A Compensatory Role of Physical Activity in the Association Between Sleep and Cognition

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SEWELL, K.R., A.M. COLLINS, M.L. MELLOW, R.S. FALCK, B.M. BROWN, A.E. SMITH, and K.I. ERICKSON. A compensatory role of physical activity in the association between sleep and cognition. *Exerc. Sport Sci. Rev.*, Vol. 52, No. 4, pp. 145–151, 2024. *We synthesize evidence investigating the hypothesis that greater engagement in physical activity (PA) may compensate for some of the negative cognitive consequences associated with poor sleep in older adults. Potential mechanistic pathways include glymphatic clearance, influences on depression, and other comorbidities. The evidence base is largely cross-sectional and observational, and further experimental studies are required.*
Key Words: physical activity, sleep, cognition, older adults, lifestyle

KEY POINTS

- Physical activity (PA) and sleep are independently associated with cognitive function; however, these behaviors are also related to one another in complex ways.
- Few studies have examined the interaction between PA and sleep in relation to cognition in older adults, but preliminary evidence suggests that these behaviors work together to influence cognition.
- Facets of exercise (such as intensity, frequency, and volume) and sleep (such as efficiency, quality, and duration) may have different pathways through which they associate with cognition.
- There are many potential mechanisms through which sleep, PA, and cognition may be associated, such as glymphatic clearance, influences on depression, and other chronic conditions.
- Future exercise intervention trials aiming to improve cognition should consider examining sleep as a moderator of exercise-induced cognitive change.

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INTRODUCTION

Dementia is one of the leading causes of disability and mortality worldwide (1), with one new case occurring every 3 s (2). Although pharmaceutical therapies for treating dementia are still under development and lack clear indications of treatment efficacy (3), there is evidence that modifiable lifestyle factors may be critical for preventing up to 40% of all dementia occurring after age 65 (4). Two key modifiable risk factors associated with reduced dementia risk are regular physical activity (PA) and good quality sleep (4,5). These behaviors are related to one another in complex ways; however, most studies have investigated both PA and sleep in relation to cognitive function in isolation and not jointly in the same sample or analysis (6).

Sleep and PA are unequivocally related to one another: they both form components of the 24-h activity cycle (24HAC; consisting of sleep, PA, and sedentary behavior (7)) and share a bidirectional association where optimal sleep can influence energy levels for PA engagement and PA can enhance sleep quality with small to moderate effect sizes (8). Further, both lifestyle factors have been independently associated with cognitive function, brain health, and dementia risk (5,9–11). These associations have led to speculation and hypotheses about how PA and sleep behaviors might impact brain health and cognition in an interactive manner. For example, several studies indicate that PA and sleep may moderate the influence of the other with cognition (6,12–16). An alternative model is that PA-induced improvements in sleep may be a mechanism (*i.e.*, mediator) by which PA influences cognitive performance (6).

In this paper, we hypothesize that greater engagement in PA may have the potential to compensate for some of the negative cognitive consequences associated with poor sleep in older adults (Fig. 1). Firstly, we briefly synthesize studies that have investigated the hypothesis that PA may be capable and effective for mitigating the negative consequences of poor sleep on cognition. We then discuss potential mechanisms for how PA may act in a compensatory manner for moderating an association between sleep and cognition, and discuss current limitations of the field including complexities in measuring movement behaviors. Finally, we propose specific directions for future research to optimize lifestyle interventions via individualized PA prescriptions based on a holistic view of movement behavior. Overall, the purpose of this manuscript is to describe a novel theoretical position of sleep and PA with testable hypotheses and not to reiterate the wealth of studies examining independent associations between sleep and cognition and PA and cognition.

DEFINING SLEEP AND PHYSICAL ACTIVITY

Both PA and sleep are broad terms used to describe multidimensional and complex behaviors. In this review, PA is defined as any movement behavior performed during waking and can be differentiated from exercise, a structured or planned form of PA (17). Throughout this manuscript, we refer to PA because a majority of the studies in this research space are observational and have examined unstructured and total PA rather than structured forms of exercise. Both PA and exercise may vary in intensity (the energy expenditure required for the activity), duration (length of time spent in activity), and frequency (number of bouts of activity in a certain time frame) (18). Sleep is similarly complex and multifaceted, and can be broadly defined as a recurring, reversible neurobehavioral state accompanied in humans typically by a recumbence, behavioral quiescence, and closed eyes (19). Several key indices of sleep have been related to health outcomes across the lifespan, including sleep duration, sleep efficiency (% of the amount of time in bed spent asleep), timing, alertness, overall sleep quality, among others (19). Importantly, the term "poor sleep" is complex and has no consensus definition, but may be operationalized as inadequacy in any one or a combination of sleep parameters (*e.g.*, suboptimal duration <7 h, low sleep efficiency <75%, long sleep latency ≥60 min, or wake after sleep onset ≥51) (20). This is the definition we adopt in the current paper, namely, suboptimal outcomes in one or a combination of sleep parameters (19,20). This definition does not include specific sleep disorders, such as insomnia or restless leg syndrome, because of a lack of studies in these populations. Both PA and sleep may be measured using devices (*e.g.*, accelerometers), via self-report, or by the "gold standard" polysomnography for sleep, which can yield measures of sleep macroarchitecture and microarchitecture. Self-report may be subject to social desirability and fallible memory, particularly in individuals on the Alzheimer's disease trajectory and in questionnaires with an extended recall window (21), and may be influenced by other confounding variables such as health status (22). However, self-report measures are useful in large, population-based studies where device-based measurement may not be feasible, and indeed self-reported PA and sleep are both associated with cognition and other health outcomes (16,23).

COULD PHYSICAL ACTIVITY COMPENSATE FOR THE INFLUENCE OF POOR SLEEP ON COGNITION?

Throughout this section, we refer to the moderator variable as whichever behavior (*i.e.*, PA or sleep) the relevant study has conceptualized as such. This does not change the statistical analysis (*i.e.*, a PA × sleep interaction term), but may change the conceptual interpretation. For example, some studies describe PA as moderating the impact of sleep on cognitive performance, whereas others describe sleep outcomes as moderating the impact of PA on cognitive performance. It is not our intention to indicate which variable should be conceptualized as the moderator, but rather to propose a novel theoretical position for the way in which these results may be interpreted.

Cross-Sectional Studies

Much of the current evidence investigating the interaction between PA and sleep on cognition has been conducted using cross-sectional designs. In support of the current hypothesis, three studies in cognitively unimpaired older adults demonstrated that greater total PA (13,15) and moderate-to-vigorous PA (MVPA) (12) attenuate the negative associations between poor sleep efficiency and executive function, episodic memory, and global cognition. Although these studies were in varying cohorts (*e.g.*, women only (12)), used different measures of sleep and PA (self-report (13), vs accelerometer (12,15)), and treated different variables as the moderator (*e.g.*, PA (12,13) vs sleep (15)), the authors' conclusions for the possible cognitive benefits of PA for poor sleepers remained consistent. Stratifying

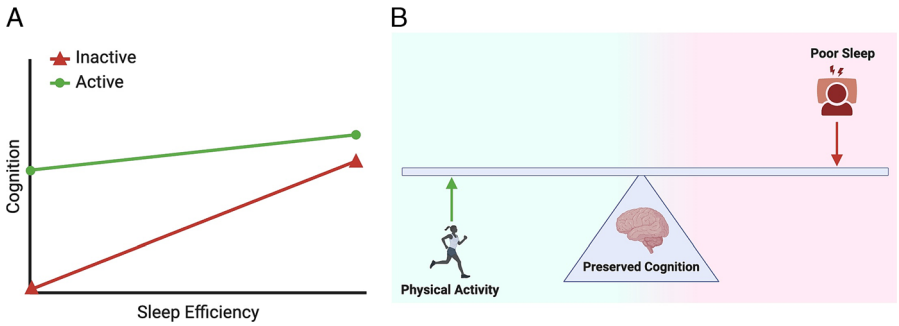

Figure 1. Visual representation of the hypothesis that physical activity compensates for the negative effect of poor sleep on cognitive function. Physical activity refers to total daily activity. Panel A represents expected statistical results. Sleep efficiency is illustrated here because a majority of studies supporting this hypothesis have demonstrated associations with sleep efficiency specifically; however, note that other studies have demonstrated associations with sleep quality and sleep duration. Panel B presents a conceptual model, adopting a wide definition of poor sleep, which may be characterized as suboptimal outcomes in one or a combination of sleep parameters, resulting in inadequate sleep satisfaction (see "Defining Sleep and Physical Activity" section). Figure created with BioRender.com.

participants into groups based on PA level or sleep quality (*i.e.*, active good sleepers, active poor sleepers, etc.), Nakakubo *et al.* (16) showed that active individuals had better cognition regardless of subjective sleep quality, and that those reporting poor sleep quality who were physically inactive had the poorest cognitive performance, partially supporting the current hypothesis. Conversely, Falck *et al.* (24) demonstrated independent associations of both PA and sleep with cognition, indicating that these lifestyle variables may influence cognitive performance through separate pathways (see "Summary" below for further discussion).

Longitudinal Studies

Only one longitudinal study (25) has examined the interaction between self-reported PA (grouped high/low based on frequency and duration) and sleep duration (<6, 6–8, >8 h), comparing slopes of cognitive decline (composite score of verbal fluency and verbal memory tasks) over 10 yr (N = 8958). Baseline cross-sectional, but not longitudinal, results from this study support the current hypothesis. At baseline, both short sleep and low PA were associated with poorer cognition; however, there were no significant differences in cognitive performance between those with higher PA and optimal sleep duration (6–8 h), and those with higher PA and short sleep duration (<6 h). This indicates that higher PA may have been compensating for the impact of short sleep duration on cognitive performance. However, short sleep duration but higher PA at baseline was associated with more rapid cognitive decline, such that at the 10-yr follow-up cognitive scores were similar to those with lower PA. Complicating these findings, the associations were moderated by age, such that this pattern of results was only significant for adults aged 50 and 60 yr at baseline, but not for adults 70 yr and older. Together, these longitudinal results appear to conflict with the cross-sectional studies. However, ~70 yr was the mean age for the above-mentioned cross-sectional studies, indicating that the age of the sample could explain these conflicting findings, but further longitudinal studies are needed to confirm these conclusions.

Randomized Controlled Trials

Results from the cross-sectional and longitudinal observational studies are provocative but do not provide causal evidence for an interaction between PA and sleep on cognition. Such evidence would have to emerge from randomized controlled trials (RCT). In fact, there is experimental evidence suggesting that sleep moderates the effects of exercise training on cognitive function (14). In a secondary analysis of an RCT, baseline self-reported sleep moderated the impact of a moderate- or high-intensity cycling exercise intervention on cognitive performance in 99 cognitively unimpaired older adults (68.76 ± 5.32 yr) (14). Sleep efficiency moderated the effect of the exercise intervention on episodic memory performance, such that those with <75% sleep efficiency in the moderate-intensity exercise group showed the greatest improvements in episodic memory and global cognition from preintervention to postintervention. In contrast, these results were not found for those randomized to the high-intensity exercise group. This supports the hypothesis that the impact of poor sleep on some cognitive domains may be offset by engaging in regular exercise, but highlights that this may be dependent on exercise intensity. These findings were corroborated by a secondary analysis of an RCT among older adults with chronic stroke (N = 120), which found that sleep moderated the effects of 6 months of twice-weekly multimodal exercise training, such that cognitive performance improved for participants with poor sleep but not for participants with good sleep (26) (under review). Although both studies were secondary analyses from randomized interventions, these data suggest that poor sleepers may be a key target population for promoting cognitive function through exercise training.

Other Methodologies: 24-h Time-Use Composition

Lifestyle behaviors within the 24HAC, including PA and sleep, are often analyzed independently of each other with respect to cognitive performance, despite overwhelming evidence that these behaviors are interrelated. One way to address this limitation is by using compositional data analysis (CoDA). Briefly, CoDA expresses components of the 24-h day (*i.e.*, PA, sleep and sedentary behavior) as a set of isometric log ratios, which are then able to be included in the same statistical model without violating assumptions of multicollinearity (27). Compositional isotemporal substitution techniques can also provide insight into the theoretical cognitive changes associated with reallocations of time between behaviors (28). In the context of the compensatory hypothesis, this technique would allow comparison of the theoretical implications of reallocating time between sleep, light PA (LPA) and MVPA across varying sleep and pathological profiles (*e.g.*, good vs poor sleepers, degrees of beta-amyloid (Aβ burden)), thereby improving our understanding of how all aspects of the 24HAC contribute to cognitive functioning.

In support of the current hypothesis, 24-h time-use composition has been associated with global cognition and executive function in older adults without dementia (65.6 ± 7.5 yr) (29). Evidence from two studies showed that modeling an increase in time spent in MVPA was beneficial for cognition, regardless of whether this time was taken from sleep or sedentary time (29,30). Hypothetically, if part of these samples was poor sleepers, as ~40% of the population is estimated to be (31), then this would support the notion that reallocating time to MVPA may compensate for the influence of poor sleep on cognition. However, sleep quality was not included as a moderator in this study. Another study examined whether sleep quality (evaluated by a single self-report question) moderated the relationship between 24-h time-use composition and cognitive performance in older adults, but the moderation was not significant and reallocation modeling was not explored further (32). Clearly, additional research is required to determine the factors that explain variability in the cognitive benefits of increasing MVPA (at the expense of other 24-h time-use behaviors).

Although theoretically reallocating time from sleep to MVPA has been associated with cognitive benefits (33), it does not necessarily mean that PA has a greater influence on cognitive function than sleep. Rather, small changes in MVPA may be proportionally greater than small changes in sleep. For example, a 20-min increase in physical activity per day for someone who was previously only engaging in 10 min of MVPA per day equates to a 200% increase, whereas a 20-min increase in sleep duration from a baseline duration of 5 h results in only a 6.6% increase. Thus, small increases in time spent in MVPA may be more potent in relation to time use for improving cognitive performance. Notably, individuals with sleep disorders such as insomnia may demonstrate large changes in sleep

duration, and thus, the same association may not exist in these clinical populations. Nevertheless, there is likely a "ceiling" effect for the extent to which PA can compensate for suboptimal sleep on cognition, because the absence of sleep would clearly outweigh the positive impact of PA on cognition. These approaches for analysis of 24-h time use are still in their infancy, and further research is required to determine optimal time use of sleep and PA for maximizing cognitive function.

Summary

Taken together, these cross-sectional and preliminary experimental studies support the hypothesis that PA may compensate for some of the negative effects of poor sleep, primarily characterized as suboptimal sleep duration or low sleep efficiency, on cognitive function in older adults (Fig. 1). However, additional experimental studies, specifically designed to investigate this hypothesis, are required. Notably, 24HAC studies are only focused on sleep duration and have not considered sleep quality measures; thus, future studies should focus not only on duration but also quality.

In addition to the hypothesis that PA could moderate the impact of poor sleep on cognitive performance, there are other ways in which PA and sleep may influence cognitive function. For example, PA and sleep may be conceptually and statistically independent from one another and independently associated with cognitive function. This, in essence, would be the null hypothesis that sleep influences cognitive performance and PA influences cognitive performance, but they act in a separate manner and possibly through separate pathways (*e.g.*, (24)). An alternative hypothesis is that sleep may mediate the influence of PA on cognitive function (6). There are several cross-sectional studies demonstrating that sleep might be acting as a mediator between the PA–cognition association (34,35), such that PA may influence cognitive performance via its influence on sleep. However, because both sleep and PA are complex and multifaceted behaviors, there is a possibility that various aspects of each may have different associations with specific cognitive domains (6). Thus, all the above hypotheses could be simultaneously true, and further research is needed to determine domain-specific associations.

MECHANISTIC LINKS BETWEEN PHYSICAL ACTIVITY, SLEEP AND COGNITION

It is likely that both sleep and PA are acting through many pathways simultaneously, with downstream consequences on many physiological systems that impact cognitive performance. Thus, our aim in this section is not to provide an exhaustive review of every possible pathway by which PA and sleep could be impacting cognitive performance, but specifically focus on several that could support the compensatory hypothesis that is described in the above sections.

Glymphatic Clearance

Glymphatic clearance is the system by which the brain clears toxic metabolites via the exchange of water and soluble contents between the cerebrospinal fluid and interstitial fluid and is most effective during sleep (36,37). Impaired glymphatic clearance is one way that poor sleep may contribute to increased Aβ accumulation (38), because lack of sleep provides limited opportunity for Aβ clearance, increasing the risk of Aβ aggregation (36). Increased PA may promote glymphatic clearance (39), compensating for impaired clearance during poor sleep (36), in turn contributing to reduced AD pathology and improved cognition (40) (Fig. 2). In support of this hypothesis, we previously showed that sleep and PA may interact to influence brain Aβ levels (13); however, in our study, the direction of this interaction was unclear and occurred at the tail ends of the observed data, so results should be interpreted with caution. Further, there has been speculation and some mixed evidence that PA may be most beneficial for cognitive function in apolipoprotein E (APOE) ε4 carriers (genetic risk factor for AD) (29), in whom glymphatic clearance may be impaired (41–43). Finally, the association between sleep and brain Aβ is moderated by genetic variation in aquaporin-4 (AQP4), which plays a pivotal role in glymphatic function (44), and evidence from animal models suggests that AQP4-dependent

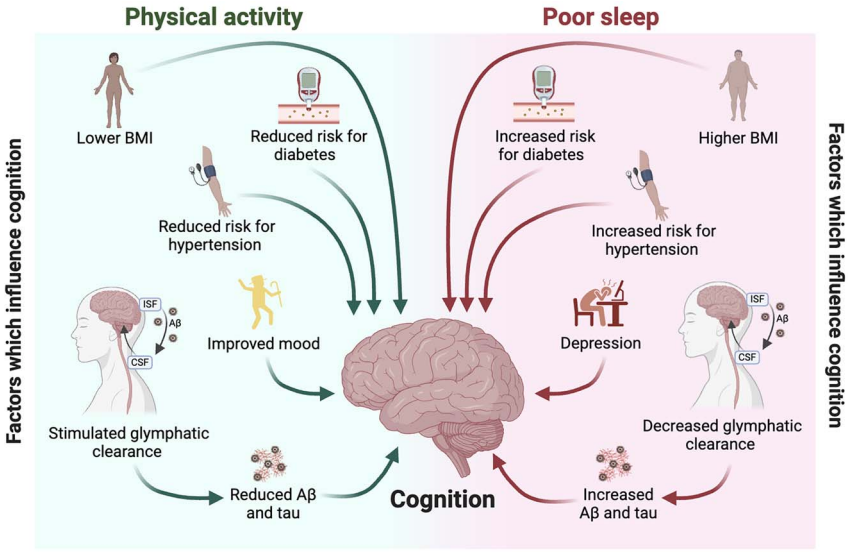

Figure 2. Illustration of potential mechanisms (not exhaustive) through which physical activity compensates for the influence of poor sleep on cognitive function. Green arrows represent a positive influence; red arrows represent a negative influence. Poor sleep, which may be characterized as suboptimal outcomes in sleep duration, sleep efficiency, timing, alertness, and overall sleep quality. BMI, body mass index; CSF, cerebrospinal fluid. Figure created with BioRender.com.

glymphatic transport is a mechanistic link between PA and AD outcomes (45). Specifically, AQP4 gene knockout mice demonstrated impaired glymphatic clearance and increased Aβ and cognitive impairments, which were not improved by exercise, whereas in mice with AQP4, an early exercise intervention improved AD-related outcomes (45). Evidence from other animal studies shows that exercise increased glymphatic clearance and improved AQP4 expression (39). A recent study in humans also demonstrated that glymphatic clearance mediates the association between brain Aβ and cognitive dysfunction in AD (40).

Despite the studies above that point to possible glymphatic clearance as a mechanism by which PA and sleep interact to influence cognitive performance, there is some evidence that raises doubts for this pathway. For example, a study conducted in humans demonstrated that brain Aβ mediated the association of sleep with cognitive function, whereas brain volume mediated the PA–cognition relationship (46). Sleep measures were not associated with brain structure, and PA measures were not associated with Aβ (46). If PA compensates for the negative influence of poor sleep on cognition through promoting glymphatic clearance (thus decreasing Aβ), we might expect a stronger association between PA and Aβ than what was found in this study. However, it remains a possibility that PA may only compensate for poor clearance in poor sleepers, resulting in relatively weaker associations between PA and Aβ (as is often observed in the literature). Thus, we may expect that the association between sleep and Aβ would be strongest in those who are physically inactive (*i.e.*, with no glymphatic compensation), but such an interaction was not reported in this study.

Taken together, the evidence described above provides a mechanistic basis for the hypothesis that PA may compensate for impaired glymphatic clearance in poor sleepers (Fig. 2), which is related to AD pathology and cognitive function, and that this association may be altered by AQP4 genotype. However, evidence for the association between PA and Aβ in humans is currently inconsistent (47), and further research in humans is required to determine whether this is a likely mechanistic link through which PA compensates for the negative impact of poor sleep on cognition.

Depressive Symptoms

PA may also compensate for the effect of poor sleep on cognitive function via its impact on depressive symptoms. Poor sleep is associated with greater depressive symptoms and is sometimes regarded as a symptom of depression, whereas PA reduces depressive symptoms and is considered an effective nonpharmaceutical therapeutic for clinical depression (48). Evidence from animal and human studies indicates that PA may influence depressive symptoms via improving sleep and circadian rhythms (48,49). Moreover, depressive symptoms are associated with poorer cognitive performance, and depression has been identified as a modifiable risk factor for neurodegenerative diseases such as dementia (4). Importantly, poor sleep and physical inactivity interact to influence depressive symptoms. For example, a recent survey-based study in >79,000 European adults (50) demonstrated that participants with poor sleep quality who were also physically inactive had greater depressive symptoms compared to those with poor sleep quality who were physically active. Similarly, participants who had good sleep quality but were physically inactive had more depressive symptoms than those with good sleep quality and higher PA. Additionally, a recent study found that self-reported PA levels mediated the relationship between sleep health and depressive symptoms and consequently reduced the effect of poor sleep on depressive symptoms (48). Taken together, physical activity may mitigate the impact of poor sleep on depressive symptoms, which may in turn have protective effects on cognitive performance.

Yet, complicating this hypothesis of depression as a mechanism explaining the moderating association of PA and sleep on cognitive function is that various aspects of sleep are both a predictor and symptom of depression. In addition, the patterns might not be linear such that both short sleep duration and long sleep duration could be a symptom of depression. Similarly, isolation and inactivity are associated with increased risk of depression while they are also symptoms of depression. Thus, disentangling predictors, symptoms, outcomes, moderators, and mediators from this complicated interplay of variables will certainly be a challenge for future research.

Chronic Conditions

Approximately 80% of older adults have multiple chronic conditions (51), and greater condition severity is linked to greater cognitive decline (52). Metabolic syndrome (marked by the coexistence of obesity, hypertension, diabetes, and hyperlipidemia) is a risk factor for AD (53), and in turn, lifestyle behaviors are modifiable risk factors for metabolic syndrome. Sleep and PA have been independently related to chronic conditions (*e.g.*, hypertension, diabetes, obesity), and both poor sleep and low PA levels contribute to higher risk and incidence of chronic conditions (54). For example, obstructive sleep apnea (OSA) is a cardiometabolic chronic condition (often comorbid with other chronic conditions such as diabetes and hypertension) that influences sleep and cognitive function and is prevalent within the older adult population (55,56). Further, PA is an important component for weight management and has been linked to favorable changes in cardiometabolic risk factors that present with OSA, and reduction in OSA disease severity (57). Given the link between PA and sleep with cardiometabolic conditions, and cardiometabolic conditions with cognitive decline, we argue that these may be plausible mechanisms by which PA and sleep act to influence cognitive function (Fig. 2).

Similar to the case with depression, determining whether chronic medical conditions are the mechanism by which PA moderates the impact of poor sleep on cognitive function is analytically and conceptually challenging. Given the vicious cycle between PA, sleep, and chronic medical conditions (low PA and poor sleep could lead to chronic medical conditions, but chronic medical conditions could lead to low PA and poor sleep), it will be difficult for future research to determine directionality of the associations. Future intervention studies that aim to alter this cycle, for example, increase PA or improve sleep quality to reduce the severity of chronic conditions, may help us better understand the causality of these relationships.

LIMITATIONS AND RECOMMENDATIONS

A limited number of RCTs make it difficult to draw causal conclusions regarding associations between sleep, PA, and cognition, and there is a need for more rigorous experimental work in this literature. In such interventions, transparency for the description of and adherence to exercise prescriptions should be

prioritized, because the parameters of PA and sleep may have a differential impact on cognitive function. Sleep should also be considered as a moderator in PA interventions to improve the efficacy of PA on cognitive function in the context of variation in sleep parameters (25). Addressing these considerations will progress the field in a standardized approach that fosters reproducibility while maximizing generalizability and applicability.

Heterogeneity in measurement approaches for both sleep and PA are also a limitation of the current literature. As stated above, these lifestyle behaviors are multidimensional, and measurement of sleep in particular may be challenging. For example, accelerometers estimate sleep through the lack of bodily movement detected as periods of sustained inactivity, made more difficult if wrist-worn devices are not properly secured (worn too loosely), introducing noise into the acceleration signals. Despite the development of algorithms validated against the "gold standard" polysomnography, accelerometers cannot characterize all sleep outcomes and largely estimate sleep duration, efficiency, and fragmentation. Therefore, objective devices may be unable to detect other aspects of sleep accurately or sensitively. Such limitations can be addressed through implementing both subjective and objective tools to measure sleep outcomes, which play a differing but important role in understanding this potential compensatory relationship (18). For example, subjective measures provide rich insight into perceptions of sleep quality and restfulness and are associated with cognition and important health outcomes (18,23). Objective measures, however, are useful for understanding sleep physiology and detecting clinically important sleep changes, and are also associated with cognition (18). Thus, using a combination of device-based and subjective measures of sleep might enhance understanding of these relationships. Additionally, polysomnography or other sleep measurement devices that can measure sleep stages (*e.g.*, WatchPAT™) (58) may advance our understanding of these associations by considering sleep architecture. Future research should consider investigating a moderating effect of sleep architecture on PA and cognition.

Cognitive function is also measured in a variety of ways across studies. Comprehensive neuropsychological testing batteries are recommended to capture performance in multiple cognitive domains, in comparison to brief batteries (*e.g.*, Mini-Mental State Examination) that may only account for a single domain or global cognition. These limited tests are often incomprehensive and unable to detect subtle change, which is especially important in cognitively unimpaired old adults. Further research utilizing comprehensive cognitive assessments is needed to better understand these relationships. Finally, the broad impact of sleep and PA on physiology and function makes it difficult to isolate particular mechanistic pathways while also potentially explaining the far-reaching impact of both behaviors on nearly all health outcomes. To complicate this further, it is difficult to differentiate age-related neurodegeneration and behavioral changes from pathological changes in disease states. At present, there is evidence that sleep and PA are associated with cognitive function in both pathological and nonpathological states, and that both may impact the development of pathology; however, further research is required to better understand these associations.

CONCLUSION

We proposed the testable hypothesis that engaging in PA may compensate for the negative effect of poor sleep on cognitive function in older adults. The high prevalence of poor sleep in older adults and difficulties with improving sleep in this population indicate that improving our understanding of potential compensatory effects and their mechanisms could be important for treating both poor sleep and poor cognitive function.

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