telomere length. A systematic review of studies that have examined sleep quality and telomere length may help to ameliorate their association.

Sleep is understood to be an important behavioural contributor to physiology and well-being (Buysse, 2014; Cappuccio et al., 2010). Research in the area of sleep quality has clinical significance since sleep is a modifiable health behaviour. It is important to increase our understanding of possible mechanisms underlying cellular aging. Such insight could warrant further research that examines whether improved sleep quality offers protective effects that help reduce the risk for age-related disease and mortality.

1. Method and materials

1.1. Protocol and registration

The current systematic literature review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009). The present study was registered on the PROSPERO register (Centre for Reviews and Dissemination [CRD], University of York, 2009) on 25th February 2021 as prospective registration of systematic reviews can help promote research transparency, reduce the risk of bias, and eliminate unintended duplication of reviews (Stewart et al., 2012).

1.2. Eligibility criteria

Study inclusion criteria were based on the five factors that comprise the PICOS approach (P = Patient, problem, or population; I = Intervention, prognostic factor, exposure; C = Comparison, control, or comparator; O = Outcomes; S = Study designs; Huang et al., 2006; Schardt et al., 2007). The population (P) under review included adult participants (i.e., individuals $\geq$18 years of age). Participants less than 18 years of age were excluded from the review since participant demographic factors, such as age, should be held as consistent as possible in biobehavioural research involving telomere length measurement (Montpetit et al., 2014). The intervention (I) under consideration included biological markers of cellular aging or telomere length. Studies also required transparent reporting of diagnostic sleep assessment criteria (e.g., insomnia). Treatment and comparison groups (C) included samples that met sleep-related diagnostic criteria (e.g., OSA) compared with healthy controls. Outcomes (O) included telomere length assessment and a measure of sleep quality, assessed using objective sleep indices or via self-report. No additional outcomes or control variables were examined in the current review. Study design (S) included randomised control trials and cross-sectional and longitudinal designs.

1.3. Information sources

Due to the developing nature of this research field, no search time parameters were set, and all sleep-related studies which met PICOS search criteria were included in the review. Unpublished studies, conference abstracts, and studies published in languages other than English were excluded from the current review. The final search was conducted on 3rd September 2021.

1.4. Search strategy

An initial broad search was conducted using the electronic databases MEDLINE/PubMed and PsycINFO, with the keywords "sleep quality" AND "telomere*". Results generated by this search were scanned for additional keywords, including "insomnia" and "telomere length", using the PICOS search protocol (Huang et al., 2006; Schardt et al., 2007). The keyword selection was based on the PICOS search method and included the following terms:

P = Most important characteristics of participants: sleep quality, poor sleep, insomnia, sleep difficulties, sleep issue*, problem* sleep, non-restorative sleep

I = Intervention, prognostic factor, or exposure: telomere*, shortened leukocyte telomere length*, cellular aging, cellular ageing, immune cell telomere length

More intricate searches were conducted with Boolean operators using the keywords in electronic databases, including MEDLINE/

PubMed, PsycINFO, Google Scholar, and Web of Science. Reference lists in identified papers were hand-searched to identify additional studies. Searches were completed in English.

1.5. Study selection

Articles that referenced sleep quality and telomere length or cellular aging in the title, abstract, and/or in-text were screened and used for data extraction. Studies that primarily investigated variables that appeared largely irrelevant to the topic of the review were examined; of those, studies were excluded from the review if sleep-related variables were identified as covariates or if sleep quality and telomere length variables were not assessed.

1.6. Risk of bias across studies

Two reviewers worked independently to ensure the validity of eligible studies. The first reviewer independently screened all titles and abstracts retrieved from the literature searches to identify studies that met the PICOS search criteria. A second reviewer was recruited to conduct an independent search to identify studies that met the study inclusion criteria at an outcome level. Studies that included quantitative measures of sleep quality and telomere length were classified as "relevant", "possibly relevant", or "irrelevant".

1.7. Summary measures

The principal summary measures included correlation coefficients, unstandardised and standardised betas, confidence intervals (CI), significance (p) values, and mean differences.

1.8. Risk of bias in individual studies

The first reviewer assessed the full texts and abstracts of all studies identified through the search process. Study suitability was based on methodological and clinical factors, such as internal and statistical validity. The first and second reviewers qualitatively identified similarities and dissimilarities between studies using the extraction criteria. Given the relatively low number of studies that met review criteria, there was no disagreement between reviewers regarding eligible studies.

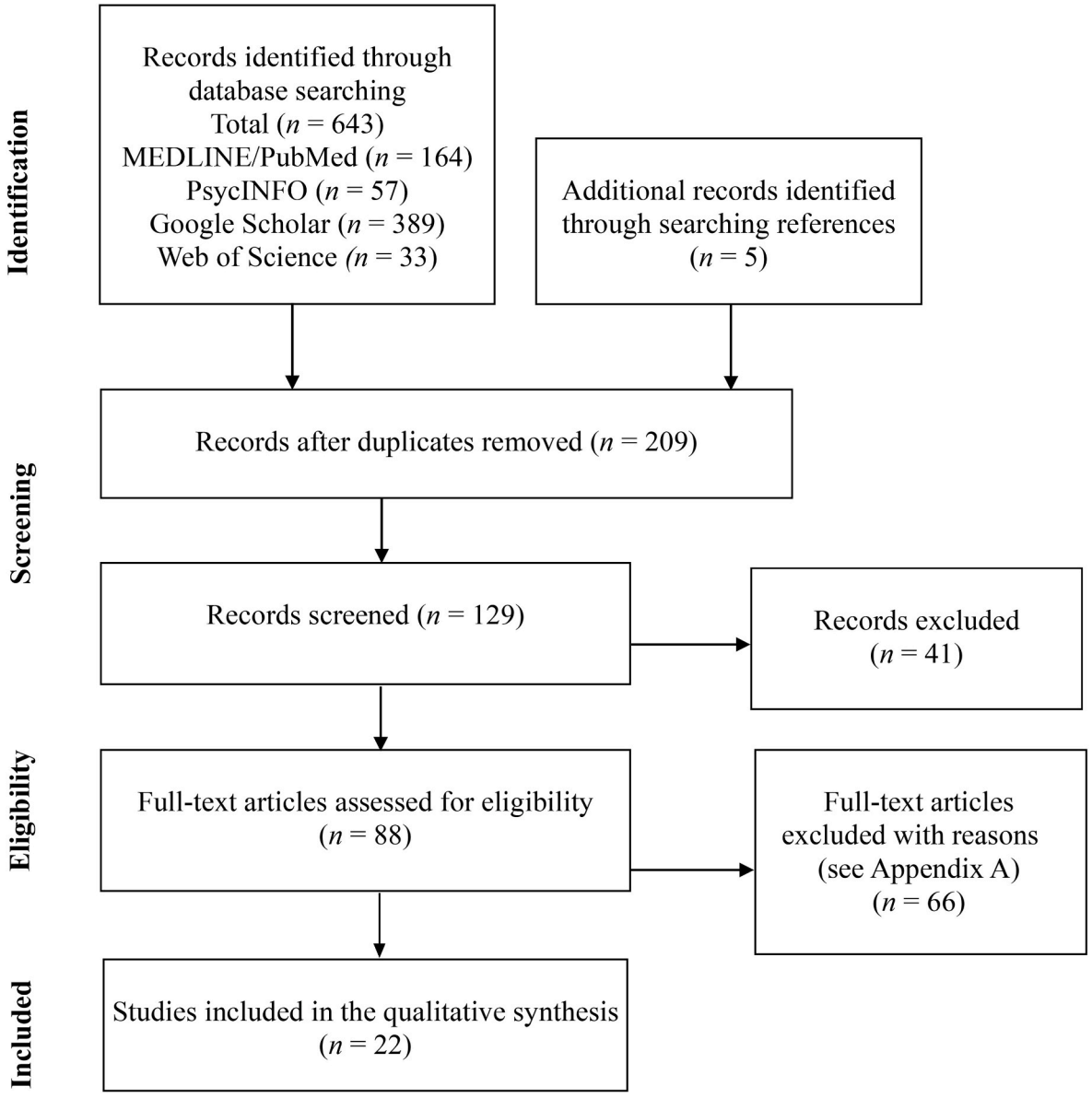

Fig. 1. PRISMA Flow diagram of included studies.

1.9. Data synthesis strategy

A systematic narrative review was completed, which summarised study characteristics and identified reported associations between sleep quality and telomere length. The retrieved quantitative data were examined to determine what effect size metric was reported (e.g., association measures, correlation coefficients), and whether this data was comparable, computable, reliable, and interpretable (Harrer et al., 2021). Due to marked differences in reported outcome measures across the included studies, and limitations in the reported raw data required for calculations of effect size, quantitative synthesis of results was not possible. Consequently, the present study was limited to a qualitative review.

2. Results

2.1. Study selection

The studies that were screened, assessed for eligibility, and included in the review are presented in Fig. 1. Reasons for study exclusion are indicated at each stage in line with PRISMA data extraction outcomes (Moher et al., 2009). Eighty-eight articles were assessed for eligibility (see Appendix B). The characteristics of the 22 studies included in the review are presented in Table 1.

2.2. Participants

The 22 studies included in the present review comprised 16,825 adult participants aged between 18 and 88 years. Sample sizes varied between studies, ranging from 33 postpartum women to 5286 older adults involved in a retrospective cohort study. Of the 10 studies that provided details on their participants' gender, 79.5% were women (20.5% men). Across the studies, participant samples represented disparate demographics, including women with early-stage breast cancer diagnoses, male prisoner-of-war (POW) veterans, post-menopausal women, and individuals with human immunodeficiency virus (HIV). The total participant pool represented a range of diverse races and ethnicities, including African American, Chinese, European White, Korean, Latino, and Lebanese. Comprehensive exclusion criteria and rigorous screening were detailed by six of the 22 studies. For example, Prather et al. (2015) excluded participants based on untreated hypothyroidism, immunomodulatory medication usage (e.g., use of corticosteroids), pregnancy, presence of a psychiatric condition, and participation in mindfulness-based therapies 2-months before their study enrolment.

2.3. Sleep quality

More than one third of the 22 studies assessed sleep quality using an overall score from the PSQI (Buysse et al., 1989). An additional three studies assessed the sleep quality variable using a single item from the PSQI; that is, participants were asked to rate their sleep quality overall using response options that ranged from *very bad* (1) to *very good* (5). Two studies assumed poor sleep quality for participants who met diagnostic criteria for OSA, primary insomnia, and general insomnia using the Structured Clinical Interview for Diagnostic Statistical Manual – Fourth Edition (SCID-IV; First et al., 2002) and the International Classification of Sleep Disorders (American Academy of Sleep Medicine [AASM], 2014), respectively. The nine remaining studies assessed sleep quality using one or more of the following self-rated scales: Epworth Sleepiness Scale (ESS; Johns, 1991), General Sleep Disturbance Scale (GSDS; Lee, 2007), Insomnia Severity Index (ISI; Bastien et al., 2001), Jenkins Sleep Problems Scale (JSPS; Jenkins et al., 1988), and Women's Health Initiative Insomnia Rating Scale (WHIIRS; Levine et al., 2003).

2.4. Telomere length

In all studies except three, telomere length was measured using real-time quantitative polymerase chain reaction (qPCR) methodology, as described in previously published telomere measurement protocols (e.g., Cawthon, 2002; Cawthon et al., 2003; Lin et al., 2010; Prather et al., 2015; Savale et al., 2009). One study provided a detailed protocol, which outlined their use of multiple immune cell subsets (e.g., granulocytes and peripheral mononuclear cells were subdivided into lymphocytes, such as T cells, B cells, natural killer cells, and monocytes), hence providing a highly reproducible telomere length measurement methodology. One study used a DNA methylation telomere length protocol. Another study used a salivary measure, in line with protocols described by Cawthon (2002), Cawthon (2009), and Montpetit et al. (2014), which is a method that is considered to provide high measurement reliability (Stout et al., 2017). One study used two methodologies to assess telomere length. The first method was monochrome, multiplex real-time quantitative polymerase chain reaction (MMqPCR), which provided a telomere/single-copy gene (T/S) ratio. MMqPCR compares the value that represents an "average" telomere length across all types of cells in a whole blood specimen (telomere repeat sequence copy number [T]) relative to the value obtained for copies of albumin (a reference single copy-gene copy number [S]). The second method was a chromosome arm-specific fluorescent in situ hybridisation (FISH) technique. More than one third of studies detailed methods of telomere measurement using qPCR in terms of base pairs, which is reported to require less DNA and be more time-efficient than the traditional Southern Blot method (Aviv et al., 2011; Cawthon, 2009; Prather et al., 2011). Further, Puterman et al. (2015) noted that the qPCR procedure provides results that are most significantly associated with the Southern Blot method.

2.5. Study designs

All study designs included in the review were cross-sectional. Regression analyses were primarily used in the studies to examine whether sleep quality was statistically significantly associated with telomere length. Multiple time points were recorded in five longitudinal studies, ranging from a 12-month interval between measurements in Carroll et al.'s (2021) study to five data collection points from 1991 to 2015 in Aloni et al.'s (2021) study. Iloabuchi et al. (2020) used a retrospective cohort design, collecting data in 2006 and 2008.

2.6. Telomere length measurement risk of bias within studies

One study by Alhareeri et al. (2020) provided a detailed quality control protocol (e.g., lab personnel were blinded to study participants' clinical history and chemotherapy status). Mean genomic telomere length was determined using five-time points across a 2-year longitudinal study. Telomere length changes were calculated using two comprehensive complementary assays (i.e., MMqPCR and FISH methods), which provided an opportunity to identify average (genome-wide) and single (potentially sentinel) telomere length changes. Alhareeri and colleagues noted that their chosen methodology to measure telomere length provided accurate estimates of individual telomeres rather than a genomic "average" length.

2.7. Data analyses

Of the 22 studies reviewed, 20 studies provided quantitative results on the association between sleep quality and telomere length. However, results were determined using disparate statistical analyses, including Wilcoxon's signed-rank test, hierarchical multiple regression, partial correlation, Mann-Whitney *U* test, stepwise multinominal logistic regression, and Analysis of Variance (ANOVA). Two studies did not report quantitative data (Barceló et al., 2010; Kwon et al., 2015); rather qualitatively reported a non-significant association between sleep

Table 1
Characteristics of Included Studies.

Author (Date)	Title	*N*	Age	Sleep Quality Measure (s)	Telomere Length Measurement	Design	Analysis
Alhareeri et al. (2020)	Telomere lengths in women treated for breast cancer show associations with chemotherapy, pain symptoms, and cognitive domain measures: A longitudinal study	70 women (30.6% = Black cohort, 69.4% = White cohort) with early-stage breast cancer undergoing medical treatment	23–71 years (*M* = 52.0 years)	General Sleep Disturbance Scale (GSDS; Lee, 2007)	Monochrome, multiplex real-time quantitative polymerase chain reaction (MMqPCR) method, and chromosome arm-specific fluorescent in situ hybridisation (FISH) technique	Cross-sectional/ longitudinal with measures taken at five time-points during breast cancer treatment across 2 years	Mixed effects linear model
Aloni et al. (2021)	Premature aging among trauma survivors - The longitudinal implications of sleep disruptions on telomere length and cognitive performance	Ex-prisoner of war (POW) veterans (*n* = 99) and veterans who were not captured (*n* = 101)	Ex-POW veterans mean age across four time points was 40.6 years, 52.6 years, 57.6 years, and 64.2 years (*SD* = 4.56)	Posttraumatic Stress Disorder Inventory (PTSD-I; Solomon et al., 1993) item: "Do you suffer from sleep disruptions, difficulty falling asleep, fragmented sleep, or early morning awakening?"	Southern Blot method using total white blood cells (leukocytes) from whole blood samples based on previously published protocol	Cross-sectional/ longitudinal study of 1973 Yom Kippur War Israeli veterans who participated in four assessments (1991, 2003, 2008, and 2015)	Intercorrelations and structural latent modelling
Barceló et al. (2010)	Telomere shortening in sleep apnea syndrome	256 adults with Obstructive Sleep Apnea Syndrome (OSAS; 82.8% men) and 148 controls without OSAS (72.8% men)	OSAS participants (*M* = 51.0 years; *SD* = 1.0) and 148 control participants (*M* = 47.0 years, *SD* = 1.0)	Abnormal sleep parameters and somnolence assessed by the Epworth Sleepiness Scale (ESS; Johns, 1991)	Quantitative PCR-based technique based on a previously published protocol	Cross-sectional	Multiple regression analysis
Boyer et al. (2016)	Telomere shortening in middle-aged men with sleep-disordered breathing	161 men	30–60 years (*M* = 46.8 years, *SD* = 6.9)	ESS (Johns, 1991), Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), and polysomnography	Real-time qPCR methodology using previously published protocols	Cross-sectional	Univariate and bivariate analyses
Carroll et al. (2016)	Insomnia and telomere length in older adults	126 men and women (45 with insomnia, 81 control participants)	60–88 years comprising two groups (60–69 years and 70–88 years)	Structured Clinical Interview for Diagnostic Statistical Manual-Fourth Edition (SCID-IV; First et al., 2002) diagnostic criterion for Primary Insomnia (PI) and International Classification of Sleep Disorders (ICSD-2; American Academy of Sleep Medicine [AASM], 2014) diagnostic criteria for general insomnia	Real-time qPCR methodology using previously published protocols	Cross-sectional	Regression
Carroll et al. (2019)	Obstructive sleep apnea, nighttime arousals, and leukocyte telomere length: The multi-ethnic study of atherosclerosis	672 women from the Multi-Ethnic Study of Atherosclerosis designed to examine risk factors for cardiovascular disease	44–84 years	Women's Health Initiative Insomnia Rating Scale (WHIIRS; Levine et al., 2003) and ESS (Johns, 1991)	Standardised real-time qPCR method based on previously published protocols	Cross-sectional/ 10-year prospective study	General linear models
Carroll et al. (2021)	Postpartum sleep loss and accelerated epigenetic aging	33 women	23–45 years (*M* = 33.6 years, *SD* = 5.29)	PSQI (Buysse et al., 1989)	DNA methylation telomere length calculated using established protocols	Cross-sectional/ 12-month longitudinal study	Independent samples *t*-test
Cribbet et al. (2014)	Cellular aging and restorative processes: Subjective sleep quality and duration moderate the association between age and telomere length in a sample of middle-aged and older adults	154 adults (89 men, 65 women)	44–77 years	PSQI (Buysse et al., 1989)	Real-time qPCR methodology using previously published protocols	Cross-sectional	Multiple regression analysis

(*continued on next page*)

Table 1 (*continued*)

Author (Date)	Title	*N*	Age	Sleep Quality Measure (s)	Telomere Length Measurement	Design	Analysis
Ding et al. (2018)	Stronger association between insomnia symptoms and shorter telomere length in old HIV-infected patients compared with uninfected individuals	244 men with HIV; 244 control participants matched by age, gender, and education	≥40 years (M = 52.4 years; SD = 9.0)	Jenkins Sleep Problems Scale (JSPS; Jenkins et al., 1988)	Real-time qPCR adapted from published methods	Cross-sectional	Linear regression models
Garland et al. (2014)	A nested case-controlled comparison of telomere length and psychological functioning in breast cancer survivors with and without insomnia symptoms	70 women with prior breast cancer diagnosis and insomnia, 70 matched controls (i.e., BMI, age, gender)	Insomnia group (42–84 years; M = 59.9 years, SD = 9.6); matched control (41–84 years; M = 59.8 years, SD = 9.4)	Insomnia Severity Index (ISI; Bastien et al., 2001)	Mean terminal restriction fragment lengths in line with previously published protocol	Cross-sectional case-control design	Wilcoxon signed rank test
Grieshober et al. (2019)	A cross-sectional analysis of telomere length and sleep in the women's health initiative	3145 post-menopausal women from the Women's Health Initiative prospective study (1796 European American, 1349 African American)	M = 64.7 years, SD = 7.0	WHIIRS (Levine et al., 2003)	Southern Blot based on a previously published protocol	Cross-sectional	Linear regression models
Iloabuchi et al. (2020)	Association of sleep quality with telomere length, a marker of cellular aging: A retrospective cohort study of older adults in the United States	5268 participants from the Health and Retirement Study (55% women)	50–80+ years (M = 67.0 years, SD = 10.0)	JSPS (Jenkins et al., 1988)	Salivary measure using qPCR technique as per previously published methods	Retrospective cohort design using data collected in 2006 and 2008	Multiple regression analysis
Kwon et al. (2015)	The association between leukocyte telomere lengths and sleep instability based on cardiopulmonary coupling analysis	381 adults (138 men, 243 women) recruited from the Korean Genome and Epidemiology Study	≥45 years (M = 58.9 years, SD = 7.1)	PSQI (Buysse et al., 1989) and sleep stability assessment using cardiopulmonary coupling (CPC) analysis	Quantitative real-time polymerase chain reaction (qRT-PCR) protocol based on previously published protocols	Cross-sectional	Generalised linear model with adjustment of significant covariates
Lee et al. (2014)	Telomere length is associated with sleep duration but not sleep quality in adults with human immunodeficiency virus	283 adults (210 men, 73 women) with human immuno-deficiency virus (HIV)	22–77 years (M = 44.9 years, SD = 8.4)	PSQI (Buysse et al., 1989) and actigraphy to measure wake time after sleep onset	Real-time qPCR methodology from previously published protocols	Cross-sectional	Hierarchical linear regression analysis
Prather et al. (2011)	Shorter leukocyte telomere length in midlife women with poor sleep quality	245 women	50–66 years (M = 57.5 years, SD = 4.4)	PSQI (Buysse et al., 1989) item: "How would you rate your sleep quality overall?"	Real-time qPCR methodology adapted from previous published methods	Cross-sectional	Linear regression models
Prather et al. (2015)	Tired telomeres: Poor global sleep quality, perceived stress, and telomere length in immune cell subsets in obese men and women	87 adults with body mass index (BMI) score between 30 and 45; 81.6% women; 62.8% White and non-diabetic	≥18 years (M = 35.4 years, SD = 3.6)	Three-model structure of PSQI (Buysse et al., 1989): sleep efficiency, perceived sleep quality, and daily disturbance	qPCR methodology from previously published protocols; T/S ratio for each sample was measured twice	Cross-sectional	Partial correlation and multiple linear regression
Puterman et al. (2015)	Determinants of telomere attrition over 1 year in healthy older women: Stress and health behaviours matter	231 women with normal BMI weight range	50–65 years	PSQI (Buysse et al., 1989) item: "How would you rate your sleep quality overall?"	qPCR method (reported use of base pairs)	Cross-sectional	Multiple regression analyses
Tempaku et al. (2018)	Long sleep duration, insomnia, and insomnia with short objective sleep duration are independently associated with short telomere length	925 adults (55.4% women)	≥18 years (M = 48.1 years; SD = 19.8)	PSQI (Buysse et al., 1989) and ESS (Johns, 1991)	MMqPCR method as per previous protocol	Cross-sectional	Mann-Whitney U test
Teo et al. (2019)	Digital phenotyping by consumer wearables identifies sleep-associated markers of cardiovascular disease risk and biological aging	482 adults	21–69 years; (M = 46.0 years)	PSQI (Buysse et al., 1989) and objective sleep consumer wearables	qPCR method (reported use of base pairs)	Cross-sectional	Hierarchical linear regression analysis

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Table 1 (*continued*)

Author (Date)	Title	*N*	Age	Sleep Quality Measure (s)	Telomere Length Measurement	Design	Analysis
Wynchank et al. (2019)	Delayed sleep-onset and biological age: Late sleep-onset is associated with shorter telomere length	2,981 participants from the Netherlands Study of Depression and Anxiety participants	18–65 years; $M = 41.8$ years, $SD = 13.1$ (Wave 1) and $M = 48.6$ years, $SD = 12.9$ (Wave 2)	WHIIRS (Levine et al., 2003) comprising self-rated questions based on prior 4 weeks (i.e., trouble falling asleep, sleep quality)	qPCR adapted from published original method and converted into base pairs	Cross-sectional/ ongoing longitudinal, naturalistic cohort study; two waves 6 years apart	Linear regression analysis over two time points
Zgheib et al. (2018)	Short telomere length is associated with aging, central obesity, poor sleep and hypertension in Lebanese individuals	497 adults	≥18 years	Single question items: "Feel that you are not getting enough sleep?" and "Sleep difficulties?"	Real-time qPCR method	Cross-sectional	Stepwise multinomial logistic regression model
Zhang et al. (2019)	Folic acid supplementation suppresses sleep Deprivation induced telomere dysfunction and senescence-associated secretory phenotype (SASP)	96 (41 men, 55 women)	$M = 57.5$ years; $SD = 10.5$	PSQI (Buysse et al., 1989) to assess sleep quality in the month preceding study commencement	Real-time qPCR method	Cross-sectional	Analysis of Variance (ANOVA)

quality and telomere length. For example, Kwon and colleagues reported that their generalised linear model (GLM), which was adjusted for covariates, indicated no significant correlation between sleep quality (assessed using the PSQI; Buysse et al., 1989) and telomere length.

Four studies reported a significant association between poor sleep quality and telomere length. Prather et al. (2011) and Prather et al. (2015) reported unstandardised betas, SE B, and p values; Teo et al. (2019) reported standardised beta and p value, and the fourth study by Zhang et al. (2019) reported p value only. Zhang et al.'s corresponding author was contacted to request access to their ANOVA data; however, to date, no response had been received. Three additional studies presented mixed results. Iloabuchi et al. (2020) reported a non-significant association between overall sleep quality and telomere length, $B(SE) = -0.03(0.04)$, $p = .33$. However, Iloabuchi et al.'s study participants who "never felt rested in the morning" had significantly shorter telomere lengths than those who "always felt rested in the morning"; that is, the sleep quality and telomere length variables were significantly inversely related, $B(SE) = -0.08(0.03)$, $p < .01$. Carroll et al.'s (2016) slope analyses revealed a significant association with age and telomere length in participants with insomnia, $B(SE) = -0.02(0.008)$, R square change = 0.15, $p = .01$. However, age was not significantly associated with telomere length in Carroll et al.'s good sleeper (control) sample. Similarly, Ding et al. (2018) reported a significant associated between insomnia symptoms and telomere length in individuals with HIV aged 55 years and older, $\beta = -0.25$, (95% CI - 40.8 to −3.7), $p = .026$ but not in participants aged between 40 and 54 years, $\beta = -0.10$ (95% CI -30.0 to 16.2), $p = .428$. The remaining 13 studies did not find a statistically significant association between sleep quality and telomere length variables. A summary of the results reported by each study in displayed in Appendix B.

2.8. Risk of bias across studies

Sleep quality was measured via self-report in 20 studies, presenting a risk that reporting bias may have influenced results. Three studies attempted to reduce this bias by obtaining objective measures of sleep parameters (e.g., sleep stability) using actigraphy, consumer wearable device technology (e.g., FitBit Charge HR), and electrocardiography, which were correlated with subjective measures. Additionally, less than one third of studies adjusted their statistical models for covariates (i.e., chronic health conditions, body mass index [BMI], depressive symptomology, physical activity, tobacco smoking, caffeine intake, and education) to avoid confounding analyses. Notably, all but one study by Iloabuchi et al. (2020) reported prior approval from an Institutional Review Board (IRB) or Human Research Ethics Committee.

3. Discussion

The present study aimed to provide a meta-analytic review of studies that have examined the association between variables of sleep quality and telomere length, a biological marker of cellular aging. It was predicted that a weighted meta-analytic effect size would indicate that sleep quality was significantly associated with telomere length. Twenty-two studies were included in the review. Four of the 22 studies presented evidence to support a significant association between sleep quality and telomere length. Three additional studies identified a positive association between sleep quality in clinical sleep samples but not in control samples. Of the 22 studies reviewed, 13 studies did not find a statistically significant association between sleep quality and telomere length. The remaining two studies qualitatively reported a non-significant association between sleep quality and telomere length. Due to marked differences in reported outcome measures across the included studies and limited reported raw data, the planned meta-analysis was not possible.

The reported association between sleep quality and telomere length variables in the literature was inconsistent across studies. The discrepant findings may be in part attributed to the disparate operationalisation of the sleep quality construct. For example, poor sleep quality was considered to represent "disrupted sleep" in some studies, while in others, the variable was defined as "frequent arousal". Iloabuchi et al. (2020) argued that while "feeling rested in the morning" provides a global measure that reflects in part sleep duration, the subjective marker provides a comprehensive indicator of overall sleep quality. Other research supports the concept that feeling refreshed upon waking is a strong indicator of sleep quality (see Harvey, 2008; Lemola et al., 2013; Liberati et al., 2009; Libman et al., 2016). Moreover, Prather et al. (2015) argue that sleep efficiency (assessed by the PSQI; Buysse et al., 1989) reflects habitual sleep efficiency and sleep duration, which define the sleep quality construct. Notably, Prather and colleagues suggested that the influence of global sleep quality on telomere attrition could be driven by the consequences of sleep loss, such as daytime sleepiness and the subjective experience of poor sleep, rather than indices of actual sleep behaviour. Notwithstanding, the varying operationalisation of sleep quality across reviewed studies highlights the need for a standardised definition of global sleep quality, as previously argued by Krystal and Edinger (2008).

One-half of the studies used an empirically based self-report measure to assess sleep quality (e.g., PSQI; Buysse et al., 1989), which provided

some consistency in the operationalisation of the sleep quality construct. However, two studies assumed poor sleep quality for participants who met diagnostic criteria for clinical sleep disorders, including OSA and insomnia. It has been suggested that sleep disturbance, such as snoring, may influence telomere attrition by reducing sleep quality in the absence of an actual sleep disorder (Shin et al., 2016). Therefore, it is possible that participants who do not meet the criteria for OSA may still experience poor sleep quality. Notably, consideration was made to exclude studies from the current review that determined sleep quality based on presenting participant characteristics (e.g., meeting clinical diagnostic criteria for insomnia). However, it was decided to retain these studies to help highlight the need for a standardised operationalisation of the sleep quality construct in future research to enable comparisons across studies.

Overall results identified in the current review appear somewhat incongruent with recent findings. Several meta-analyses have identified significant associations between various sleep parameters (i.e., sleep duration, sleep apnoea, and insomnia) and shorter telomeres as a biomarker of cellular aging (Barceló et al., 2010; Huang et al., 2018; Irwin et al., 2016). Multiple factors are hypothesised to impact the relationship between such sleep parameters and cellular aging. For example, the effects of sleep quality may differ based on sex, and this difference can appear more pronounced in individuals aged 50 years and older (Redline et al., 2004). Other factors that can confound the assessment of sleep quality include age-related chronic disease (Epel et al., 2008) and telomere biology, such as the rate of loss of telomere length and their role across the life span (Tricola et al., 2018; Vera and Blasco, 2012). Such findings highlight the importance of quantitative assessment to control for potential confounding variables, such as participant age when assessing the relationship between sleep quality and telomere attrition.

The current review has several strengths at the study, outcome, and review level. At the study level, included studies were consistent in their approach to measure telomere length, drawing on published protocols. Several studies carefully detailed their approach to telomere length measurement, which provided a reproducible methodology. At the outcome level, more than one third of reviewed studies controlled for lifestyle variables and adjusted statistical models to control for significant covariates such as age and medical and clinical mental health factors. At the review level, reporting bias was addressed using a second reviewer, and the retrieval of identified research followed a rigorous and comprehensive protocol. Additionally, the current review has helped to provide insight into an emerging topic relating to sleep and telomeres.

3.1. Limitations

3.1.1. Methodological considerations

Several limitations at the study and outcome level should be addressed. The body of work on sleep quality and telomere length lacks study design homogeneity. The reviewed studies ranged from prospective cohort designs (with multiple data collection points) to simple cross-sectional designs (with one data collection point). While a causal relationship cannot be inferred between the constructs examined, the cross-sectional nature of the reviewed data does not exclude the possibility that shorter telomere length results in poorer sleep quality. For example, significant associations are reported between shorter telomere length and human inflammation elevations (Effros et al., 2005; O'Donovan et al., 2011; Révész et al., 2016), which are exacerbated by problematic sleep (Bryant et al., 2004). Moreover, the absence of randomised control trials (RCT) in the literature means it is not possible to determine whether observed differences in telomere length are impacted by sleep quality. Experimental designs with controls would help to increase the internal validity of future research. In particular, the effects of improved sleep quality on telomere attrition could be experimentally tested using adequate sampling timeframes and aged-matched controls. Psychological sleep interventions designed to improve sleep quality could be tested against telomere length measures using epigenetic age-adjusted estimates in linear regression models.

Another methodological limitation at the study level relates to confounding variables. Since the association between sleep quality and telomere length may be confounded by third variables, such as age-related chronic disease (Epel et al., 2008; Tricola et al., 2018; Vera and Blasco, 2012), it is important to assess for potential confounding variables. Moreover, it is important to recognise that the experience of sleep quality can significantly vary due to dimensions such as dysfunctional sleep cognitions, selective attention biases, and coping strategies, which occur in unique combinations (Morin et al., 2011); therefore, such variables would need to be controlled in future study designs.

The reviewed studies represented a participant pool comprising diverse ethnicities and demographic factors. Participants included trauma survivors, women with breast cancer undergoing chemotherapy treatment, and ex-POW veterans. This participant heterogeneity has limited the generalisability of current findings to a non-clinical adult population. Caution is also warranted when interpreting present findings from smaller samples as effects are likely to vary even within samples. Larger samples are recommended to increase the statistical power to detect changes in telomere length and contribute greater insight into the mechanisms that underlie telomere attrition as it relates to sleep quality.

3.1.2. Theoretical assumptions

A selection of the reviewed studies posited that poor sleep quality might produce cellular damage that negatively influences telomere length by increasing inflammation and oxidative stress levels (see Prather et al., 2015; Puterman et al., 2015; Zhang et al., 2019). Poor sleep quality has been associated with an increased risk for declining physical and mental functioning, which in turn predicts the risk of age-related morbidity and mortality and altered molecular pathways linked to inflammation and biological aging. While there appears a lack of causal data support in human research, animal studies have provided initial support for this theory (Snyder et al., 2017; Zygmunt et al., 2017). Prior research has also linked poor sleep quality with increased cortisol and cytokines secretion and reduction in melatonin (an anti-inflammatory sleep regulator), which adds support to the theory that telomere attrition may result from exposure to oxidative stress (Zgheib et al., 2018). It is therefore plausible that biological mechanisms, such as stress reactivity, oxidative stress, and inflammation, may mediate the link between feeling rested in the morning and telomere length. For example, research has identified links between stress and worry and non-restorative sleep (i.e., not feeling rested in the morning; Stone et al., 2008). Sleep-stress reactivity, as a symptom of primary insomnia, appears to be associated with elevations in the cortisol hormone, which has been linked to decreases in telomere activity (Choi et al., 2008; Tomiyama et al., 2012). This theory offers a potential direction for future research.

An alternative theoretical assumption that could provide direction for future research on sleep quality and telomere length draws from a neuropsychological perspective (Harrison and Horne, 2000). This model attributes sleep disruptions to focal cognitive functioning impairment. Controlled attention, hypervigilance, and arousal mechanisms – which are responsible for sleep drive and attention – are thought to destabilise neurobiological systems that impact sleep quality. It may be helpful to identify the impact of impaired focal cognitive functioning on sleep quality using experimental study designs. Additionally, indices of cellular aging on circadian and homeostatic processes could offer further insight into the mechanics through which sleep may impact cellular aging (Cribbet et al., 2014). As sleep quality appears to fluctuate over time more than sleep duration (Lee et al., 2014), longitudinal designs with multiple time-point measurements may provide more accurate data related to cumulative cellular aging.

3.1.3. Telomere length measurement

The approach to measure telomere length varied across studies in the review. Telomere length was measured in most studies using leukocytes as opposed to multiple immune cell subsets. This single measure of relative telomere length may have biased findings since this approach can make it difficult to distinguish between the proportion of telomeres that show actual shortening against shortening resulting from differences in cell composition or measurement error (Wynchank et al., 2019). Telomere attrition can also vary across different cell types (i.e., T cells, B cells, and monocytes), which may bias relative telomere length results. Future research could look to directly compare telomere length results from each assay method, which would enable estimates of validity for each method based on intercorrelations of the methods and their independent correlations with measures of sleep quality.

The field of telomere research is not without controversy (Tobler et al., 2021). Some researchers argue that telomere shortening rate (rather than telomere length) provides a more useful critical determinant of cellular aging and longevity (Benetos et al., 2013; Daniali et al., 2013; Ehrlenbach et al., 2009). Telomere shortening rate, as opposed to length (a more transient measure), may provide a more useful measure of cellular aging/life span/longevity across time. Therefore, future longitudinal research could examine whether poor sleep is differentially associated with telomere length across different cell types and shortening rates. Further, while telomere shortening is considered a biological marker of accumulated cellular damage and human aging (Bernadotte et al., 2016; Chen et al., 2011), the association between telomere shortening and changes in telomerase activity has been implicated in various age-related diseases, such as cardiovascular disease (CVD) and Alzheimer's disease (Fitzpatrick et al., 2007; Rizvi et al., 2014). Shortened telomeres stimulate telomerase. Telomerase is an enzyme that can lengthen telomeres (Blackburn, 2000). Assessment of cellular aging through telomerase activity as part of the telomere maintenance system could offer a more dynamic measure of cellular aging (Blackburn, 2001, 2005; Prather et al., 2011; Rizvi et al., 2014). It was noted that none of the studies in the present review provided a measure of telomerase activity. Future research may look to assess whether diminished telomerase activity varies by sleep quality.

3.1.4. Self-report measures

Self-report measures of sleep quality entail a risk of reporting bias; therefore, future studies could include additional methods of sleep data collection using ecologically valid measures of sleep, such as in-home polysomnography and actigraphy (Krystal and Edinger, 2008). Objective indices of sleep can help to examine sleep quality, including sleep duration using wearable technologies (e.g., FitBit) that offer a cost-effective alternative to laboratory-based assessment of sleep metrics (Scott et al., 2020; Teo et al., 2019). Screening for primary sleep disorders is also an important design feature for future research involving sleep quality (Aloni et al., 2021). Sampling within a population with greater variation in the quality of their sleep could be accomplished by including a more comprehensive measure of subjective sleep quality (Prather et al., 2011). There also appears the need for more objective biological measures of sleep quality, such as sleep stability using cardiopulmonary coupling (CPC) analysis based on electrocardiogram (ECG) results and inflammation markers associated with sleep deprivation (Cribbet et al., 2014; Kwon et al., 2015) to contribute insight to the research field.

3.1.5. Statistical analysis

Causal relationships cannot be inferred between the constructs examined in the review due to the correlational research design of included studies. The statistical relationship examined between telomere length and sleep indices were largely constructed using a linear model. Although the models were adjusted for significant covariates, it is important to note that the prediction errors could have increased if other variables or unobserved confounding factors were significant. Few studies used a power analysis; therefore, current sample sizes may have been inadequate to show statistically significant associations or have reduced the effect size of the reported association between sleep quality and telomere length. Most notably, the limited reporting of statistical data (e.g., a measure of the precision of the effect size or raw data, such as standard error to enable effect size calculation; Harrer et al., 2021) precluded the possibility of conducting a meta-analysis.

3.2. Future directions

Sleep quality is a term that has been used to describe an array of aspects related to the sleep experience, including sleep duration. It is also a construct thought to characterise the perception of feeling rested independent of sleep duration (Grandner and Kripke, 2004; Jarrin et al., 2013; Matricciani et al., 2018). Sleep quality arguably reflects a "subjective experience" that is more than the duration or number of wakings (Krystal and Edinger, 2008). Interestingly, several studies have found that approximately two thirds of clinical insomnia samples report poor sleep even when their objective sleep parameters (e.g., sleep onset latency, total sleep time, wake time after sleep onset) are comparable to normal sleepers (Coleman et al., 1982; Hermans et al., 2019; Krystal et al., 2002). Since objective indices of sleep parameters do not necessarily characterise the sleep experience, sleep quality appears to comprise more subtle and subjective factors (Krystal and Edinger, 2008). Findings of the current literature review emphasise the need for the standardised operationalisation of sleep quality and measurement consistency in future empirical research, which should include refinement of coarse measures of the sleep construct.

Additional studies are needed to help determine whether psychological factors may account for an association between sleep quality and telomere length and whether shortened telomeres could mediate poorer sleep. For example, feeling well-rested in the morning may be a clearer indication of overall sleep quality (Harvey, 2008; Iloabuchi et al., 2020), which could reflect dispositional optimism. Greater optimism may contribute to the biological process that promotes telomere repair and maintenance (Schutte and Malouff, 2020), and in this same way, sleep quality may buffer exposure to adverse factors that contribute to telomere attrition. In this way, it is possible that dispositional optimism moderates dysfunctional sleep beliefs to improve sleep quality and lower insomnia risk (Weitzer et al., 2021). Current equivocal findings in the literature indicate a complexity in the relationship between the sleep construct and telomere attrition that warrants further research attention.

3.3. Conclusion

The present study aimed to provide a meta-analytic review of studies that have examined the association between sleep quality and telomere length. Twenty-two studies met review inclusion criteria. Qualitative analyses indicated a significant relationship between sleep quality and telomere length in four of the total studies reviewed, while three additional studies identified a positive association between sleep quality and telomere length in clinical sleep samples but not in non-clinical samples. A non-significant statistical association between sleep quality and telomere length was reported in 13 studies, while two additional studies reported non-significant qualitative findings only. The inconsistent findings contrast prior research that has identified significant associations between sleep parameters, including sleep duration, sleep apnoea, and insomnia, and shorter telomeres. Present findings highlight important targets for future research, such as the standardised operationalisation of the psychological construct of sleep quality. Longitudinal study designs that obtain prospective data on sleep parameters and telomere lengths are recommended. The effects of improved sleep quality on telomere length could be experimentally tested in larger samples using an adequate sampling timeframe and matched controls. Additionally, telomere measurement could be supplemented with other biological

measures such as telomerase to help determine whether sleep quality contributes to accelerated cellular aging. As sleep is a modifiable health behaviour, research in this area has clinical importance to help determine whether improved sleep quality provides protective effects on cellular aging, thereby reducing the risk for age-related disease and mortality.

Declaration of competing interest

All authors have approved the manuscript and agree with submission to *Brain, Behavior & Immunity – Health*. We have no conflicts of interest to declare.

Appendix A. Full-Text Articles Assessed for Eligibility

Study	Author (Year)	Title	Reason for Exclusion/Uncertainty
1	Aiello et al. (2020)	The link between sleep duration and telomere length: An exploratory study in Sicilian centenarians	Conference publication
2	Albuquerque et al. (2017)	Sleep restriction increases telomere length in skin of rats	Non-human subjects
3	Alhareeri et al. (2020)	Telomere lengths in women treated for breast cancer show associations with chemotherapy, pain symptoms, and cognitive domain measures: A longitudinal study	
4	Aloni et al. (2021)	Premature aging among trauma survivors - The longitudinal implications of sleep disruptions on telomere length and cognitive performance	
5	Ämmälä et al. (2020)	Maternal stress or sleep during pregnancy are not reflected on telomere length of newborns	Participants under 18 years of age
6	Banks et al. (2017)	Telomere length and salivary DNA methylation after 48 h of sleep deprivation	Oral abstract
7	Barceló et al. (2010)	Telomere shortening in sleep apnea syndrome	
8	Boyer et al. (2016)	Telomere shortening in middle-aged men with sleep-disordered breathing	
9	Carlson et al. (2017)	Protocol for the MATCH study (Mindfulness and Tai Chi for cancer health): A preference-based multi-site randomized comparative effectiveness trial (CET) of Mindfulness-Based Cancer Recovery (MBCR) vs. Tai Chi/Qigong (TCQ) for cancer survivors	Randomised comparative effectiveness study (CET) protocol
10	Carroll et al. (2013)	Telomere length predict the inflammatory response to sleep deprivation in older adults	Conference publication
11	Carroll et al. (2016)	Insomnia and telomere length in older adults	
12	Carroll et al. (2019)	Obstructive sleep apnea, nighttime arousals, and leukocyte telomere length: The multi-ethnic study of atherosclerosis	
13	Carroll et al. (2021)	Postpartum sleep loss and accelerated epigenetic aging	
14	Chae et al. (2020)	Racial discrimination and telomere shortening among African Americans: The Coronary Artery Risk Development in Young Adults (CARDIA) Study	Sleep quality not assessed
15	Choi et al. (2008)	Interaction between obstructive sleep apnea and shortened telomere length on brain white matter abnormality	Association between sleep variables and telomere length not analysed
16	Cribbet et al. (2014)	Cellular aging and restorative processes: Subjective sleep quality and duration moderate the association between age and telomere length in a sample of middle-aged and older adults	
17	Ding et al. (2018)	Stronger association between insomnia symptoms and shorter telomere length in old HIV-infected patients compared with uninfected individuals	
18	Garland et al. (2014)	A nested case-controlled comparison of telomere length and psychological functioning in breast cancer survivors with and without insomnia symptoms	
19	Gaspar et al. (2017)	Obstructive sleep apnea and hallmarks of aging	Review article
20	Grieshober et al. (2019)	A cross-sectional analysis of telomere length and sleep in the women's health initiative.	
21	Huang et al. (2018)	The association between obstructive sleep apnea and shortened telomere length: A systematic review and meta-analysis	Systematic review and meta-analysis
22	Iloabuchi et al. (2020)	Association of sleep quality with telomere length, a marker of cellular aging: A retrospective cohort study of older adults in the United States	
23	Innes et al. (2018)	Effects of meditation and music-listening on blood biomarkers of cellular aging and Alzheimer's Disease in adults with subjective cognitive decline: An exploratory randomized clinical trial	Sleep quality not assessed
24	Irwin and Opp (2017)	Sleep health: Reciprocal regulation of sleep and innate immunity	Review article
25	Jackowska et al. (2012)	Short sleep duration is associated with shorter telomere length in healthy men: Findings from the Whitehall II Cohort Study	Sleep quality not assessed
26	James et al. (2017)	Sleep duration and telomere length in children	Participants under 18 years of age
27	Kananen et al. (2010)	Childhood adversities are associated with shorter telomere length at adult age both in individuals with an anxiety disorder and controls	Participants under 18 years of age
28	Kiecolt-Glaser et al. (2011)	Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation	Sleep quality acknowledged as a control variable only
29	Kim et al. (2010)	Leukocyte telomere length and plasma catestatin and myeloid-related protein 8/14 concentrations in children with obstructive sleep apnea	Participants under 18 years of age
30	Kim et al. (2016)	Oxidative stress-induced telomere length shortening of circulating leukocyte in patients with obstructive sleep apnea	Inseparable data on participants under 20 years of age
31	Knowles et al. (2018)	0036 Sleep, inflammation and telomere length	Full article requested via researchgate.net but not supplied
32	Kwon et al. (2015)	The association between leukocyte telomere lengths and sleep instability based on cardiopulmonary coupling analysis	
33	Ledda et al. (2020)	Telomere length as a biomarker of biological aging in shift workers	Review article
34	Lee et al. (2014)	Telomere length is associated with sleep duration but not sleep quality in adults with human immunodeficiency virus	
35	Li et al. (2017)	The association between post-traumatic stress disorder and shorter telomere length: A systematic literature review	Systematic review

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Study	Author (Year)	Title	Reason for Exclusion/Uncertainty
36	Liang et al. (2011)	Associations between rotating night shifts, sleep duration, and telomere length in women	Sleep quality not assessed; poor sleep inferred by night shift employment
37	Lin et al. (2019)	Effect of oral appliance on circulating leukocyte telomere length and SIRT1 in obstructive sleep apnea	Sleep quality not assessed
38	Lin and Tao-Ping (2011)	Alteration of telomere length of the peripheral white blood cells in patients with obstructive sleep apnea syndrome	Non-English (Chinese) full text
39	Liu et al. (2017)	Association between sleep and leukocyte telomere length in middle-aged and older adults	Non-English (Chinese) full text
40	Maeda et al. (2021)	Telomere shortening velocity of patients administered with hypnotics is accelerated in a gender-differential manner	Sleep quality not assessed; poor sleep inferred by use of hypnotics
41	Nguyen et al. (2020)	Objectively measured sleep and telomere length in a population-based cohort of children and midlife adults	Sleep quality not assessed
42	O'Donovan et al. (2009)	Pessimism correlates with leukocyte telomere shortness and elevated interleukin-6 in post-menopausal women	Sleep quality and telomere length relationship not analysed
43	O'Donovan et al. (2011)	Cumulative inflammatory load is associated with short leukocyte telomere length in the Health, Aging and Body Composition Study	Sleep quality and telomere length relationship not analysed
44	Oerther and Lorenz (2019)	State of the science: Using telomeres as biomarkers during the first 1000 days of life	Review article
45	Osum and Serakinci (2020)	Impact of circadian disruption on health: SIRT1 and telomeres	Narrative literature review
46	Ouyang et al. (2017)	Restless roosts: Light pollution affects behavior, sleep, and physiology in a free-living songbird	Non-human subjects
47	Park et al. (2015)	Where you live may make you old: The association between perceived sleep neighbourhood quality and leukocyte telomere length	Sleep quality not assessed
48	Parks et al. (2009)	Telomere length, current perceived stress, and urinary stress hormones in women	Sleep quality and telomere length relationship not analysed
49	Parks et al. (2011)	Employment and work schedule are related to telomere length in women	Sleep quality and telomere length relationship not analysed
50	Pavanello et al. (2019)	Higher number of night shifts associates with good perception of work capacity and optimal lung function but correlates with increased oxidative damage and telomere attrition	Sleep quality not assessed; poor sleep inferred by night shift employment
51	Pinilla et al. (2021)	Association of obstructive sleep apnea with the aging process	Sleep quality not assessed
52	Polonis et al. (2017)	Moderate-to-severe obstructive sleep apnea is associated with telomere lengthening	Sleep quality not assessed
53	Polonis et al. (2019)	Telomere length and risk of major adverse cardiac events and cancer in obstructive sleep apnea patients	Sleep quality not assessed
54	Prather et al. (2011)	Shorter leukocyte telomere length in midlife women with poor sleep quality	
55	Prather et al. (2015)	Tired telomeres: Poor global sleep quality, perceived stress, and telomere length in immune cell subsets in obese men and women	
56	Prather et al. (2016)	Factors related to telomere length	Response to Tasdemir and Oz (2016) Letter to the Editor
57	Puterman et al. (2013)	Multisystem resiliency moderates the major depression –telomere length association: Findings from the Heart and Soul Study	Sleep quality not isolated as an aspect of the sleep variable
58	Puterman et al. (2015)	Determinants of telomere attrition over 1 year in healthy older women: Stress and health behaviors matter	
59	Puterman et al. (2016)	Lifespan adversity and later adulthood telomere length in the nationally representative US Health and Retirement Study	Sleep quality not assessed
60	Rensing et al. (2001)	Biological timing and the clock metaphor: Oscillatory and hourglass mechanisms	Review article
61	Rentscher et al. (2020)	Psychosocial stressors and telomere length: A current review of the science	Review article
62	Révész et al. (2016)	Baseline biopsychosocial determinants of telomere length and 6-year attrition rate	Sleep quality not assessed
63	Riestra et al. (2017)	Obstructive sleep apnea risk and leukocyte telomere length in African Americans from the MH-GRID study	Assessed OSA risk and their telomere lengths but not sleep quality
64	Salihu et al. (2015)	Association between maternal symptoms of sleep disordered breathing and fetal telomere length	Transgenerational impact of sleep quality on pregnant mothers with telomere length measured in newborns
65	Samavat et al. (2019)	Association between prediagnostic leukocyte telomere length and breast cancer risk: The Singapore Chinese Health Study	Sleep quality not assessed
66	Savolainen et al. (2014)	The history of sleep apnea is associated with shorter leukocyte telomere length: The Helsinki Birth Cohort Study	Sleep quality not assessed; poor sleep inferred by OSA and snoring
67	Shalev et al. (2013)	Stress and telomere biology: A lifespan perspective	Review summary article
68	Shin et al. (2016)	Association between snoring and leukocyte telomere length	Sleep quality not assessed; poor sleep inferred by snoring
69	Starkweather et al. (2014)	An integrative review of factors associated with telomere length and implications for biobehavioral research	Review article
70	Tasdemir and Oz (2016)	The factors causing bad sleep	Letter to the Editor
71	Tempaku et al. (2015)	Telomere length as a marker of sleep loss and sleep disturbances: A potential link between sleep and cellular senescence	Systematic review
72	Tempaku et al. (2016)	The importance of sleep in the association between perceived stress and telomere length	Editorial comment on Mathur et al.'s (2016) review
73	Tempaku et al. (2016b)	The effect of the severity of obstructive sleep apnea syndrome on telomere length	Sleep quality not assessed
74	Tempaku et al. (2016c	Letter to the editor: Sleep as a contributing factor in the relationship between depression and cell aging	Letter to the Editor on Lin et al.'s (2016) meta-analysis
75	Tempaku et al. (2018)	Long sleep duration, insomnia, and insomnia with short objective sleep duration are independently associated with short telomere length	
76		The paradigm of obstructive sleep apnea in aging: Interactions with telomere length	

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Study	Author (Year)	Title	Reason for Exclusion/Uncertainty
	Tempaku et al. (2018)		Comment on Huang et al.'s (2017) systematic review and meta-analysis
77	Tempaku et al. (2021)	Klotho genetic variants mediate the association between obstructive sleep apnea and short telomere length	Sleep quality not assessed
78	Teo et al. (2019)	Digital phenotyping by consumer wearables identifies sleep-associated markers of cardiovascular disease risk and biological aging	
79	Vgontzas et al. (2018)	Short telomere length and endophenotypes in sleep medicine	Comment on Tempaku et al.'s (2018a) article
80	Wang et al. (2017)	Associations of alcohol consumption and alcohol flush reaction with leukocyte telomere length in Korean adults	Sleep quality not assessed
81	Werlang et al. (2019)	Exposure to different intrauterine environments: implications for telomere attrition in early life	Review article with focus on impact of maternal sleep issues on newborn telomeres
82	Whiteman et al. (2017)	Telomere length and fetal programming: A review of recent scientific advances	Review article
83	Wolf et al. (2019)	The goddess who spins the thread of life: Klotho, psychiatric stress, and accelerated aging	Sleep quality and telomere length not assessed
84	Wynchank et al. (2019)	Delayed sleep-onset and biological age: Late sleep-onset is associated with shorter telomere length	
85	Wysocki and Seibert (2020)	Genomics of aging. Genes, adducts, and telomeres	Article series summary
86	Zgheib et al. (2018)	Short telomere length is associated with aging, central obesity, poor sleep and hypertension in Lebanese individuals	
87	Zhang et al. (2019)	Folic acid supplementation suppresses sleep deprivation-induced telomere dysfunction and senescence-associated secretory phenotype (SASP)	
88	Zhao et al. (2017)	Social-demographics, health behaviors, and telomere length in the Mexican American Mano a Mano Cohort	Sleep quality not assessed

Appendix B. Summary of Results Reported by Study

First Author (Date)	Reported Findings
Alhareeri et al. (2020)	Association between sleep disturbance and telomere length (T/S ratios) across five time points was statistically non-significant after stepwise removals (base model[a]; $p = .825$)
Aloni et al. (2021)	Association between sleep disruptions and telomere length measurements (i.e., at the fourth and final time point the correlation between telomere length and sleep disruptions was statistically non-significant, $r = .12$, $p > .06$)
Barceló et al. (2010)	Association between Epworth Sleepiness Scale (ESS; Johns, 1991) scores and telomere length in patients with obstructive sleep apnoea scores (OSAS) was statistically non-significant
Boyer et al. (2016)	Association between telomere length and Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and ESS (Johns, 1991) was statistically non-significant, $r = .10$, $p = .467$, and $r = .02$, $p = .320$, respectively. No statistically significant association was detected between telomere values and sleep quality; $\beta = 0.03$ (95% CI -0.03 to 0.08, $p = .299$) or sleepiness; $\beta = 0.00$ (95% CI -0.04 to 0.05), $p = .906$
Carroll et al. (2016)	Association of age with telomere length in insomnia cases was statistically significant, B(SE) = −0.02(0.008), R square change = 0.15, $p = .01$. Specifically, insomnia was associated with shorter telomere length in adults aged between 70 and 88 years, but not in participants younger than 70 years of age
Carroll et al. (2019)	Unadjusted estimates of telomere length by insomnia symptoms (Women's Health Initiative Insomnia Rating Scale; WHIIRS; Levine et al., 2003) scores >2; B (SE) = −0.008(0.016), $p = .63$) and sleepiness (ESS score >16 indicating clinical range (18.4% participants), B(SE) = −0.007(0.050), $p = .89$) after controlling for age, sex, and ethnicity were statistically non-significant
Carroll et al. (2021)	Independent samples t-test of postpartum telomere length as a function of sleep quality at 12-months postpartum. Good sleep quality PSQI (Buysse et al., 1989; score ≤5), M (SD) = 0.049 (0.172) compared with poor sleep quality (score >5), M (SD) = −0.013(0.18) was statistically non-significant, $p = .302$
Cribbet et al. (2014)	PSQI (Buysse et al., 1989) score did not significantly predict telomere length – no statistical data reported
Ding et al. (2018)	Telomere length was independently associated with insomnia symptoms in participants 55 years and older among the HIV-infected individuals, $\beta = -0.25$, (95% CI - 40.8 to −3.7), $p = .026$ but not in participants aged 40–54 years, $\beta = -0.10$ (95% CI -30.0 to 16.2), $p = .428$
Garland et al. (2014)	Association between insomnia severity and telomere length was statistically non-significant ($p = .31$)
Grieshober et al. (2019)	Association between sleep disturbance and telomere length were directionally similar and not statistically significant, $\beta = -3.0$ (95% CI -7.0 to 2.0), $p = .95$
Iloabuchi et al. (2020)	Association between overall sleep quality and telomere length was statistically non-significant, $B(SE)$ = −0.03(0.04), $p = .33$. However, respondents who never felt rested in the morning had significantly shorter telomere length than those who always felt rested in the morning, with the variables significantly inversely related, B(SE) = −0.08(0.03), $p < .01$; that is, the measure of sleep quality (i.e., feeling well rested in the morning) was significantly and inversely associated with telomere length after adjustment for multiple demographic, lifestyle, and health-related factors
Kwon et al. (2015)	Association between PSQI (Buysse et al., 1989) score and telomere length was non-significant – no statistical data reported
Lee et al. (2014)	Sleep quality measured by PSQI (Buysse et al., 1989) was not statistically significant in accounting for variance in telomere length in men, $\beta = -0.098$, $p = .241$ and in women, $\beta = 0.116$, $p = .324$
Prather et al. (2011)	Association between poor sleep quality and shorter telomere length (base pairs) independent of covariates was statistically significant, B(SE) = 55.46(27.43), $\beta = 0.133$, $t = 2.02$, $p = .044$
Prather et al. (2015)	Association between PSQI (Buysse et al., 1989) global sleep quality scores and shorter telomere length was statistically significant, B(SE) = −56.83(20.44), $p = .007$
Puterman et al. (2015)	Sleep quality did not independently attenuate the association between life stress on telomere attrition over time, B(SE) = −17.2(9.5), $p = .38$
Tempaku et al. (2018)	No statistically significant differences were found between non-short telomere length (48.8% participants) and short telomere length (44.7% participants) and daytime sleepiness and poor sleep quality, $p = .617$ and $p = .433$, respectively.
Teo et al. (2019)	Association between insufficient sleep and telomere attrition was statistically significant, $\beta = 0.253$ (95% CI 0.079 to −0.427), $p = .005$
Wynchank et al. (2019)	Association between WHIIRS (Levine et al., 2003) score ≥9 and telomere length was non-statistically significant over two time points, B(SE) = 11.91(18.91), $F = 0.86$ (1,3795), $p = .529$, $\eta p2 = .000$
Zgheib et al. (2018)	Association between poor perceived sleep quality and telomere length was non-statistically significant; odds ratio (95% CI) = 1.49 (0.87–2.55), $p = .15$
Zhang et al. (2019)	Poor sleep group had statistically significantly shorter telomere lengths compared with good sleeper group, $p < .0001$

Note. [a] The base model determined by the study design was telomere length = visit + chemotherapy (3 types) + radiation therapy + visit by chemotherapy + visit by radiation therapy with the participant being the random effect.

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