INVESTIGATING THE ASSOCIATIONS BETWEEN CARDIORESPIRATORY FITNESS, SLEEP AND COGNITION IN AGING.

INVESTIGATING THE ASSOCIATIONS BETWEEN CARDIORESPIRATORY FITNESS, SLEEP AND COGNITION IN AGING.

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B.Sc. Honours Combined Biology and Psychology

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

MASTER OF SCIENCE (2020) McMaster University
(Kinesiology) Hamilton, Ontario

TITLE: Investigating the associations between cardiorespiratory fitness, sleep and cognition in aging.

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NUMBER OF PAGES: xi, 91

ABSTRACT

With increasing age there is a decline in cognitive functions, including episodic memory and executive functioning. This decline is thought to be related to changes in sleep, as sleep quality and quantity also decline with aging. Physical activity is a promising tool that has been found to increase both sleep and cognition in older adults. Physical activity has been shown to protect executive functions against poor sleep in older adults. However, it is unknown if physical activity also helps to protect memory against poor sleep, and if this relationship differs by age. The present study investigated the relationship between cardiorespiratory fitness, sleep, and memory in both older and young adults. Twenty-six older adults ($M \pm SD$: 70.7 ± 2.8) and thirty-five young adults ($M \pm SD$: 21.0 ± 3.1) completed the Rockport 1-mile walk test to measure cardiorespiratory fitness. Participants wore an actigraph for one week to measure habitual sleep, and returned for a second visit to perform tasks assessing episodic memory and executive functioning. An interaction was found between sleep quality and cardiorespiratory fitness (p = .021), in that sleep enhanced memory for low fit older adults (p = .047) but not for high fit older adults (p = .19). Sleep also predicted executive functioning performance in older adults (p = .007), but this association was observed regardless of cardiorespiratory fitness. No significant relationships were observed between cardiorespiratory fitness, sleep, and cognition in young adults. Overall, these results suggest the relationship between cardiorespiratory fitness and sleep may differ for episodic memory and executive functions. Given that these aspects of cognition are supported by different underlying neurological processes, fitness and sleep may provide

complementary support for the aging brain. Future research should further investigate the underlying mechanism for the relationship between sleep, cardiorespiratory fitness, and cognition.

ACKNOWLEDGEMENTS

I would like to first thank my supervisor, Dr. Jennifer Heisz. From your guidance and mentorship, I have grown as a researcher and as a person. I am confident in my abilities as an academic by not questioning my knowledge or decisions, and I will always make sure to find the story whenever I am trying to communicate ideas. You have provided me with every opportunity that I have asked for, and I am grateful to have had the opportunity to study under you.

Thank you to my supervisory committee, Dr. Audrey Hicks and Dr. Sue Becker, for your thoughtful suggestions, support, and critical evaluation, as you have helped me grow to become a stronger researcher.

I'd also like to thank Dr. Joyce Obeid for all of your support and guidance with teaching me how to use actigraphy.

Thank you to the NeuroFit Lab, past and present. I would not be here without your amazing guidance and support, your encouragement, and the positive environment you have created. Thank you for always being there for me and for helping create an amazing Master's experience. I'd also like to thank my research team. Thank you for being the best thesis and 3RP3 students in the world. Although mornings were a struggle, it was a pleasure starting each day with you all.

Finally, I want to say thank you to my friends, my kin, and my (Mac) Kin. Your unconditional love, support, and encouragement has allowed me to flourish into the person I am today.

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LIST OF ABBREVIATIONS

Aß	Amyloid-beta
BDI	Beck Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
CRF	Cardiorespiratory Fitness
DG	Dentate Gyrus
DSST	Digit Symbol Substitution Test
EEG	Electroencephalogram
EF	Executive Functioning
EM	Episodic Memory
HC	Hippocampus
MoCA	Montreal Cognitive Assessment
MST	Mnemonist Similarities Test
MVPA	Moderate-Vigorous Physical Activity
NREM	Non-Rapid Eye Movement
N1	NREM Stage 1
N2	NREM Stage 2
N3	NREM Stage 3
OA	Older Adults
PA	Physical Activity
PFC	Prefrontal Cortex
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
REM	Rapid Eye Movement
SWS	Slow-Wave Sleep
TST	Total Sleep Time
TMT	Trail Making Test
WASO	Wake After Sleep Onset
YA	Young Adults

DECLARATION OF ACADEMIC ACHIEVEMENT

Tara Kuhn's role:

- Wrote and submitted ethics application at McMaster University
- Designed study protocol and selected measures
- Recruited procedure
- Scheduled visits and set up lab equipment and materials
- Trained and supervised undergraduate research students to assist with data collection
- Led data collection, analysis, and interpretation
- Prepared manuscript

Role of co-authors:

- JH obtained study funding
- JH assisted TK with ethics amendment
- JH assisted TK with study design and selection of measures
- JH assisted TK with data interpretation

INTRODUCTION

Sleep is vital for brain health and we require certain amount of sleep every night for optimal cognitive functioning. The National Sleep Foundation recommends adults between the ages of 18-65 years old should sleep between 7-9 hours per night and older adults over the age of 65 years old should sleep between 7-8 hours per night (Hirshkowitz et al., 2015). Yet, approximately 1/3 of Canadians fail to meet those guidelines (Chaput, Wong, & Michaud, 2017), and even more people struggle to fall asleep or stay asleep (Chaput et al., 2017). Short sleep duration and poor sleep quality are associated with a host of negative brain health consequences, which can accumulate with chronic impaired sleep and cause cognitive decline (Altena, Ramautar, Van Der Werf, & Van Someren, 2010; Bruce & Aloia, 2006) as well as increase the risk and severity of dementia (Beaulieu-Bonneau & Hudon, 2009; Lim, Kowgier, Yu, Buchman, & Bennett, 2013; Sterniczuk, Theou, Rusak, & Rockwood, 2013). Physical activity is a promising tool that improves both sleep and cognition (Kredlow, Capozzoli, Hearon, Calkins, & Otto, 2015; Middleton, Barnes, Lui, & Yaffe, 2010) and reduces dementia risk (Blondell, Hammersley-Mather, & Veerman, 2014). Though to date, only one study has examined the moderating effect of physical activity on the relationship between sleep and cognition (Lambiase, Gabriel, Kuller, & Matthews, 2014). That study demonstrated worse cognitive performance for low active participants who slept poorly. Notably, participants who were high active performed similarly regardless of how poor they slept, suggesting a protective effect of exercise. However, this study only looked at executive functioning in older women. The present thesis sought to extend the generalizability by testing whether fitness

also moderates the relationship between sleep and memory function in a sample of young and older adult men and women.

Cognitive functions in aging.

Are all cognitive functions equally affected by aging?

In aging, certain cognitive abilities decline while others are relatively spared. Life-long accumulation of abilities which are familiar and well-practiced, such as general knowledge or vocabulary (crystalized intelligence), remain relatively intact or even improve with age (Christensen, 2001; Harada, Natelson Love, & Triebel, 2013; Salthouse, 2019). Obversely, "fluid" abilities related to processing and learning new information, attending to one's environment, reasoning, and problem solving, decline with age (Harada et al., 2013; Salthouse, 2010). Fluid abilities tend to peak around the age of 30 and start to decline linearly until around the age of 65, at which point this decline accelerates (Salthouse, 2019). Two key cognitive functions that decline in aging include executive functioning (EF) and episodic memory (EM).

How does executive functioning change with age?

EF is an umbrella term for the interrelated processes necessary for goal or future directed behavior. EF is thought to depend on the frontal regions of the brain, particularly the prefrontal cortex (PFC). EF can generally be broken down into three domains: inhibitory control, working memory, and cognitive flexibility (Diamond, 2013). When examining the relationship between physical activity, sleep, and EF, the prior study examined cognitive flexibility (Lambiase et al., 2014), which involves adjusting to new demands, rules, or priorities, learning from mistakes, or developing new strategies to

solve a problem (Anderson, 2002; Diamond, 2013). For example, one of the tasks Lambiase et al. (2014) used required participants to connect a series of alternating numbers and letters in ascending order (1-A-2-B-3-C, etc.), known as the Trail Making Test B.

EF peaks around 20-30 years of age and accordingly this demographic is best able to perform complex and demanding tasks that depend on inhibitory control, working memory, and cognitive flexibility (Anderson, Jacobs, & Anderson, 2011). EF declines with aging (Blaskewicz Boron, Haavisto, Willis, Robinson, & Schaie, 2018), with the most rapid declines beginning around the ages of 50-65 years and continuing to accelerate thereafter (Anderson et al., 2011). These declines in EF reflect several age-related changes to the frontal lobes. As the brain ages, the frontal lobes experience considerable declines in grey matter compared to posterior regions (Cabeza & Dennis, 2012; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Dramatic changes in the white matter of the PFC and the corpus callosum are also seen with aging (Persson et al., 2006; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Resnick et al., 2003), and are directly associated with EF impairments in aging (Gunning-Dixon & Raz, 2000).

How does episodic memory change with age?

Episodic memory is the memory related to personal experiences (Tulving, 1972), and much like EF, episodic EM declines linearly with age and accelerates around the age of 65 (Christensen, 2001; Salthouse, 2003, 2009, 2019). EM, along with spatial memory, is dependent on a substructure in the medial temporal lobes known as the hippocampus (HC) (Tulving, 1972). With aging there are significant declines in HC volumes which

accelerate after 50 years of age (Driscoll et al., 2003; Raz et al., 2010, 2005). Moreover, HC integrity has been associated with memory performance for spatial memories (Driscoll et al., 2003) and EM (Persson et al., 2006). Although much of the research around memory focuses on the HC, it is critical to note the HC does not work alone: EM has been found to depend on the connections between the HC and the PFC (Walker, 2009; Wilckens, Erickson, & Wheeler, 2012), as the PFC helps with both the sustaining attention and the organization of information needed for encoding and retrieving memories (Blumenfeld & Ranganath, 2007).

HC-dependent memory helps one discern between highly similar events, such as where one placed their keys today versus yesterday or identifying one's glasses from their partners glasses. These "similar but different" representations create interference, and are known as high-interference memories. High-interference memories may be accurately recalled as distinct or mistakenly recalled as identical, and this depends on the function of HC substructures: the dentate gyrus (DG), CA3, and CA1. The DG performs pattern separation, which stores similar inputs as distinct, non-overlapping representations (Holden & Gilbert, 2012). In this process, the DG received inputs from the entorhinal cortex via the perforant path and the DG projects powerful signals to the CA3 through mossy fibers (Yassa & Stark, 2011). In contrast, the CA1 performs pattern completion, which uses a prior memory representation to instate a partial or degraded cue. Interestingly, the CA3 can be involved in both pattern separation and pattern completion depending on the degree of similarity between stimuli (Yassa & Stark, 2011).

Distinguishing high-interference memories is thought to depend on hippocampal neurogenesis in the sub-granular cells of the DG, which is one of the few regions in the brain where adult neurogenesis occurs (Zhao, Deng, & Gage, 2008). Critically, neurogenesis declines with aging (Kuhn, Dickinson-Anson, & Gage, 1996), as does the integrity of the perforant pathways (Yassa, Muftuler, & Stark, 2010) impairing DG and CA3 function (Yassa, Mattfeld, Stark, & Stark, 2011). Consequently, the ability to process high-interference memories is compromised, as older adults show impaired high-interference memory compared to younger adults (Driscoll et al., 2003; Stark & Stark, 2017; Stark, Yassa, Lacy, & Stark, 2013) It appears older adults may need larger degrees of dissimilarity to separate identical stimuli, resulting in a shift towards pattern completion and reflecting an inclination for "gist" memories rather than detailed accounts (Holden & Gilbert, 2012; Stark, Yassa, & Stark, 2010).

Sleep, and how it relates to brain health.

What happens when we sleep?

Sleep is dynamic and consists of different stages that repeat in sequence throughout the night. These stages are divided into two distinct states: non-rapid eye movement (NREM), consisting of three stages (N1, N2, N3), and rapid eye movement (REM) sleep. These stages are recorded using polysomnography (PSG), which measures a variety of physiological processes, including brain activity using electroencephalograms (EEG).

Using EEG, wakefulness is characterized by high frequency (15-60Hz), low amplitude brain activity. N1 sleep is the first stage of sleep and is the transition between

wakefulness and sleep. N2 sleep is considered the first true stage of sleep, with brain activity decreasing in frequency and increasing in amplitude. During N2, intermittent bursts of high-brain activity (sleep spindles) and high amplitude spikes (k-complexes) occur. These k-complexes and sleep spindles are associated with the deactivation of the brain's arousal system. N3 sleep is the deepest and final stage of NREM sleep, and is also referred to as slow-wave sleep (SWS). Using EEG, SWS is characterized as low frequency, high amplitude delta waves generated in the medial PFC (Murphy et al., 2009). These slow wave oscillations are thought to reflect cortical and thalamic synchronization, with increased synchrony indicating less brain activity and decreased consciousness (Pace-Schott & Spencer, 2011). During the progression through NREM sleep, brain activity gradually becomes more synchronized while autonomous functions (heart rate, breathing, temperature regulation, etc.) become less variable, with these processes being at their lowest during N3. The progression from N1 to N3 sleep takes approximately 30-60 minutes.

Following N3, sleep transitions into a starkly different state: REM sleep. During REM, there is high frequency, low amplitude brain activity resembling wakefulness. This brain activity reflects cortical networks becoming desynchronized and shifting towards a more conscious state, possibly in the form of dreams (Pace-Schott & Spencer, 2011). During REM, eyes rapidly dart back and forth, muscle tone is completely lost, and autonomic processes fluctuate (heart rate and respiration increase, while body-temperature becomes unregulated). In all, humans spend about 10-20 minutes in REM sleep. Overall, the cycle through the three stages of NREM sleep and REM sleeps takes

about 90 minutes. As sleep progresses, the duration spent in NREM sleep decreases while the duration of REM sleep increases (Figure 1A).

What other tools measure sleep?

Actigraphy.

One common tool to measure sleep is actigraphy. Actigraphs are devices typically worn on the non-dominant wrist, but can also be worn on the hip or ankle, and contain accelerometers to measure bodily movements in the X-, Y-, and Z- directions (Sadeh & Acebo, 2002). When measuring sleep, actigraphy measures bodily movements to infer wake or sleep, and have high sensitivity to detecting sleep periods (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992). Typically, actigraphy is used to measure the total time asleep (TST), the onset of sleep (sleep latency), time awake after sleep has been initiated (wake after sleep onset; WASO), sleep efficiency (the time spent in bed asleep ÷ total time in bed), and sleep fragmentation.

There are several advantages to using actigraphy over PSG. PSG is quite costly and often requires participants to come into an unfamiliar sleep lab. As a result of this, much of the research using PSG relies on small sample sizes (Scullin & Bliwise, 2015). In contrast, actigraphy is cheap, easy to implement, and allows for the participant to maintain their normal routine in their home environment. Furthermore, actigraphy can be collected over several days, obtaining a more natural and habitual measure of sleep, which may be better at capturing typical sleeping patterns compared to PSG (Cole et al., 1992). These strengths allow actigraphy to be utilized in large scale and longitudinal studies, providing rich information about habitual sleep patterns.

Some of the limitations related to actigraphy is that it can only measure bodily movements, and as such is unable to measure sleep architecture. Furthermore, when compared to PSG, actigraphy has high sensitivity to detecting periods of sleep, but it has low specificity in detecting periods of wakefulness (Slater et al., 2015), resulting in underestimations of nighttime awakenings (de Souza et al., 2003), sleep efficiency (Rupp & Balkin, 2011), and sleep onset (Scullin & Bliwise, 2015).

Subjective Sleep.

Another way to measure sleep is through subjective measures. Sleep diaries are often used to obtain self-reported sleep over the duration of the study. Although there are variations to these sleep journals, they typically capture measures of sleep duration (time in bed, sleep latency, time out of bed), sleep quality (awakenings in the night), and overall ratings of sleep. The Pittsburgh Sleep Quality Index (PSQI) is another common measure of subjective sleep (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a questionnaire asking participants about their sleep habits over the previous month, broken into several components asking about sleep quality, sleep duration, medications, and sleepiness. Using the PSQI, a global sleep score can be obtained, which can be used to reliably categorize people into “good” or “poor” sleepers. The PSQI compares favorably with PSG in categorizing good and poor sleepers, but PSQI sub-components (e.g., sleep efficiency) do not correlate with their respective PSG measure (Buysse et al., 1989). Nonetheless, meta-analysis suggest the PSQI is a reliable and valid screening tool for sleep dysfunction (Mollayeva et al., 2016).

What happens to our sleep when we age?

The perception, architecture, and quality of sleep changes with age. Fifty percent of older adults complain about difficulties initiating and maintaining sleep, as well as excessive daytimes sleepiness (Foley et al., 1995). Sleep architecture also changes (Figure 1B), as older adults spend less time in SWS (Mander, Winer, & Walker, 2017; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004), with the amplitude and density of slow wave activity decreasing in the frontal areas (Carrier et al., 2011). The duration and number of REM cycles declines (Mander et al., 2017; Ohayon et al., 2004; Pace-Schott & Spencer, 2011) while N1 and N2 sleep duration increases (Mander et al., 2017; Ohayon et al., 2004). Furthermore, older adults experience increasing difficulty initiating sleep (increased sleep latency), greater WASO, lower sleep efficiency, and decreased TST (Mander et al., 2017; Ohayon et al., 2004; Pace-Schott & Spencer, 2011). When examining the magnitude of these changes across the lifespan, Moraes et al. (2014) found the greatest decline in WASO, moderate declines in TST, SWS and sleep efficiency, and small declines in sleep latency, N2, percent in SWS, and the duration and percent of REM sleep (Moraes et al., 2014).

Does sleep determine the trajectory of cognitive decline?

Sleep quantity and quality play a critical role in cognitive aging, as demonstrated by self-reported short sleep duration being associated with worse cognitive impairment (Ohayon & Vecchierini, 2005; Potvin et al., 2012). In older men, poor subjective sleep quality was associated with cognitive decline and impairment (Blackwell et al., 2014; Potvin et al., 2012), whereas in women, cognitive impairment was associated with reported sleep disturbances and long sleep durations (Potvin et al., 2012). In studies using

actigraphy, sleep efficiency and sleep fragmentation were related with cognitive decline in older men and women (Blackwell et al., 2014; Yaffe, Blackwell, Barnes, Ancoli-Israel, & Stone, 2007), however TST was not. In a longitudinal study of over 700 older adults, researchers found increased sleep fragmentation at baseline was associated with a 22% decrease in cognition (Lim et al., 2013). Critically, when compared to low fragmented sleepers, highly fragmented sleepers had a 1.5-fold risk of developing AD (Lim et al., 2013). Furthermore, poor sleep quality increases the risk of developing MCI or dementia in both healthy populations (Beaulieu-Bonneau & Hudon, 2009; Sterniczuk et al., 2013) and in individuals with disordered-breathing conditions such as sleep apnea (Yaffe et al., 2011). These results highlight the role that adequate sleep plays in promoting cognition in aging.

How does sleep relate to normal cognition?

In healthy aging populations, large studies using actigraphy provide strong evidence that worse sleep quality is related to worse cognitive functioning in older adults (Blackwell et al., 2011, 2006; Lim et al., 2013, 2012). However, the results with subjective sleep measures are mixed. Although some of these studies have reported an association between worse cognition and short sleep (Schmutte et al., 2007), others report a U-shape function whereby cognition is impaired by having too little or too much sleep (Kronholm et al., 2009; Lo, Groeger, Cheng, Dijk, & Chee, 2016; Richards et al., 2017). That said, some studies fail to support the role of sleep duration on cognition in older adults altogether (Blackwell et al., 2006; Wilckens, Woo, Kirk, Erickson, & Wheeler, 2014). For example, one study found worse subjective sleep durations were associated

with poor cognition (Blackwell et al., 2014), however, this effect did not remain significant after controlling for covariates including age, education, and body mass index (BMI). Likewise, when examining subjective sleep quality, several studies report a null relationship with cognition in older adults (Blackwell et al., 2011; Jaussent et al., 2012; Saint Martin, Sforza, Barthélémy, Thomas-Anterion, & Roche, 2012). The inconsistency between subjective sleep and cognitive functioning suggest more objective measures should be employed.

How does sleep relate to executive functioning across the lifespan?

When exploring the relationship between sleep and EF, subjective measures are often used, and older adults are typically categorized as either "poor" or "good" sleepers. Poor sleepers tend to perform worse on tasks of EF than good sleepers (Blackwell et al., 2014; Nebes, Buysse, Halligan, Houck, & Monk, 2009), and this has more to do with sleep *quality* than sleep *quantity.*

With respect to sleep *quality*, low sleep efficiency and high sleep fragmentation has been found to be associated with worse EF in older women (Blackwell et al., 2006; Lambiase et al., 2014; Yaffe et al., 2007), as well as in young and older adults (Wilckens, Erickson, & Wheeler, 2018; Wilckens, Woo, Kirk, et al., 2014). Furthermore, longer sleep latencies are also associated with worse EF (Blackwell et al., 2006, 2014; Yaffe et al., 2007). In individuals with sleep apnea, a sleep condition characterized by cessation of breathing while sleeping causing fragmented sleep, meta-analysis and reviews reveal that EF are impaired in this population (Beebe & Gozal, 2002; Beebe, Groesz, Wells, Nichols, & McGee, 2003; Olaithe & Bucks, 2013; Saunamäki & Jehkonen, 2007). Treatment of

sleep apnea using continuous positive airway pressure (CPAP) machines have been proven effective at improving EF outcomes (Olaithe & Bucks, 2013; Saunamäki & Jehkonen, 2007). These studies highlight the importance of high *quality* sleep to support EF, and the potential for EF to be rescued with effective interventions that promote sleep.

The relationship between sleep *quantity* and EF remains unclear, as results are mixed for both self-report and actigraph measures. Studies using self-report find a negative relationship between short sleep duration and EF performance in older adults (Lambiase et al., 2014; Lo et al., 2016). In a large study consisting of over 500,000 individuals between the ages of 15-89, self-reported sleep duration of 7 hours was associated with peak EF performance for all age groups up to 65 years of age (Richards et al., 2017). Blackwell et al. (2014) found that self-report sleep duration was associated with worse EF, with this effect disappearing when controlling for other variables.

Studies using actigraphy to measure sleep quantity provide some converging evidence with self-report measures, as one study found TST was related to EF in young adults but not older adults (Wilckens, Woo, Kirk, et al., 2014). Other studies using actigraphy provide mixed results, as some studies do find a relationship between EF and TST (Wilckens, Woo, Erickson, & Wheeler, 2014), but most fail to find this relationship (Blackwell et al., 2014; Lambiase et al., 2014; Wilckens, Woo, Kirk, et al., 2014). These inconsistent findings suggest that in older adults, sleep quality might be more critical for cognitive health than sleep quantity.

When considering the relationship between sleep and EF in young adults, the literature is sparse and the results null. One analysis of three larger studies looking at

PSQI scores and cognition found no association between PSQI scores tasks assessing EF (Zavecz, Nagy, Galkó, Nemeth, & Janacsek, 2020). Another study failed to find a significant correlation between PSQI global sleep and EF in young adults after controlling for mental health variables (Benitez & Gunstad, 2012).

How does sleep relate to episodic memory across the lifespan?

Objective measures of sleep impairment reveal a relationship between sleep and memory. In one study of over 200 older adults, greater WASO, sleep latency, and TST were associated with poorer memory performance when assessed using actigraphy, but not when using the PSQI (Cavuoto et al., 2016). Likewise, the association between HC volume and poor sleep is only revealed when participants are dichotomized into poor versus good sleepers using the PSQI, and but not when using the PSQI global scores (Fjell et al., 2020; Sexton, Storsve, Walhovd, Johansen-Berg, & Fjell, 2014). A key issue with using subjective measures to assess the impact of sleep on memory is that they rely on the individual's ability to remember their sleep activity; thus, responses made by people with memory impairment may be unreliable as they would have poorer recollection of their sleep (Scullin & Bliwise, 2015).

A stronger case for the impact of sleep on EM is made by experimentally depriving sleep. Such sleep deprivation studies typically involve restricting the participant from sleeping for a period of time. Participants can undergo partial sleep deprivation, where they get limited hours of sleep (<7 hours of sleep), or acute total sleep deprivation, where participants do not sleep for up to 48 hours (Goel, Rao, Durmer, & Dinges, 2009). Total sleep deprivation has been found to impair HC functioning and connectivity (Yoo,

Hu, Gujar, Jolesz, & Walker, 2007), as well as reducing synaptic plasticity (Campbell, Guinan, & Horowitz, 2002) and basal levels of neurogenesis (Guzmán-Marín et al., 2003). In one study, high-interference memory performance was assessed in young adults following a full nights rest, one night of total sleep deprivation, and following a recovery nap (Saletin et al., 2016). Following total sleep deprivation, participants had worse high-interference memory performance when compared to a fully rested night. However, high-interference memory performance was recovered following a 90-minute nap, as performance was similar to a full-night's sleep. The degree of impairment and recovery was associated with HC structure, in which those who had larger DG/CA3 had greater learning deficits (Saletin et al., 2016), suggesting HC volume and its function might be an indicator of sleep deprivation vulnerability.

Why might sleep promote cognitive functioning?

It is thought that SWS, the deepest and most restorative phase of sleep, plays a critical role in healthy cognitive aging and disease. SWS is directly related to the PFC, as slow-wave activity is generated in the frontal lobes and correlated with better EF (Anderson & Horne, 2003). Furthermore, SWS is critical for memory processing (Walker, 2009), and when SWS is artificially enhanced through brain stimulation, young adults experienced significant increases in EM performance (Antonenko, Diekelmann, Olsen, Born, & Mölle, 2013). SWS begins to gradually decline mid-life (Van Cauter, Leproult, & Plat, 2000), and older adults who have a greater decrease in SWS are more likely to exhibit cognitive decline (Wilckens et al., 2012).

During SWS, cerebral spinal fluid (CSF) dynamics change, resulting in metabolite clearance from the brain (Fultz et al., 2019; Xie et al., 2013). One of the metabolites cleared from the brain are extracellular proteins known as amyloid-beta plaques (A*ß)*. Although these plaques arise naturally with aging, they are a hallmark of Alzheimer's disease. Typically, following a rested night's sleep there is decline in A*ß* levels; but with sleep deprivation A*ß* levels remain elevated (Ooms et al., 2014). Similarly, short sleep durations and poor sleep quality are associated with greater A*ß* burden (Spira et al., 2013). Critically, elevated A*ß* is associated with atrophy of both the PFC (Mander et al., 2015) and the HC (Bourgeat et al., 2010) which has several consequences. First, PFC and HC atrophy are associated with deficits in EF and EM, as well as disruptions to HC-PFC connectivity which further impair EM (Mander et al., 2015, 2013; Oh & Jagust, 2013; Wilckens et al., 2012). Second, PFC atrophy is associated with greater sleep fragmentation (Lim et al., 2016) and reductions of SWS (Mander et al., 2013), which creates a vicious cycle whereby poor sleep increases A*ß* burden, disrupts PFC-HC connectivity, and worsens sleep to perpetuate cognitive decline and AD pathology (Ju et al., 2013; Lucey & Bateman, 2014).

Exercise, a powerful tool to promote healthy aging.

What is the difference between physical activity, exercise, and physical fitness?

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure (Caspersen, Powell, & Christenson, 1985). PA can be done in a variety of forms, including sports, household activities, or occupational activities. *Exercise* is a subset of PA, which is activity that is planned, structured, and

repetitive with the objective to improve or maintain physical fitness (Caspersen et al., 1985). *Physical fitness* is a set of attributes in which people have or aim to achieve, and can be either health- or skill- related (Caspersen et al., 1985). Health-related physical fitness includes cardiorespiratory fitness (CRF), which is the ability of the circulatory and respiratory systems to supply oxygen during sustained PA (Caspersen et al., 1985). Although PA, exercise and fitness are related, they are still distinct from each other. Activities with varying intensities and duration can produce differences in CRF. For example, engaging in bursts of high-intensity activity for a short period of time can produce greater increases in CRF than engaging in a lighter exercise for a longer period of time (Ramos, Dalleck, Tjonna, Beetham, & Coombes, 2015).

Can exercise improve sleep?

Both acute and chronic PA has been found to have a positive effect on sleep. Acute PA has been found to increase in SWS, TST, sleep efficiency, REM latency, as well as decreased REM sleep and sleep latency (Chennaoui, Arnal, Sauvet, & Léger, 2015; Kredlow et al., 2015). Similarly, engaging in regular, chronic exercise is associated with greater SWS, TST, and sleep efficiency, with decreases in REM sleep, sleep latency, and WASO (Kredlow et al., 2015; Kubitz, Landers, Petruzzello, & Han, 1996; Uchida et al., 2012) Additionally, regular exercise is associated with better subjective sleep (Kredlow et al., 2015; Şahįn, 2018).

Exercise interventions have shown to be effective at improving sleep. Poor sleepers report improved subjective sleep (Benloucif et al., 2004) and increased SWS after just two weeks of an exercise intervention (Naylor et al., 2000). In a pivotal study,

King et al. (1997) had 20 older adults engage in 16-weeks of brisk walking and found the exercise group improved in subjective sleep scores, whereas the control group did not see any improvements. Furthermore, the exercise group decreased sleep latency and TST increased TST by 42 minutes (King et al., 1997). Exercise interventions are also effective at improving subjective sleep quality in adults with sleep complaints, including those with insomnia (King et al., 2008; Yang, Ho, Chen, & Chien, 2012). Objective sleep measures reveal a similar effect of exercise on increasing TST and sleep efficiency while also decreasing sleep latency (Kredlow et al., 2015).

One question concerning the benefits of exercise on sleep concerns dose-dependency. A study looking at menopausal women had participants engage in moderate intensity walking for 20-30 minutes four times a week (Wilbur, Miller, McDevitt, Wang, & Miller, 2005). Following the intervention, there was no significant improvement in sleep in the exercise group compared to the control group. However, further analysis revealed adherence to the exercise intervention significantly predicted sleep improvements, suggesting frequency of exercise may play a role in improving sleep (Wilbur et al., 2005). It is important to note this study did not meet the recommended Canadian guidelines of 150 minutes of moderate-vigorous physical activity (MVPA) per week (Tremblay et al., 2011). Two studies which had participants meeting the recommended PA guidelines found improvements in subjective sleep scores (King et al., 2008; Singh et al., 2005) and objective sleep (King et al., 2008), suggesting weekly duration may also be a factor in improving sleep quality. Exercise intensity has received mixed results, as some studies have found more intense exercise improves sleep quality

(Singh et al., 2005), while other studies suggest too high of intensity may actually worsen sleep quality (Bullock, Kovacevic, Kuhn, & Heisz, 2019; unpublished). Further research examining the intensity, frequency, and duration of exercise is needed.

How does fitness relate to sleep?

The role of CRF in sleep remains unclear. Shaprio et al. (1984) found following an 18-week training program, army recruits had increased CRF which was associated with increases in SWS and sleep efficiency, and decreases in sleep latency and WASO. Although some studies have found improvements in CRF to be directly relate to improvements in sleep, other studies have reported sleep changes to be independent of CRF. It is unclear whether CRF itself is related to sleep, or if other factors related to CRF, such as lean body mass (Meintjes, Driver, & Shapiro, 1989) or sympathetic nervous system activity, are underlying the observed improvements in sleep quality (Buman & King, 2010).

Why might exercise promote sleep?

It is not fully understood why exercise improves sleep, but there are two primary hypotheses. The first and most prominent hypotheses is the effect of exercise on thermoregulation. During exercise, there is an increase in body temperature that stimulates thermal down-regulation during sleep, which promotes deeper sleep (McGinty & Szymusiak, 1990; Van Someren, 2000). In support of this hypothesis are studies that passively increase body temperature using warm baths, which lead to deeper sleep (Bunnell, Agnew, Horvath, Jopson, & Wills, 1988; Dorsey et al., 1996). In contrast, when participants are actively cooled during exercise, the benefits to sleep are eliminated

(Horne & Moore, 1985). The second hypothesis relates to sleep being a restorative process. Exercise acts as a stressor as it creates physical demands that requires greater metabolism for fuel, and this helps build up greater drive of sleep to replenish resources and repair the body (Buman & King, 2010; Driver & Taylor, 2000). Although there is evidence in support both hypotheses, further research is needed to understand how exercise changes the body to promote sleep.

Can exercise prevent cognitive decline?

Physical activity is critical for maintaining healthy cognitive aging as higher levels of activity – especially earlier in life – are associated with better cognitive functions and a reduced risk of cognitive decline (Blondell et al., 2014; Chang et al., 2010; Middleton et al., 2010; Sofi et al., 2011). Furthermore, a physically active lifestyle reduces the risk of developing dementia, including AD (Blondell et al., 2014; Fenesi et al., 2017; Guure, Ibrahim, Adam, & Said, 2017; Larson et al., 2006; Nyberg et al., 2014). Critically, physical inactivity is the largest modifiable risk factor for developing AD in the United States, and is the 3rd largest world-wide (Barnes & Yaffe, 2011). Decreasing the prevalence of physical inactivity by 25% would prevent one-million cases of dementia world-wide (Barnes & Yaffe, 2011).

That said, exercise interventions show mixed regarding the benefits of exercise on cognition. Several reviews and meta-analysis support the positive benefits of exercise interventions for improving cognition (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Colcombe & Kramer, 2003; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018; Smith et al., 2010), while other reviews and meta-analysis do not

(Snowden et al., 2011; Uffelen, Chin A Paw, Hopman-Rock, & Mechelen, 2008; Young, Angevaren, Rusted, & Tabet, 2015). These equivocal findings may be due to a variety of reason. Some intervention studies are relatively short, lasting only several weeks or months and may not be long enough to produce noticeable effects. There is also huge variability in the cognitive measures used, and it has been suggested having a smaller cognitive battery may allow for easier comparison between studies (Young et al., 2015).

How does fitness relate to cognition?

Speculation as to why physical activity protects against cognitive decline in aging and dementia relates to gains in CRF. One of the first studies to suggest a direct link of CRF examined young males enlisted in mandatory military service. After a 25-year follow up, those with low CRF at baseline had a two-fold increased risk of early-onset dementia (HR = 2.49) and over a three-fold increased risk of mild cognitive impairment (HR = 3.57) (Nyberg et al., 2014). Furthermore, a longitudinal study in older adults aged 55+ found that poorer CRF at baseline predicted greater cognitive decline 6 years later, and the association was strongest for EF (Barnes, Yaffe, Satariano, & Tager, 2003). Likewise, a seminal meta-analyses of CRF from exercise intervention also found the greatest benefits for EF (Colcombe & Kramer, 2003); though this association is not observed in all intervention studies, possibly for the reasons noted above (Angevaren et al., 2008; Etnier, Nowell, Landers, & Sibley, 2006; Young et al., 2015).

How does exercise relate to executive functioning?

Neurological evidence has found exercise is associated with greater grey matter volumes in the frontal regions (Colcombe et al., 2003; Erickson et al., 2010, 2011;

Tamura et al., 2015), greater white matter integrity in the PFC (Colcombe et al., 2003, 2006), and increased functional connectivity between the PFC and HC in both young adults (Stillman et al., 2018; Talukdar et al., 2018) and older adults (Voss et al., 2010). For example, Tamura et al. (2015) had 75 older adults engage in calisthenics for 10 minutes, 3 times a day for 2 years and found that grey matter volumes were preserved (with no signs of the expected age-related decline) at the end of the intervention and predicted EF and EM performance. However, after a 6-month period of inactivity, PFC grey matter volumes reduced to a similar size as the control group, suggesting that *maintaining* a physically active lifestyle is critical for the brain health benefits.

Behavioral evidence demonstrates engaging in midlife PA is associated with better EF, and this effect was stronger when engaging in >5 hours of PA per week (Chang et al., 2010). In a two-part study, high-fit and aerobically trained adults were found to have performed better on inhibition tasks than either low-fit or untrained adults (Colcombe et al., 2004). Furthermore, the fit or trained adults also had decreased brain activity indicating greater neural efficiency, and this was correlated to PA (Colcombe et al., 2004). Meta-analyses further support that EF preferentially improves with exercise, in both healthy adults (Colcombe & Kramer, 2003) and adults with MCI (Öhman, Savikko, Strandberg, & Pitkälä, 2014).

One aspect of EF that exercise has also been found to improve is cognitive flexibility (Barnes et al., 2003; Guiney & Machado, 2013; Themanson, Pontifex, & Hillman, 2008). In one study, participants were instructed to be aerobically active for five to seven days a week, engaging in 30-45 minutes of activity for ten weeks (Masley,

Roetzheim, & Gualtieri, 2009). Those who complied and exercised five to seven days a week experienced significant improvement in cognitive flexibility. However, those who participated in the intervention but only exercised three to four times a week (and thus fell short of the PA guidelines) did not improve highlighting a dose-response relationship between PA and cognitive flexibility.

How does exercise relate to memory?

Neuroimaging studies find positive associations between exercise and greater HC grey matter (Colcombe et al., 2003; Erickson et al., 2010; Erickson et al., 2009; Stillman et al., 2018). For example, older adults who engaged in one year of aerobic training increased HC volumes by 2%, and volume gains were localized to the anterior HC where the DG resides (Erickson et al., 2011). In contrast, the stretching control group's HC volume decreased by 1.4%. Critically, the exercise-related gains in HC volume were associated with increased CRF in that participants with the greatest gains in CRF also experienced the greatest increases in HC volume. CRF was also related to improvements in memory but the association was with baseline CRF and post CRF, not with the change in CRF from the intervention (Erickson et al., 2011). Furthermore, similar to the findings with PFC and exercise, maintaining a physically active lifestyle is critical to retain the benefits of exercise on the HC, as one study found that HC gains in volume following an exercise intervention reduce back to baseline following 6-weeks of inactivity (Thomas et al., 2016).

Given the strong neurological evidence to support a link between exercise and the HC, one would expect a similarly strong association between exercise and EM; however,

this is not the case. Some studies fail to link the observed changes in CRF and HC volumes with changes in EM or other cognitive functions (Stillman et al., 2018; Thomas et al., 2016)**.** Although two recent reviews suggest exercise improves EM in young to middle-aged adults (Loprinzi, Frith, Edwards, Sng, & Ashpole, 2018) and those with cognitive impairment (Loprinzi, Blough, Ryu, & Kang, 2019), an early review failed to find an effect (Roig, Nordbrandt, Geertsen, & Nielsen, 2013). However, in that review, Roig et al. (2013) found *acute* exercise provides consistent benefits to cognition and suggests *acute* and *chronic* exercise may differentially effect memory. They propose that acute exercise primes the molecular mechanisms for memory, and chronic exercise maintains these mechanisms**.** Further research is required to better understand how exercise and memory work together.

One reason for this discrepancy may be related to the variety of memory tests used. Indeed, there is stronger evidence for an exercise-memory link when hippocampal neurogenesis sensitive tests are employed, such as tests that examine high-interference memory. In several rodent studies, voluntary exercise has been found increase hippocampal neurogenesis (Brown et al., 2003; Van Praag, Kempermann, & Gage, 1999), which was related to improvements in high-interference memory performance (Creer, Romberg, Saksida, Van Praag, & Bussey, 2010; Pereira et al., 2007; Van Praag, Christie, Sejnowski, & Gage, 1999). In human research, behavioral evidence supports that exercise is able to improve high-interference memory, which is a proxy of neurogenesis. In a study conducted in our lab, we compared CRF and high-interference memory in both young and older adults using archival data. We found CRF was positively correlated with high-

interference memory in older adults but not younger adults (Bullock, Mizzi, Kovacevic, & Heisz, 2018). However, other research within the lab has failed to find this relationship in older adults, though this was likely a result of a highly fit sample (Bullock, 2015). Critically, when CRF is increased by an exercise intervention, increases in CRF predicted improvements in high-interference memory in younger adults (Heisz et al., 2017) and older adults (Kovacevic, 2017). These results are supported in other labs finding similar results when examining young adults (Déry et al., 2013). Overall, there is evidence for a relationship between exercise and high-interference memory, however, the roles of age and CRF still remain unclear.

Tying it all together: Exercise, Sleep, and Cognition.

To date, there is limited research looking into exercise, sleep, *and* cognition, especially in humans. Using animal models, Zagaar et al. found regular exercise can protect against memory impairment in sleep deprived rats (Zagaar et al., 2012; Zagaar, Dao, Alhaider, & Alkadhi, 2013; Zagaar, Dao, Levine, Alhaider, & Alkadhi, 2013). These protective effects were specific to the HC, particularly in the CA1 (Zagaar et al., 2012; Zagaar, Dao, Levine, et al., 2013) and the DG (Zagaar, Dao, Alhaider, et al., 2013), and linked to brain-derived neurotrophic factor (BDNF), which was low in sleep deprived rats but elevated in the exercise rats (Zagaar et al., 2012). BDNF is a neurotrophin that is neuroprotective and positively related to cognitive function (Bekinschtein et al., 2013; Leckie et al., 2014). Basal BDNF levels decrease in aging, and individuals with Alzheimer's disease have even greater decreases in BDNF (Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008). Critically, BDNF levels increase following acute and chronic

exercise (Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014), and interestingly, the BDNF response following acute exercise is enhanced in individuals who have higher fitness levels (Dinoff, Herrmann, Swardfager, & Lanctôt, 2017). Moreover, BDNF has been causally linked to increasing slow-wave activity (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008). Taken together, the results from Zagaar et al. (2012; 2013) suggest that although BDNF decreases with sleep deprivation, it increases with exercise to prevent memory impairment. This provides promising evidence that exercise may help protect memory against poor sleep, but to our knowledge, no other research has investigated this relationship in humans and further research is required.

Few studies have examined the relationship between exercise, sleep, *and* cognition in humans. One study used a global measure of cognition and found that PA and sleep efficiency were independently associated with higher global cognition, but they did not interact (Falck, Best, Davis, & Liu-Ambrose, 2018). However, there are several limitations to this study, namely, they only examined global cognition rather than cognitive subdomains and they only measured PA without distinguishing between leisure activity, moderate activity, or overall daily PA.

Another study reported that sleep may mediate the relationship between PA and EF. Using 112 older and younger adults, Wilckens, Erickson, & Wheeler (2018) measured habitual sleep over one week using actigraphy, and had participants perform a cognitive battery. They found that sleep efficiency, but not TST, significantly mediated the relationship between physical activity and EF, including cognitive flexibility. They also found the association was not impacted by age, suggesting exercise improves EF

through enhanced in sleep quality in both young and old adults (Wilckens et al., 2018). These results provide theoretical evidence that PA may improve sleep quality, and this improved sleep quality may result in better EF. However, this study was a cross-sectional design that cannot conclude causation and the mediation analysis must be interpreted with caution. Further research using exercise interventions are required to establish a causal relationship between changes in activity enhancing sleep thus improving cognition.

The primary study which motivated the current thesis examined the relationship between sleep and cognition using a subset of data from the Healthy Women Study (Lambiase et al., 2014). The study consisted of 121 older women who had actigraphy data for sleep and physical activity and completed cognitive tests assessing verbal fluency and cognitive flexibility. Their initial analysis revealed sleep efficiency, but not MVPA, was correlated with cognitive flexibility. They then analyzed the data for a moderating role of PA on sleep and cognition and discovered that those who were low active had the greatest deficits in cognitive flexibility when they also had poor sleep (Figure 2). However, those who were high active performed similarly well regardless of how poor they slept. These results are promising and suggest that PA may help protect against poor sleep. However, they only assessed PA and EF in older women and generalizability of the results remains unknown.

Purpose and hypothesis

The purpose of this study was to investigate whether CRF moderates the relationship between sleep and EM, and whether the relationship differs by age. It was hypothesized that older adults would have worse sleep than younger adults, and that age

may moderate potential relationships between sleep and cognition. Moreover, we expect to replicate the results of Lambiase et al. (2014), such that CRF was expected to moderate the relationship between sleep and cognition. Specifically, low fit older adults with poor sleep would have the worst cognition whereas high fit older adults with poor sleep would be protected. Additionally, we tested whether a similar moderating effect of fitness on sleep and cognition would be seen in younger adults.

METHODS

Participants

A sample size estimate was calculated using G*Power (Version 3.1.9.3, www.gpower.hbu.de), based on the age differences in memory (d = 0.71) found in Stark et al. (2013). Using the parameters of power being 0.90 and alpha equaling .05, G*Power indicated a total of 86 participants would be required: 43 young adults (YA) and 43 older adults (OA). Participants were recruited through posters and advertisements in local news outlets, posted throughout the Hamilton community. Participants were also recruited from a participant database consisting of participants who have previously completed studies in the NeuroFit Lab or through McMaster's SONA system.

A total of 73 participants were recruited (YA, n = 44; OA, n = 29). 3 participants did not complete both visits, due to ineligibility requirements (OA, n = 1), scheduling conflicts (YA, n = 1), or complications due to COVID-19 (YA, n = 1). Additionally, because of the COVID-19 pandemic, seven participants that were scheduled could not participate (YA, n = 5; OA, n = 2) and data collection was stopped. In total 63 participants completed the study (YA, n = 37; OA, n = 26).

Participants were eligible to participate if they were between the ages of 18-30 or 65-79 and free from diagnosis of cognitive impairment, sleep disorders, psychiatric and neurological conditions, and were non-smokers, not obese (class I, BMI <35), not taking hormone replacement therapy and/or beta-blockers. Additionally, participants were required to have normal sleep patterns: regularly going to bed between 2100-0100 and waking-up between 0600-1000. Fulfillment of these criteria was confirmed verbally or written, either over the phone or by email. Prior to their first visit, older adults who deemed eligible were required to gain written consent form their physician, to participate in a sub-maximal CRF assessment. This study received ethics clearance from McMaster Research Ethics Board (MREB #2079). Participants were compensated with either $30 or three SONA credits for their participation.

Materials

Cardiorespiratory Fitness

CRF was estimated using the Rockport 1-mile walk test (Kline et al., 1987). The Rockport 1-mile walk test has been validated in adults, and correlates highly with traditional treadmill tests to assess CRF (Colcombe et al., 2003; Colcombe et al., 2004; Kline et al., 1987). Participants were instructed to walk one mile as fast as they could, without running or powerwalking. Two trained research assistants supervised the test: one member of the research team recorded heart rate (using Polar FT1 heart rate monitors) at one-minute intervals and upon completion, while the second research assistant recorded distance using a surveyor's wheel. Participants completed the Rockport 1-mile walk test on an indoor track located in the Physical Activity Center of Excellence at McMaster

University. Using the estimated CRF scores, participants were placed into health benefit rating zones based on their age grouping and sex (CSEP, 2013). The following equation was used to estimate the CRF:

Estimated VO2max ml·kg^{-1}·min^{-1} = 132.853 – 0.0769(Weight in pounds) – 0.3877(Age in years) + 6.315(If male) – 3.2649(Time in minutes) – 0.1565(Final heart Rate)

Cognition

Global Cognition

Global cognition was measured using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The MoCA is a cognitive screening tool to test for cognitive impairment. The MoCA is used to assess several cognitive domains including: visual spatial skills, executive functioning, categorical fluency, memory, attention, language, abstraction, and orientation. The maximum score is 30, indicating higher cognitive functioning, while the minimum score is 0. A normal score is considered to be ≥ 26, and a score of < 23 has been suggested to differentiate healthy cognition from cognitive impairment (Carson, Leach, & Murphy, 2018).

Memory

High-interference memory was measured using set C of the Mnemonic Similarities Task (MST; Stark & Stark, 2017; Stark et al., 2013). During the incidental coding phase, participants were shown 60 full colored images, presented on the screen for 2 seconds. A blank screen preceded each trial for 500 milliseconds. Participants were instructed to classify items as indoor, pressing the “N” key, or outdoor, pressing the “V”

key. After this phase of the task, participants watched a video with instructions for the test phase of the task. During the test phase, participants were shown more images that they had to classify as either "Old" (repetitions), "Similar" (lures), or "New" (foils) using the "V" key, the "B" key and the "N" key, respectively. The test phase consisted of 192 items in total: 64 repetitions, 64 lures, 64, foils. Items were presented for 2.5 seconds, followed by a blank screen.

Performance was quantified using a bias metric, which subtracted the proportion of lures that were correctly identified as "Similar" from the proportion of foils identified as "Similar" [p("Similar"|Lure) - p("Similar"|Foil)] (Stark & Stark, 2017; Stark et al., 2013). This corrects for any overall bias of responding "Similar" to stimuli. Data was screened to ensure task comprehension. If participants did not use all keys, it was thought they did not understand the task, and would be removed from all memory analyses.

Executive Functioning.

Executive functioning was assessed using two tasks: the Trail Making Test Part B (TMT B) and the Digit Symbol Substitution Test (DSST) (Wechsler, 1997). Both of these tasks are a measure of cognitive flexibility.

The Trail Making Tests consist of two parts, part A (TMT A) and part B (TMT B). TMT A requires participants to connect an array numbers in ascending order and was used to familiarize participants to the task. TMT B requires participants to connect an array of numbers and letters in ascending order (1-A-2-B-3-C, etc.) as fast as they can. During both test, participants were instructed to complete the task as quickly as possible and timed to completion. The longer the participant took to complete this task indicated

worse performance. If an error was made, the participant was corrected and continued on. Errors were not recorded, as errors would be reflected in increased time to perform test. TMT A was used to familiarize participants to the task. TMT B was used to measure cognitive flexibility, and TMT B completion times tend to slow with increasing age (Tombaugh, 2004).

During the DSST, participants were presented with a series of symbols which were paired with a number ranging from 1 through 9. Participants were given a sheet with a random serious of numbers, with an empty box below. Participants were instructed to fill in each box with the appropriate symbol for each letter, doing them in order and without skipping any. Participants completed as many boxes as they could in 90 seconds. The number of correct symbols was counted, with a maximum score of 90. DSST is a measure of processing speed and cognitive flexibility, and shows considerable decline with aging (Hoyer, Stawski, Wasylyshyn, & Verhaeghen, 2004).

Sleep

Sleep Journal

A sleep journal created by the National Sleep Foundation was used to measure and record participants bed and wake times (Appendix A). Participants were instructed to record each morning the time they went to bed the night before, and the time they woke up that morning. These times were used to determine the in-bed and awake times for the actigraph measures, as restless sleep would be mistaken for awake time (Morgenthaler et al., 2007).

Actigraphy

A CenterPoint Insight watch (ActiGraph, LLC, Pensacola, FL, USA) was used to measure sleep. Sleep periods were determined using the Cole-Kripke algorithm (Cole et al., 1992), which measures sleep using the y-axis epochs over a 7 minute period to determine wake from sleep. A trained research assistant uploaded, compared, and adjusted sleep periods based on the participants sleep diary to ensure restless sleep was not mistaken for wakefulness. Participants wore the actigraphy on their non-dominant hand, and participants were considered compliant if they wore the actigraph for at least five nights.

Pittsburg Sleep Quality Index

To measure subjective sleep quality, the Pittsburgh Sleep Quality Index (PSQI) was used (Appendix B; Buysse et al., 1989). This questionnaire asks participants about their sleep habits during the last month by looking at seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, difficulties sleeping, use of sleeping medications, and their sleepiness. Participants scores are categorized into severity/frequency of sleep disturbances (0 = least severe, 3 = most severe), for a maximum score of 21. A higher score in indicative of greater sleep disturbance, and a score of > 5 indicates a poor sleeper (Buysse et al., 1989).

Stress

Stress was assessed using the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983). This is a 10-item questionnaire, requiring participants to select which response describes their feelings or thoughts during the last month, with increasing frequency (0 = Never, 4 = Very Often). The maximum score is 40, with a higher score

indicating greater perceived stress. The PSS has been validated in adults as a measure of perceived chronic stress in college students (Roberti, Harrington, & Storch, 2006) and older adults (Ezzati et al., 2014).

Procedure

This study was completed over the course of two visits. During the first visit, anthropometric measurements were taken, including weight and height, which were used to calculate BMI. Participants also completed the MoCA to screen for cognitive impairment and then performed the Rockport 1-Mile walk test. Upon completion, participants returned to the lab and filled out a demographic questionnaire and PSQI. Participants were then given an actigraph and instructed to wear it at all times for one week, with the exception of during bathing or swimming activities. Participants were also given a sleep journal to record their sleep over the week.

Following one week of tracking, participants returned to the lab and performed several cognitive tests: TMT B, the DSST, and the MST, in that order. Finally, participants filled out the PSS and were debriefed.

Statistical analysis

Data was analyzed using *R* programming software. Descriptive variables were calculated for all study variables. Normality was assessed using Shapiro-Wilkes tests and through visual inspection of histograms. Normality of residuals was inspected using QQ plots. Independence was measured using Durbin-Watson tests. Influential cases were screened using Cook's distance. For all statistical analysis, significance was considered at $p < .05$. Covariates included sex, years of education, BMI, and perceived stress.

To test the hypothesis that sleep quality and quantity would be better in YA than OA, two-tailed *t*-tests were used. A moderation was conducted using age category (YA versus OA) as the moderator. To test the moderating effect of CRF on the relationship between sleep and cognition, several multiple linear regressions were used to examine the interaction between CRF and sleep variables. These analyses were done separately for younger and older adults. In the event of a significant interaction, CRF was dichotomized into "high fit" and "low fit" using a median split, stratified by sex. This categorical CRF variable was entered into the model and used for further sub-analysis. For all moderations, when a significant moderating effect was present further sub-analyses of that model were done using the "simple_slopes" function from the "reghelper" package. Slopes were visualized with the "plotSlopes" function from the "rockchalk" package.

RESULTS

Data screening and assumptions

A total of 63 participants (OA, n =26; YA, n =37) completed both visits in the study. Two participants were removed from all analysis due to low actigraph compliance (wearing < 5 nights; YA, n =2). The final sample consists of 61 participants (OA, n =26; YA, n =35)

The data was screen for missing data; 0.70% of the data was missing. Two participants failed to properly fill out the PSQI (YA, n =1; OA, n =1), so any of their PSQI measures were removed, but their actigraphy data remained included. Three TMT B scores were removed due to improper procedure (OA, n =2) and technical difficulties

(YA, *n* =1). MST scores were removed if participants failed to understand the task, as indicated by failing to press all three keys (OA, *n* =1).

All data met the assumption of normality using the Shapiro-Wilkes test and visual inspection of histograms. All variables were normally distributed except for TMT B, which were log-transformed for all *t*-tests and moderations to meet this assumption. All other assumptions were met.

Descriptive statistics

Descriptive characteristics of the sample are presented in Table 1. YA were between 18-30, mostly female (24/35), and most were categorized as good sleepers (23/34). OA were between 66-76, half were female (13/26), most were categorized as good sleepers (18/25), and all were well educated. Compared to younger adults, older adults had lower fitness, higher BMI and less psychological stress. Older adults also performed worse on tests of high-interference memory and EF but had similar MoCA scores and years of education compared to younger adults.

When looking at CRF levels (Table 2), 6.7% of YA aged 18-19 and 15% of YA aged 20-30 had poor or fair fitness ratings, whereas 73.1% of older adults had poor or fair fitness rating. Furthermore, 53% of YA aged 18-19 and 50% of YA aged 20-30 have health benefit ratings of "very good" compared to 11.5% of older adults having similar health ratings. Compared to Canadian norms, the present sampled tended to have higher fitness ratings (Statistics Canada, 2012).

Age differences in sleep quality

Table 3 presents the mean values for sleep variables. YA slept worse than OA, in that YA had more nighttime awakenings (*M* ± *SD*: 19.4 ± 5.7) than OA (*M* ± *SD*: 15.4 ± 6.0) (*t*(52.82= 2.65, *p* = .011, *d* = 0.51). Sleep duration was also significantly shorter in YA (*M* ± *SD*: 7.1 ± 0.7) than in OA (*M* ± *SD*: 7.5 ± 0.7) (*t*(55.81) = -2.08, *p* = .042, *d* = 0.83). No significant differences were found for sleep efficiency or PSQI scores.

Exploratory Analysis: The observation that YA slept worse than OA was contrary to our hypothesis. To further examine this effect, we did an exploratory analysis of covariance (ANCOVA) on sleep variables with a between-subject factor of age (YA, OA), and used stress as a covariate, which disrupts sleep (Vitiello, 2007). This was done to see if psychology stress, which was higher in YA than OA, explained the poorer sleep in YA. Indeed, stress was a significant covariate for PSQI scores when controlling for stress alone, $F(1,56) = 5.04$, $p < .05$, $r = .29$, and when controlling for stress with the other covariates, $F(1,53) = 7.13$, $p < .05$, $r = .37$, demonstrating that higher stress was associated with worse subjective sleep, and thus could account for the poorer subjective sleep for YA relative to OA. However, stress was not a significant covariate for any actigraph measures.

The moderating effect of age on sleep and cognition

Table 4 presents the regression values for the moderating effect of age on sleep and cognition. Age significantly moderated the relationship between TST and DSST performance, (*b* = 0.09, *SE b* = 0.05, p =.05). Simple slopes analysis revealed greater TST significantly predicted better DSST performance for OA (*b* = 0.1, *SE b* = 0.03, p = .007)

but not YA (b = 0.0, $SE\ b$ = 0.03, p = .89; Figure 3). The relationship between sleep and TMT B and MST scores were not moderated by age.

The moderating effect of fitness on sleep and cognition by age group

Table 5 presents regression values for the moderating effect of CRF on sleep and cognition in OA. Fitness significantly moderated that relationship between nighttime awakenings and MST performance (b = 0.31, $SE\ b$ = 0.12, p = .021; Figure 4). The data was then stratified by sex into high and low CRF groups, and this model were reanalyzed. Simple slopes analysis revealed that more nighttime awakenings significantly predicted worse high-interference memory performance in low fit OA (b = -3.85, $SE\ b$ = 1.08, p = .002), whereas nighttime awakenings predicted better performance in high fit OA (b = 1.60, $SE\ b$ = 0.66, p = .028). CRF did not moderate the relationship between any sleep variables and EF test scores.

In young adults, CRF was associated with TMT B performance (b = -0.09, $SE\ b$ = 0.04, p = .048), which indicated that young adults with increased CRF had better TMT B performance. However, this effect was not moderated by CRF (p = .07) therefore sub-analyses were not performed. CRF did not moderate the relationship between sleep and cognition in young adults (Table 6)

DISCUSSION

The current study aimed to examine the relationship between CRF, sleep, and cognition in both young and older adults. Overall, all of our participants slept well and were getting the recommended hours per night of sleep, though young adults were sleeping less and had more nighttime awakenings than OA. Cognitive functions of EF and

memory were worse for OA than YA. Sleep was associated with cognition in OA but not YA such that more sleep predicted better EF regardless of fitness. Better sleep quality also predicted better memory but only in low fit OA; high fit OA had similarly good memory regardless of sleep.

A primary objective of this study was to examine the moderating effect of CRF on sleep and high-interference memory in older adults. This was the first study to do so. Poor sleep is typically associated with poorer EM (Cavuoto et al., 2016), and poorer EM is typically associated with older age and lower fitness (Bullock et al., 2018). Thus, our observation of worse high-interference memory for low fit OA who slept poorly was expected (Figure 4). Critically, this group of low fit poor sleeping OA is at greatest risk of developing memory impairment (Barnes et al., 2003; Nyberg et al., 2014). The novel contribution here is that good sleep seemed to negate memory deficits from low fitness. In fact, low fit OA who slept well had the best memory performance overall. This may be due to the relationship between A*ß*, sleep, and memory such that good sleep is related to less A*ß* burden (Spira et al., 2013), which can protect the HC from atrophy (Bourgeat et al., 2010) and preserve EM performance (Mander et al., 2015, 2013).

High fit OA did not show the same association between sleep and high-interference memory and instead performed better with worse sleep quality, suggesting exercise might protect against increasingly worse sleep quality. This may be because their memory is already maximized by their high levels of fitness. Indeed, prior research shows CRF is associated with better high-interference memory in older adults (Bullock et al., 2018), and reduces the risk of age-related declines in cognition and dementia (Barnes et

al., 2003; Nyberg et al., 2014). The benefits of CRF are thought to be due to its positive relationship with HC integrity (Erickson et al., 2011), neuroplasticity (Brown et al., 2003; Van Praag, Kempermann, et al., 1999), and BDNF release (Erickson et al., 2011; Leckie et al., 2014; Ruscheweyh et al., 2011) — all things that typically decline with aging and worsen with sleep. It follows that the fitness-related benefits to HC structure and function may help counteract the typical deleterious effects of aging and poor sleep on EM (Cavuoto et al., 2016).

Unlike memory, more sleep was related to better EF in all older adults, regardless of their CRF level. These results align with studies finding that sleep is positively related to EF in older adults (Lambiase et al., 2014; Lo et al., 2016), but suggests that the relationship between CRF and sleep in OA may differ between EF and EM. This may reflect differences in the underlying neurobiological processes that support these cognitive functions. Specifically, EF is more dependent on the PFC, whereas EM is more dependent on the HC. Although CRF impacts both PFC and HC functioning, its positive benefits on BDNF may be enough to counteract the effects of poor sleep on the HC. Released during exercise (Huang et al., 2014; Szuhany, Bugatti, & Otto, 2015) BDNF supports HC integrity (Erickson et al., 2011; 2010) and memory function (Bekinschtein et al., 2013) by promoting neural plasticity (Tapia-Arancibia et al., 2008). Furthermore, meta-analysis reveal that BDNF in individuals with greater CRF are more responsive to acute exercise, where a bout of exercise results in greater increases in peripheral BDNF (Dinoff et al., 2017). Although exercise increased BDNF in the PFC to support (Leckie et al., 2014), it has a *stronger* impact on the HC due to the higher density of BDNF

receptors there (Murer et al., 1999). It follows that in high fit individuals, the increase in BDNF from exercise may selectively protect the HC from poor sleep, and indeed this has been demonstrated in animal models in which exercise-induced increases in BDNF protected the HC and memory from sleep deprivation deficits (Zagaar et al., 2012; Zagaar, Dao, Alhaider, et al., 2013; Zagaar, Dao, Levine, et al., 2013).

Our study was based off Lambiase et al. (2014). Although our results were similar to theirs in that we both found a moderating effect of fitness on sleep and cognition, they observed this for EF whereas we did not. We only observed this effect in memory. This discrepancy in results may reflect several key differences between our study and theirs. Compared to Lambiase et al. (2014), our primary measure of exercise was CRF whereas theirs was PA. Although CRF and PA are related constructs, they capture different aspects of health. PA is a measure of behavior, whereas CRF is a physiological measure. Although higher activity is typically correlated with higher fitness, a person who spends less time doing vigorous activity may have a similar fitness to another person who spends more time doing moderate activity (Ramos et al., 2015). Consequently, PA and CRF may differentially affect brain regions and the cognitions they support.

Another major different between our study and Lambiase's is that our participants slept better. The participants in the Lambiase et al. (2014) study slept much worse than the participants in our study, in that their average sleep efficiency was lower and had a larger range (*M* ± *SD*: 84.7 ± 6.2, Range: 66.6–98.2) than the present study (*M* ± *SD*: 89.5 ± 3.7, Range: 82.1-95.4). Sleep quality plays a critical role for PFC functioning, as poor sleep increases metabolites (Ooms et al., 2014; Spira et al., 2013), which result in PFC

atrophy (Mander et al., 2015) and impaired EF (Wilckens et al., 2012). It is possible that EF only benefits from CRF when sleep is really poor thus the present sample might have been sleeping well enough for PFC to function properly without the need of further support by CRF.

Another unique factor of our study was that we examined the association of CRF, sleep, and cognition in younger adults. As expected, younger adults had higher fitness and cognitive performance than older adults, but their sleep was not associated with either EF or memory. These results at first appear to conflict with sleep deprivation studies, as these studies tend to find that young adults have greater cognitive deficits than older adults under these conditions (Scullin & Bliwise, 2015). However, sleep deprivation studies are typically acute and employed over one night, whereas this study looked at *habitual* sleep over one week. Similar to our OA, our YA slept well, with an average of average 7.1 hours per night, which is within the National Sleep Foundation's recommendation of 7-9 hours (Hirshkowitz et al., 2015). Additionally, their sleep efficiency was ~90%, which is well above the cut-off of 70% used to denote poor sleep (Blackwell et al., 2011, 2014). Seeing as our subjects were sleeping well, it is possible that sleep deficiencies in young adults need to be much more severe (e.g., total sleep deprivation) to negatively impact cognition. Given that cognition peaks around 20-30 years of age —the exact age of our YA participants (Anderson et al., 2011; Salthouse, 2019), a potential ceiling effect might have made it difficult to see the benefits of CRF on cognition in young adults, as we have previously found (Bullock et al., 2018).

Strengths and limitations

A key strength of this study is in its novelty and scope, as discussed above. So too is the use of actigraphy to measure sleep, thought it also has its limitations. Actigraphy is a strength because it is a more accurate and reliable measure of sleep than subjective measurements of sleep, such as the PSQI, which are often uncorrelated with objective measures of sleep (Buysse et al., 2008) but highly correlated with mental health (Buysse et al., 2008; Dietch et al., 2016). Moreover, subjective recollection of sleep quality is difficult in older adults with memory impairments, as they may fail to remember any sleep disturbances and may erroneously report their sleep quality to be better than it actually is (Scullin & Bliwise, 2015). Another strength of actigraphy is that it can naturalistically measure sleep over an extended time period. The limitation of actigraphy is it can only detect periods of wakefulness and sleep, but cannot capture sleep architecture. Although PSG is able to produce a more detailed account of sleep, actigraphy is advantageous as it is more naturalistic, cost-effective, and easier to implement than PSG.

A second limitation is the small sample size and cross-sectional design of the study. As the study prematurely ended due to COVID and two participants had low compliance, the final sample size of the study was 61; 25 participants short of the targeted sample size of 86. Therefore, this study may have lacked sufficient power to detect other moderating effects.

A third limitation is the fitness measure used. While the Rockport walking test is a validated measure and provides an estimate of CRF, it has been found to overestimate CRF in young adults. Although alternative equations have been suggested for younger

adults, due to COVID the present study was unable to perform VO_2 max tests that had gained ethics approval. Validating the Rockport equation in a subset of the sample would have allowed for greater confidence in this measure.

A fourth and final limitation is that the overall sample was convenient and may not have been representative of the general population. All of the young adults were university students,1/3 of which were post-graduate students, which is not reflective of the general population. The exclusion criteria for PA meant they could not have any cardiovascular conditions, sleep disorders, or a high BMI; all of these conditions impair sleep and are prevalent in OA. Thus, our sample may have had better sleep than the general population, limiting the generalizability of this study.

Future directions

Future studies should employ a randomized control trial to examine if changes in CRF leads to changes in sleep, which would then improve cognition. This would provide causal evidence for the relationship between exercise, sleep, and cognition. Furthermore, these studies should examine physiological factors, such as BDNF or A*ß* plaques, to further understand the underlying mechanism of how sleep and exercise may differentially improve EM and EF.

Future research should also be conducted in populations with sleep disorders, such as individuals with sleep apnea or insomnia. As the present study used healthy adults without any sleep conditions, this might underestimate the true benefits of sleep and fitness on cognition. The use of a clinical population would allow us to examine the full extent to which fitness moderates the relationship between sleep and cognition.

CONCLUSION

The present study suggests that sleep and fitness may interact to enhance cognition in aging. While poor sleep was associated with worse cognition in OA, the detriment to high-interference memory from poor sleep was negated by high levels of fitness, suggesting that CRF may protect OA from sleep-deficits in memory. In contrast, poor sleep was associated with worse EF, regardless of fitness; though, our sample of OA slept well relative to prior studies, and thus may not have had sufficient sleep deficiency to demonstrate the association. Finally, we did not see an association between CRF or sleep for cognition in young adults, suggesting that the interplay between CRF, sleep and cognition may be more pronounced as we get older. Taken together, our finding suggest that exercise may help older adults with poor sleep maintain their memory function.

TABLES AND FIGURES

Table 1. Descriptive characteristics of the present sample.

	Young Adults Mean (SD)		Older Adults Mean (SD)		*p*
Demographics					
n	35		26		
Age (years)	20.9	(3.1)	70.7	(2.8)	**<.001**
Education (years)	17.3	(2.5)	17.7	(3.1)	.62
BMI	22.6	(3.5)	25.7	(3.4)	**<.001**
MoCA	26.9	(1.6)	27.0	(2.1)	.85
Perceived Stress	15.0	(4.9)	10.0	(4.0)	**<.001**
Actigraph Wear Details					
Wear Percentage	95.9	(7.8)	97.7	(2.6)	.17
Total Days Worn	7.9	(0.2)	8.0	(0.2)	.17
Cognitive Measures					
TMT B† (seconds)	39.0	(10.9)	59.3	(22.0)	**<.001**
DSST (# completed)	71.3	(8.2)	51.5	(9.1)	**<.001**
MST (% correct)	42.2	(16.5)	15.5	(21.0)	**<.001**
Activity Measures					
Estimated VO_2	45.9	(5.7)	24.8	(5.6)	**<.001**

Note: BMI = body mass index; MoCA = Montreal Cognitive Assessment; TMT B = trail making test part B; DSST = digit symbol substitution test; MST = mnemonic similarities test. *P*-value denotes results of independent *t*-test comparing young and older adults.
† Log transformed

Table 2. Fitness zones by age categories.

	Young Adults (18-19 years of age)		Young Adults (20-30 years of age)		Older adults	
	Frequency	(%)	Frequency	(%)	Frequency	(%)
Health Benefit Rating Zone						
Poor	0	(0)	2	(10.0)	9	(34.6)
Fair	1	(6.7)	1	(5.0)	10	(38.5)
Good	5	(33.3)	4	(20.0)	4	(15.4)
Very Good	8	(53.3)	10	(50.0)	3	(11.5)
Excellent	1	(6.7)	3	(15.0)	0	(0)

Note: Health Benefit Rating zones based on the Canadian Society of Exercise Physiology Physical Activity Training for Health (CSEP-PATH; CSEP, 2013).

Table 3. Mean values or frequencies for sleep variables.

	Young Adults			Older Adults			
	Mean (SD)		Range	Mean (SD)		Range	*p*
Nighttime Awakenings (# of awakenings)	19.4	(5.7)	8.4-29.9	15.4	(6.0)	4.3-35.6	**.011**
Sleep Efficiency (%)	89.3	(4.1)	79.3-95.7	89.5	(3.7)	82.1-95.4	.83
TST (hours)	7.1	(0.7)	5.6-8.9	7.5	(0.7)	6.0-8.7	**.042**
PSQI Global Score	4.7	(1.8)	2-9	4.4	(2.5)	1-10	.60

Note: TST = total sleep time; PSQI = Pittsburgh Sleep Quality Index. *P*-value denotes results of independent *t*-test comparing young and older adults.

Table 4. Regression coefficients of the moderating effect of age on sleep and cognition.

	R^2	b	SE b	p
TMT B†				
	0.36			
Nighttime Awakenings		0.00	0.01	.78
Age		0.33	0.30	.29
Interaction		0.01	0.02	.61
	0.38			
Sleep Efficiency		0.00	0.01	.92
Age		3.42	2.14	.12
Interaction		-0.03	0.02	.17
	0.37			
TST		0.00	0.00	1.00
Age		1.33	0.87	.13
Interaction		0.00	0.00	.31
	0.34			
PSQI - Global Score		-0.01	0.04	.72
Age		0.43	0.23	.06
Interaction		0.00	0.05	.96
DSST				
	0.70			
Nighttime Awakenings		-0.38	0.26	.15
Age		-21.26	7.19	**<.001*** **
Interaction		0.01	0.37	.98
	0.72			
Sleep Efficiency		0.33	0.34	.35
Age		-92.61	48.97	.06
Interaction		0.81	0.55	.14
	0.71			
TST		0.00	0.03	.89
Age		-59.58	19.96	**<.001*** **
Interaction		0.09	0.05	**0.05***
	0.68			
PSQI - Global Score		-0.86	0.85	.32
Age		-24.73	5.19	**<.001*** **
Interaction		1.38	1.03	.19
MST				
	0.47			

Nighttime Awakenings		-0.52	0.60	.40
Age		-45.58	16.68	**0.01****
Interaction		0.53	0.86	.54
	0.47			
Sleep Efficiency		-0.09	0.83	.91
Age		-80.23	120.24	.51
Interaction		0.51	1.34	.71
	0.50			
TST		0.07	0.07	.34
Age		-67.38	46.46	.15
Interaction		0.07	0.11	.51
	0.51			
PSQI - Global Score		1.60	1.86	.39
Age		-31.02	11.57	**.01****
Interaction		-1.16	2.30	.61

Note: TST = total sleep time; PSQI = Pittsburgh Sleep Quality Index In all moderation models, Age group served as the moderator, sleep acted as the independent variable, and cognitive performance acted the dependent variable. Covariates included sex, body mass index, perceived, and years of education.

† Log transformed

* p <.05

** p < .01

*** p < .001

Table 5. Regression coefficients of the moderating effect of cardiorespiratory fitness on sleep and cognition, in older adults.

	R_2	**b**	**SE b**	**p**
TMT B †				
	0.26			
Nighttime Awakenings		-0.05	0.07	.47
Predicted VO2 Peak		-0.02	0.05	.66
Interaction		0.00	0.00	.38
	0.39			
Sleep Efficiency		0.03	0.09	.72
Predicted VO2 Peak		0.31	0.31	.32
Interaction		0.00	0.00	.37
	0.24			
TST		0.00	0.01	.79
Predicted VO2 Peak		0.10	0.22	.64
Interaction		0.00	0.00	.67
	0.21			
PSQI - Global Score		-0.11	0.20	.58
Predicted VO2 Peak		0.00	0.04	.98
Interaction		0.00	0.01	.54
DSST				
	0.24			
Nighttime Awakenings		-0.49	1.71	.78
Predicted VO2 Peak		-0.16	1.22	.90
Interaction		0.01	0.06	.91
	0.40			
Sleep Efficiency		-0.47	2.02	.82
Predicted VO2 Peak		-6.36	7.12	.38
Interaction		0.07	0.08	.41
	0.45			
TST		0.25	0.22	.29
Predicted VO2 Peak		3.10	4.40	.49
Interaction		-0.01	0.01	.56
	0.21			
PSQI - Global Score		1.06	4.56	.82
Predicted VO2 Peak		0.01	0.86	.99
Interaction		-0.02	0.17	.89

MST

	0.49			
Nighttime Awakenings		-8.31	3.32	**.02***
Predicted VO2 Peak		-5.44	2.43	**.04***
Interaction		0.31	0.12	**.02***
	0.43			
Sleep Efficiency		9.43	4.58	.06
Predicted VO2 Peak		31.60	16.21	.07
Interaction		-0.36	0.18	.07
	0.38			
TST		0.23	0.59	.69
Predicted VO2 Peak		2.46	11.60	.83
Interaction		0.00	0.02	.89
	0.51			
PSQI - Global Score		11.79	8.75	.20
Predicted VO2 Peak		2.16	1.76	.24
Interaction		-0.47	0.34	.18

Note: TST = total sleep time; PSQI = Pittsburgh Sleep Quality Index. In all moderation models, cardiorespiratory fitness served as the moderator, sleep acted as the independent variable, and cognitive performance acted the dependent variable. Covariates included sex, BMI, PSS, and years of education.

† Log transformed

* p <.05

** p < .01

*** p < .001

Table 6. Regression coefficients of the moderating effect of cardiorespiratory fitness on sleep and cognition, in young adults.

	R_2	b	SE b	p
TMT B†	0.22			
Nighttime Awakenings		-0.17	0.09	.08
Predicted VO2 Peak		-0.09	0.04	**.048***
Interaction		0.00	0.00	.07
	0.13			
Sleep Efficiency		0.10	0.13	.43
Predicted VO2 Peak		0.19	0.23	.42
Interaction		0.00	0.00	.40
	0.10			
TST		0.00	0.01	.75
Predicted VO2 Peak		0.03	0.11	.79
Interaction		0.00	0.00	.73
	0.11			.
PSQI - Global Score		-0.19	0.32	.57
Predicted VO2 Peak		-0.03	0.04	.48
Interaction		0.00	0.01	.59
DSST				
	0.47			
Nighttime Awakenings		-2.74	2.22	.23
Predicted VO2 Peak		-0.66	1.01	.52
Interaction		0.05	0.05	.31
	0.45			
Sleep Efficiency		3.90	2.95	.20
Predicted VO2 Peak		6.57	5.33	.23
Interaction		-0.07	0.06	.25
	0.40			
TST		-0.05	0.29	.87
Predicted VO2 Peak		-0.38	2.68	.89
Interaction		0.00	0.01	.82
	0.39			
PSQI - Global Score		-6.34	7.56	.41
Predicted VO2 Peak		-0.39	0.89	.66
Interaction		0.12	0.16	.45
MST				

	0.31			
Nighttime Awakenings		-1.02	5.08	.84
Predicted VO2 Peak		1.57	2.32	.50
Interaction		0.00	0.10	.97
	0.26			
Sleep Efficiency		1.75	6.85	.80
Predicted VO2 Peak		4.02	12.40	.75
Interaction		-0.03	0.14	.84
	0.33			
TST		-0.59	0.61	.34
Predicted VO2 Peak		-4.78	5.68	.41
Interaction		0.01	0.01	.28
	0.30			
PSQI - Global Score		-5.41	16.63	.75
Predicted VO2 Peak		0.58	1.95	.77
Interaction		0.14	0.35	.69

Note: TST = total sleep time; PSQI = Pittsburgh Sleep Quality Index. In all moderation models, cardiorespiratory fitness served as the moderator, sleep acted as the independent variable, and cognitive performance acted the dependent variable. Covariates included sex, BMI, PSS, and years of education.

† Log transformed

* p <.05

** p < .01

*** p < .001

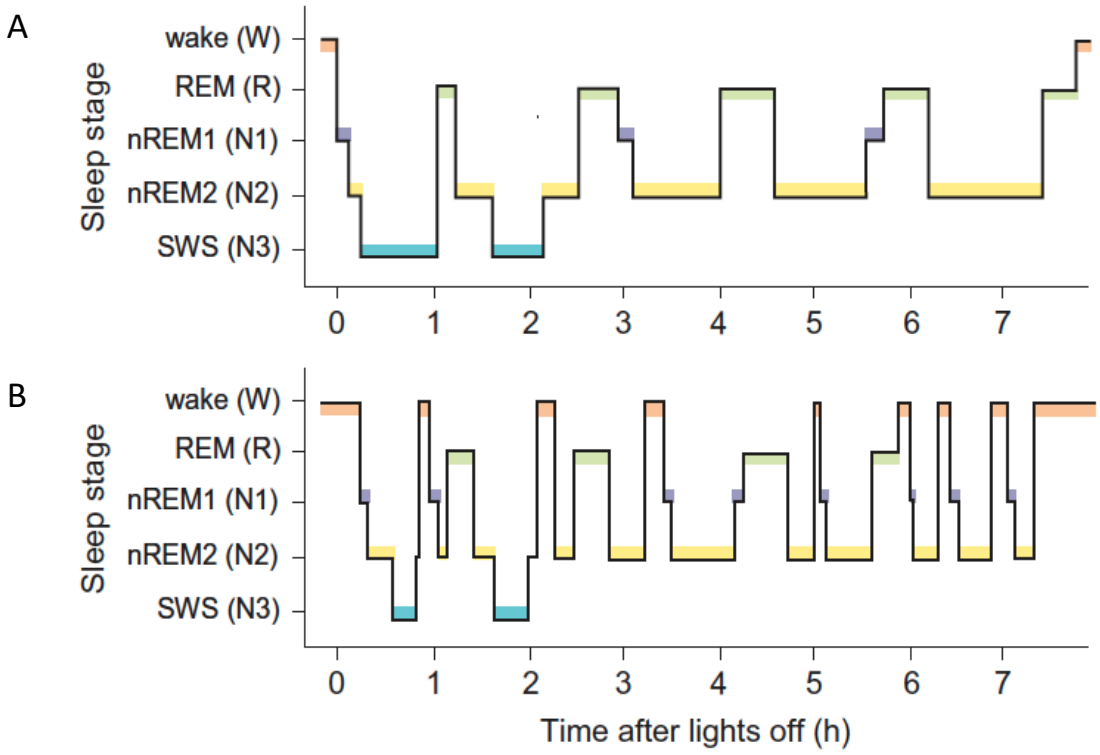


Figure 1. Sleep architecture in aging. The timing and transition through sleep stages in (A) young adults and (B) older adults. Borrowed from Pace-Schott & Spencer (2011).

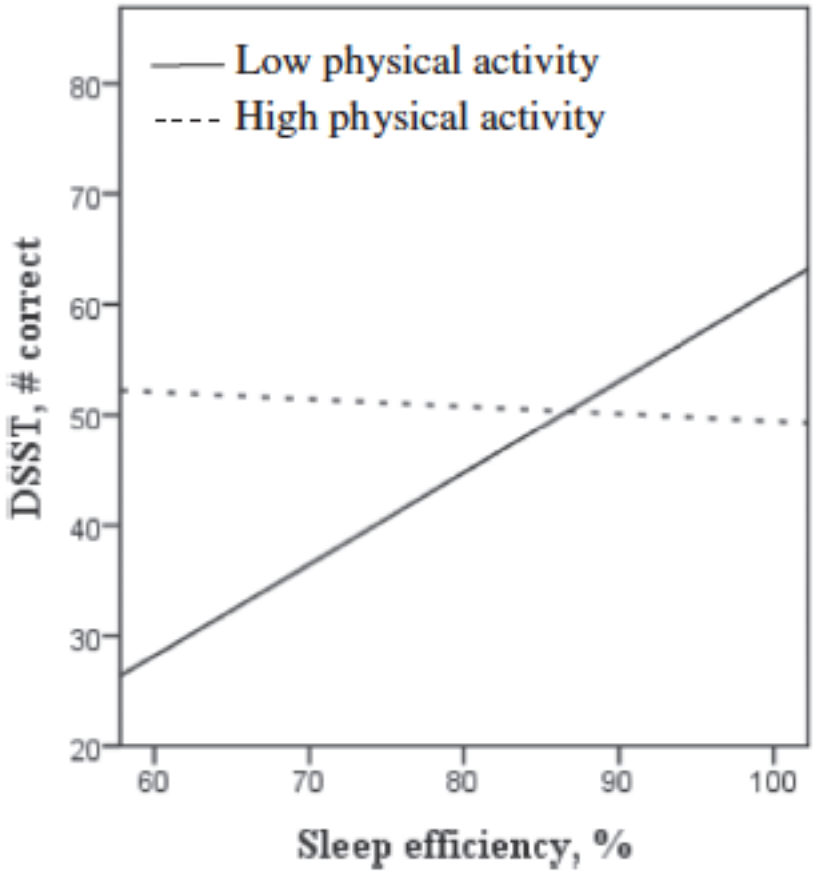


Figure 2. Results from Lambiase et al. (2014). Graphs represent the unadjusted association between actigraphy-assess sleep efficiency and performance on the digit symbol substitution test. High and low physical activity was establish using a median split of accelerometer-based measures.

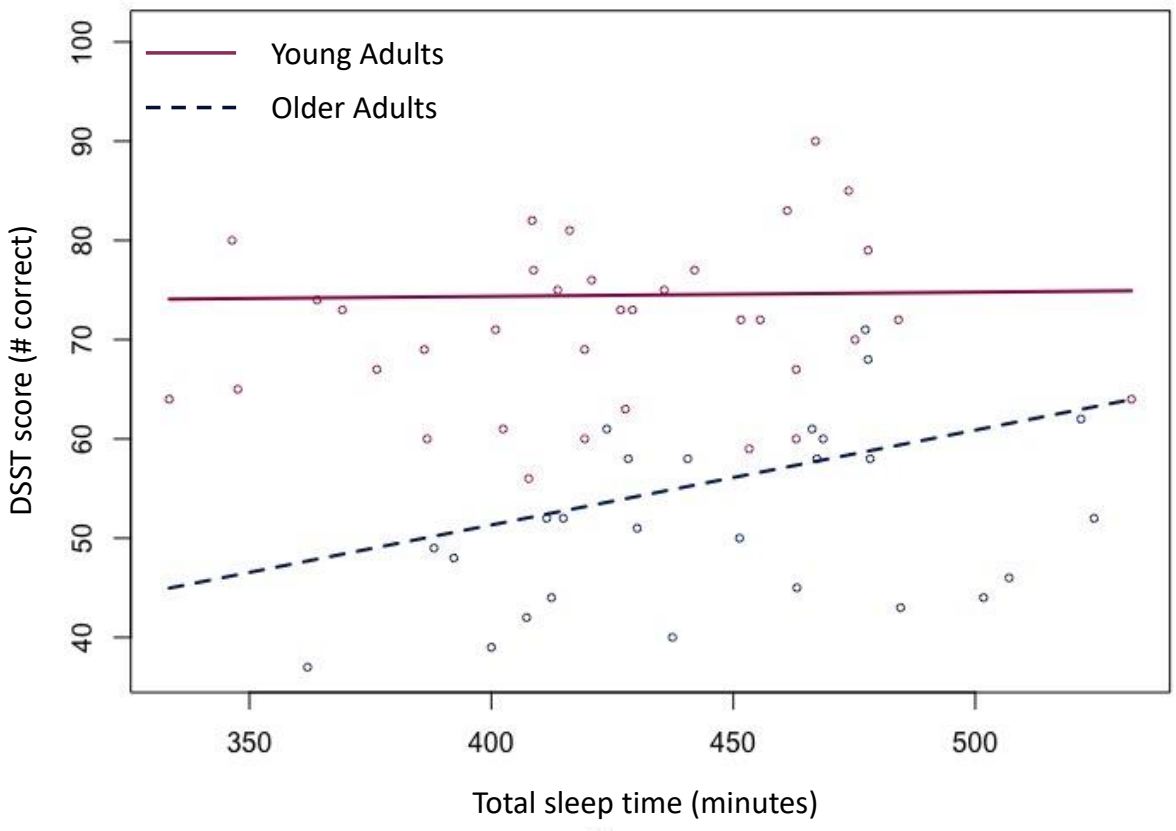


Figure 3. The moderating effect of age on TST and DSST performance. TST duration significantly predicted DSST performance in older adults (b = 0.1, $SE\ b$ = 0.03, p = .007) but not younger adults (b = 0, $SE\ b$ = 0.03, p = .89).

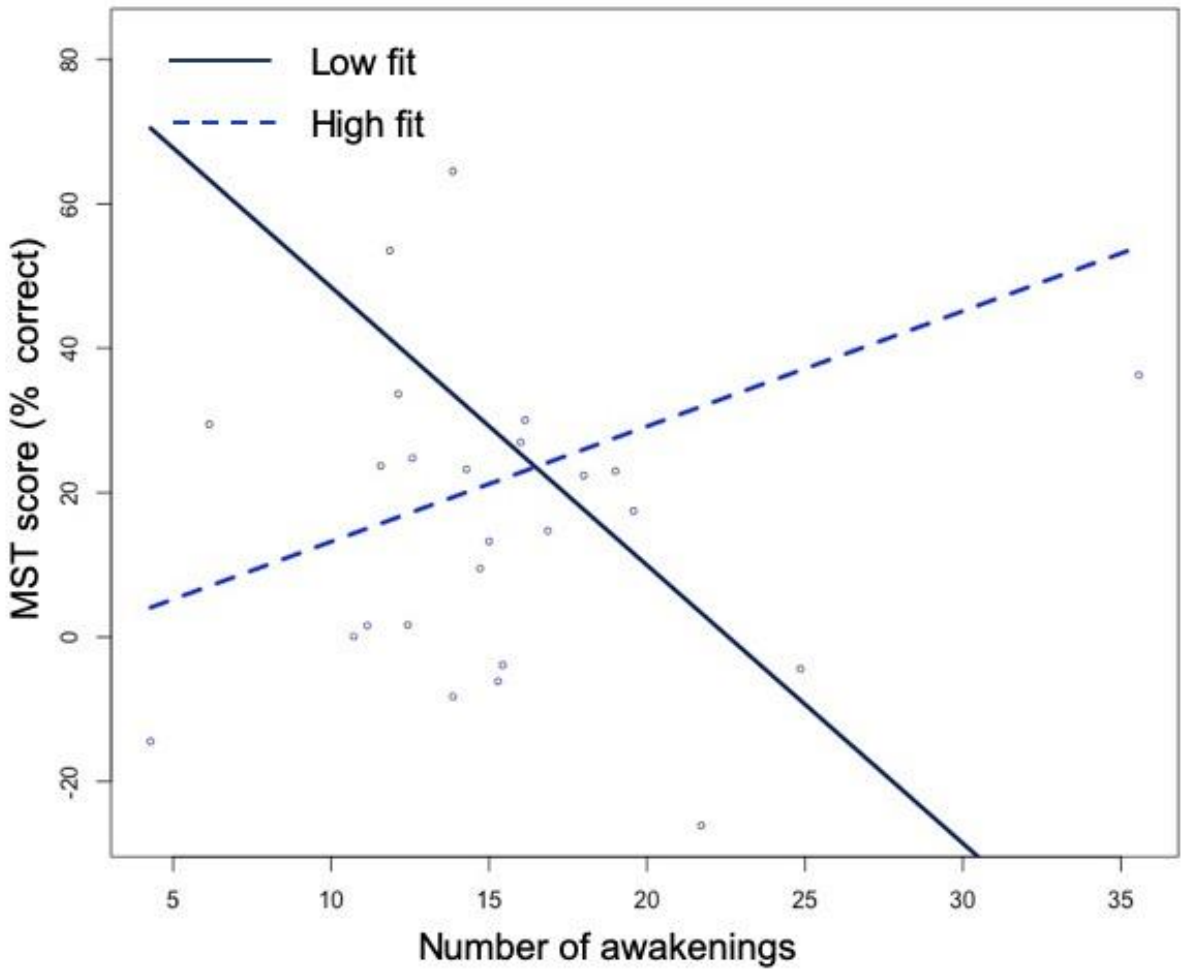
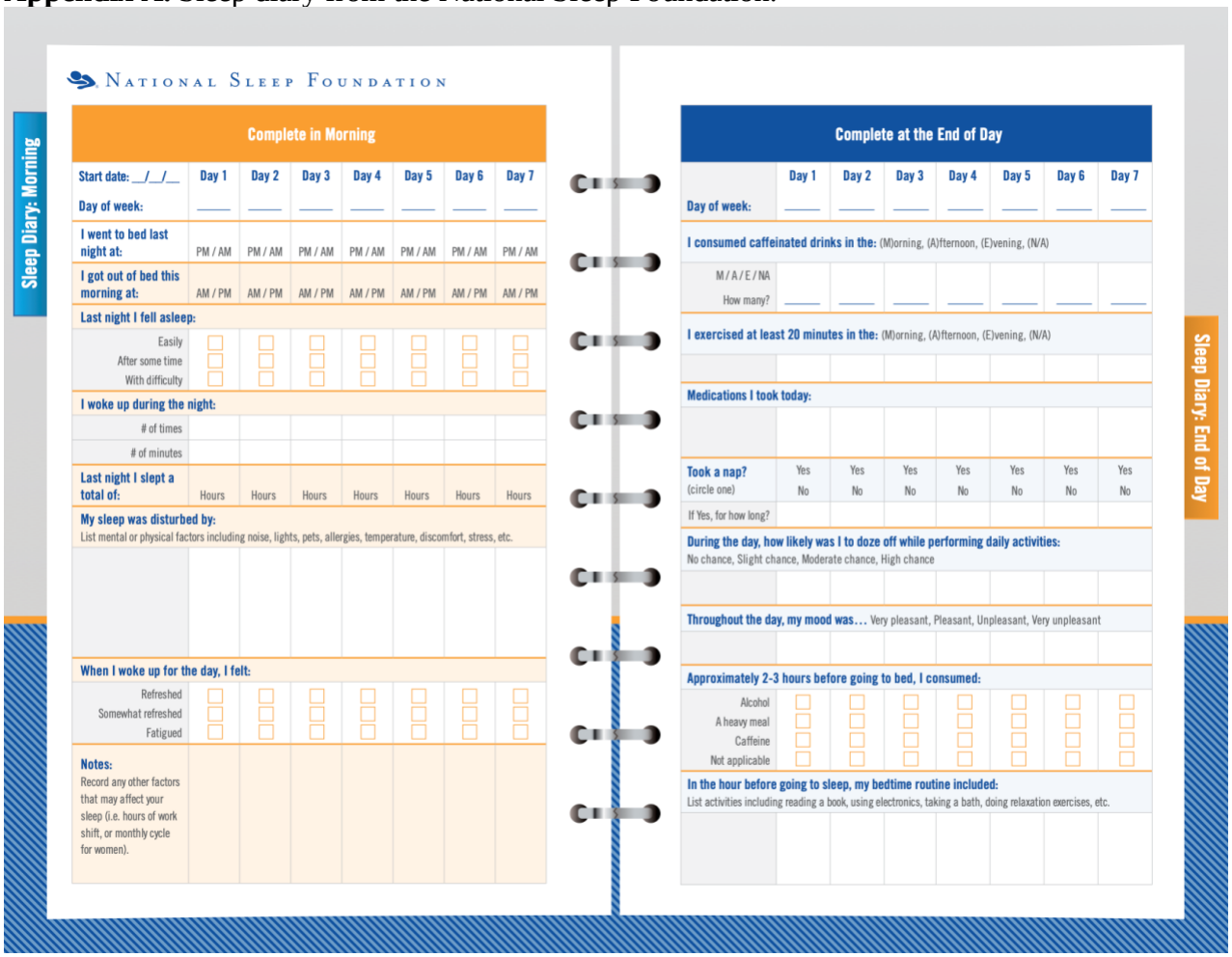


Figure 4. The moderating effect of CRF on sleep quality and MST performance in older adults. Participants were dichotomized into high and low fitness using a median split, stratified by sex. Nighttime awakenings significantly predict memory performance in low fit older adults (b = -3.85, $SE\ b$ = 1.08, p = .002) but predicted better memory performance in high fit older adults (b = 1.60, $SE\ b$ = 0.66, p = .028).

APPENDIX

Appendix A. Sleep diary from the National Sleep Foundation.



NATIONAL SLEEP FOUNDATION

Sleep Diary: Morning

Complete in Morning

Start date: __/__/__	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day of week:							
I went to bed last night at:	PM / AM	PM / AM	PM / AM	PM / AM	PM / AM	PM / AM	PM / AM
I got out of bed this morning at:	AM / PM	AM / PM	AM / PM	AM / PM	AM / PM	AM / PM	AM / PM
Last night I fell asleep:							
Easily	☐	☐	☐	☐	☐	☐	☐
After some time	☐	☐	☐	☐	☐	☐	☐
With difficulty	☐	☐	☐	☐	☐	☐	☐
I woke up during the night:							
# of times							
# of minutes							
Last night I slept a total of:	Hours	Hours	Hours	Hours	Hours	Hours	Hours
My sleep was disturbed by: List mental or physical factors including noise, lights, pets, allergies, temperature, discomfort, stress, etc.							
When I woke up for the day, I felt:							
Refreshed	☐	☐	☐	☐	☐	☐	☐
Somewhat refreshed	☐	☐	☐	☐	☐	☐	☐
Fatigued	☐	☐	☐	☐	☐	☐	☐
Notes: Record any other factors that may affect your sleep (i.e. hours of work shift, or monthly cycle for women).							

Complete at the End of Day

Day of week:	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
I consumed caffeinated drinks in the: (M)orning, (A)fternoon, (E)vening, (N/A)							
M / A / E / NA							
How many?							
I exercised at least 20 minutes in the: (M)orning, (A)fternoon, (E)vening, (N/A)							
Medications I took today:							
Took a nap? (circle one)	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
If Yes, for how long?							
During the day, how likely was I to doze off while performing daily activities: No chance, Slight chance, Moderate chance, High chance							
Throughout the day, my mood was… Very pleasant, Pleasant, Unpleasant, Very unpleasant							
Approximately 2-3 hours before going to bed, I consumed:							
Alcohol	☐	☐	☐	☐	☐	☐	☐
A heavy meal	☐	☐	☐	☐	☐	☐	☐
Caffeine	☐	☐	☐	☐	☐	☐	☐
Not applicable	☐	☐	☐	☐	☐	☐	☐
In the hour before going to sleep, my bedtime routine included: List activities including reading a book, using electronics, taking a bath, doing relaxation exercises, etc.							

Sleep Diary: End of Day

Appendix B. Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Component 1	#9 Score	C1_____
Component 2	#2 Score (≤15min=0; 16-30 min=1; 31-60 min=2, >60 min=3) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2_____
Component 3	#4 Score (>7=0; 6-7=1; 5-6=2; <5=3)	C3_____
Component 4	(total # of hours asleep)/(total # of hours in bed) x 100 >85%=0, 75%-84%=1, 65%-74%=2, <65%=3	C4_____
Component 5	Sum of Scores #5b to #5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5_____
Component 6	#6 Score	C6_____
Component 7	#7 Score + #8 Score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7_____

Add the seven component scores together _____ **Global PSQI Score** _____

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