Physical Activity and Executive Function in Midlife

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Greater participation in physical activity (PA) is associated with better executive functioning (EF) and lower rates of cognitive impairment. Midlife may be a critical period when the risk for cognitive decline begins to be conferred, making health behaviors particularly important. It is likely that multiple parameters of PA (e.g., intensity, volume, pattern of activity) work in concert to improve cognitive functioning. However, few studies have evaluated these PA parameters as one PA index or parsed them into distinct features. Prior evidence suggests that age and/or sex may moderate PA-EF relationships, though these studies have almost exclusively investigated effects in older adults or children. The aims of the current study were to investigate whether PA modulated EF during midlife and to test the moderating effects of age and sex. Exploratory factor analyses derived two factors (moderate-to-vigorous PA (MVPA) and total PA) from objectively monitored PA in 456 healthy midlife adults (mean age=43 years). Additional factor analyses derived an underlying EF factor and EF subdomain components (i.e., working memory, inhibitory control, abstraction, processing speed). Regression models controlling for relevant demographic and health characteristics explored the relationships between PA engagement and EF. Secondary analyses tested whether these relationships differed between using a PA factor or individual PA parameters as predictors of EF. Neither PA factor nor their interactions with age or sex were associated with the exploratory EF factor. Analyses focusing on the EF subdomains revealed that higher MVPA factor scores were associated with poorer inhibitory control. Separating the PA factors into individual parameters demonstrated that longer

time spent in MVPA bouts and lower active energy expenditure were associated with better abstraction. There were no significant associations or interactions with age or sex on working memory or processing speed. Total PA was not related to EF or any EF subdomain. Taken together, achieving moderate intensity PA may uniquely contribute to EF during midlife. However, overall factor scores of PA and EF were not related in this sample. The unexpected negative and nonsignificant associations may be explained by a truncated range of PA or by unexplored physiological mechanisms that might mediate the PA-EF relationship.

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1.0 Background and Significance

Greater participation in physical activity (PA) is associated with lower rates of dementia (Xu et al., 2017), cardiovascular disease (Sattelmair et al., 2011), and all-cause mortality (Arem et al., 2015; Warburton, Nicol, & Bredin, 2006), among other health outcomes (Daskalopoulou et al., 2017; Kubota et al., 2017). However, there is considerable variability in the types of activities, duration of activity, and extent of physical exertion across individuals that influence the efficacy of PA to improve health outcomes, including cognitive functioning (Hillman, Erickson, & Kramer, 2008; X. Liu et al., 2017). Most of the research examining how PA is related to cognitive functioning has been done in older adults or children, and there is currently a gap in the evidence characterizing how midlife PA is related to cognitive functioning. Midlife may be a critical period during which the risk for late-life cognitive impairment begins to be conferred. Health behaviors in midlife (e.g., PA) influence later-life risk for neurodegenerative disorders (e.g., cerebrovascular disease, Alzheimer's disease pathology (Meng et al., 2014; Tolppanen, Solomon, Soininen, & Kivipelto, 2012)) and alter cognitive aging trajectories (Viswanathan et al., 2015). Understanding the factors that contribute to the risk of developing these impairments can influence recommendations for preventative steps that can be pursued earlier in life.

Health behaviors are a key feature of disease risk and are critical for understanding cognitive aging. Executive functioning (EF) is a cognitive domain that is highly sensitive to the effects of aging and poor health. Maintenance of EF allows individuals to move through daily life by multitasking, using working memory, and utilizing self-control, among other abilities (Diamond, 2013). Some of the earliest signs of cognitive decline may be related to difficulty with managing finances, maintaining daily routines, or completing tasks – activities that rely on EF.

Given the sensitivity of these cognitive processes, examining EF during midlife may provide insight to aging trajectories that could, in turn, inform methods for reducing risk of cognitive impairment later in life.

1.1 Executive Functioning

Executive function is an umbrella term that encompasses multiple abilities involved in cognitive control and goal-directed behaviors (Jurado & Rosselli, 2007; Lezak, 1982). The specific processes within this cognitive domain include inhibitory control, set shifting, working memory, updating, reasoning, and cognitive flexibility (Diamond, 2013; Miyake & Friedman, 2012). EFs show a pattern of distinct but shared abilities, which is referred to as their "unity and diversity" (Friedman & Miyake, 2017; Miyake et al., 2000). The diversity is captured in the wide range of abilities that encompass EF, each of which can be evaluated with a variety of neuropsychological tests and considered as individual cognitive processes. The unity of EF underscores the latent factor of these abilities, such that executive processes are often closely related to one another (Baddeley & Della Sala, 1996; Miyake et al., 2000). This unity between EF measures has also been linked to other common terms within the field, such as 'cognitive control,' which is an umbrella term often used to describe a subset of EFs including selective and sustained attention (McCabe, Roediger III, McDaniel, Balota, & Hambrick, 2011). Conceptualizing EF as a unitary construct that is composed of a diverse set of cognitive processes can help to understand how these cognitive processes change or remain stable throughout the lifespan by evaluating performance on both a broad and specific scale.

EFs are particularly vulnerable to health factors (Jurado & Rosselli, 2007). In general, cross-sectional studies indicate that poorer cardiometabolic health is associated with poorer EF. In several studies with samples ranging from 90-1,543 participants between 44-89 years old, participants with hypertension or Metabolic Syndrome had lower scores on individual EF tests and lower EF composite scores (Bokura, Nagai, Oguro, Kobayashi, & Yamaguchi, 2010; Saxby, Harrington, McKeith, Wesnes, & Ford, 2003; Vicario, Martinez, Baretto, Casale, & Nicolosi, 2005). Specifically, Metabolic Syndrome patients performed worse on tests of working memory, switching, and inhibitory control when compared with healthy controls, highlighting the breadth of EF deficits associated with metabolic dysfunction. The patients also exhibited lower EF latent scores compared with controls, which suggests that executive dysfunction is pervasive across several component cognitive processes.

Poorer health (e.g., hypertension, diabetes) earlier in life is also associated with faster rates of EF decline and poorer follow-up performance both for individual neuropsychological tests and composite or factor scores (Critchton, Elias, Davey, & Alkerwi, 2014; Kuo et al., 2005; Oveisgharan & Hachinski, 2010; Yasar, Ko, Nothelle, Mielke, & Carlson, 2011). Specifically, poorer health is linked with poorer working memory, switching, and abstract reasoning task performance (Kuo et al., 2005; Yasar et al., 2011). Composite scores show similar results, such that a latent EF score was reduced in individuals with poorer baseline health (Critchton et al., 2014). Further, faster progression to dementia among individuals with chronic health conditions, such as hypertension, suggests that maintaining better health could be a protective factor against poor cognitive aging (Oveisgharan & Hachinski, 2010). What remains unclear is which modifiable lifestyle factors influence EFs. PA is low-cost and easily accessible, making it a prime target for examining how lifestyle is related to cognitive health.

1.2 Physical Activity

PA is defined as any bodily movement produced by skeletal muscles that increases energy expenditure (Caspersen, Powell, & Christenson, 1985). PA can be any activity that raises energy expenditure above the resting rate, including intentional exercise or everyday activities like walking or housework. PA is distinct from cardiorespiratory fitness (CRF), which refers to cardiovascular efficiency and is a physiological measure influenced by various factors including habitual PA, demographics, and genetics. Engaging in any amount of PA has been shown to reduce all-cause mortality relative to maintaining a sedentary lifestyle, suggesting that it is a viable target for maintaining good health. In 661,137 participants ranging from 21-90 years old pooled from six observational longitudinal cohorts, any amount of leisure-time PA was associated with at least a 20% reduction in risk for mortality (Arem et al., 2015). Over an average of 14 years' follow-up, participating in less than the public health recommended PA minimum (i.e., 150 minutes per week) showed the lowest mortality risk reduction (i.e., 20%), with risk reduction increasing as PA engagement increased. Individuals engaging in one to two times the minimum recommended PA had a 31% reduction in risk, those engaging in two to three times the recommended amount of PA had a 37% reduction in risk, and those engaging in three to 10 times more than the recommended minimum had a 39% reduction in risk (Arem et al., 2015). Thus, *any* engagement in PA conferred benefits to all-cause mortality and there may be an upper threshold at which additional benefits are negligible. Over the past several decades, the benefits of PA have been shown in both healthy and patient populations across the lifespan. These benefits extend to cognitive functioning and brain health, in addition to reduced risk for disease and mortality.

1.2.1 A Protective Factor for Cognitive Functioning

Decades of research evaluating the effects of exercise on cognition suggest that greater PA engagement is associated with better functioning, both overall and specifically in the domains of EF and memory (Bherer, Erickson, & Liu-Ambrose, 2013; Daly, McMinn, & Allan, 2014; Donnelly et al., 2016; Falck, Davis, & Liu-Ambrose, 2017; Kramer & Colcombe, 2018; Tomporowski & Ellis, 1986). Cross-sectional studies reveal that greater PA engagement and higher CRF are associated with better performance on EF tasks, specifically within the subdomains of inhibitory control, working memory, and switching, in healthy adults (Cox et al., 2016; Voelcker-Rehage, Godde, & Staudinger, 2010). It is noteworthy that cross-sectional studies might detect a bidirectional relationship between higher PA engagement and better cognitive functioning. That is, individuals who engage in more activity might perform better on cognitive tests, but it may also be that those who score higher on cognitive tests choose to participate in more PA. Cross-sectional studies are limited by an inability to determine causality between PA and cognitive functioning. In fact, longitudinal evidence suggests that cognitively normal older adults with lower scores on EF tests at baseline are associated with less PA engagement six years later (Daly et al., 2014). This study highlighted the limited understanding of whether individuals with poorer EF struggle to set and maintain goals, which might include engaging in PA relative to those with better baseline EF. Longitudinal studies and RCTs have sought to clarify these relationships.

Numerous reviews synthesizing the longitudinal literature indicate that greater PA engagement earlier in life is associated with lower rates of conversion to cognitive impairment and/or dementia at follow-up between two and 44 years later (Bherer et al., 2013; Hamer & Chida, 2009; Sofi et al., 2011). A meta-analysis of 37 studies demonstrated that higher levels of PA engagement were associated with a 14% reduction in risk of developing dementia compared with

lower levels of PA (Blondell, Hammersley-Mather, & Veerman, 2014)., The authors provided compelling evidence that PA earlier in life can preserve cognitive functioning later in life. Overall, engaging in greater volume of PA is related to better current and future cognitive functioning, especially when compared with sedentary behavior or low PA. RCTs have further sought to manipulate PA to better elucidate these relationships and understand the causal mechanisms underlying positive associations between PA engagement and cognitive performance.

To date, RCTs have largely been conducted during childhood and late adulthood to understand how increasing PA may influence cognitive functioning. Meta-analyses of RCTs in children suggest that increasing PA over a period of 12-24 weeks is associated with better performance on academic (de Greeff, Bosker, Oosterlaan, Visscher, & Hartman, 2018) and EF tests (Alvarez-Bueno et al., 2017) compared with control groups. In older adults, increasing aerobic PA over a period of 12-56 weeks can maintain cognitive functioning in healthy populations (Erickson et al., 2011; Lautenschlager et al., 2008) and reduce the burden of cognitive impairment in mild cognitive impairment (MCI) and dementia populations compared with controls (Groot et al., 2016; Heyn, Abreu, & Ottenbacher, 2004; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018). While less work has been done in young and middle-aged adults, a recent RCT demonstrated that increasing aerobic PA over six months improves EF task performance in 94 adults aged between 20-67 years (Stern et al., 2019). Using PA RCTs to improve cognitive functioning or mitigate age-related decline puts PA at the forefront of methods to prevent cognitive impairment. Critically, PA RCTs show heterogeneous effects on cognitive functioning (Etnier & Chang, 2009; Hillman et al., 2008). Differences in the frequency, intensity, or type of activity employed in these RCTs may explain some of the variability across studies.

Engagement in PA may influence EF differently across age groups, given that EF performance peaks in young adulthood and declines through the remainder of the lifespan (Guiney & Machado, 2012; Jurado & Rosselli, 2007). It has been argued that older adults achieve greater cognitive benefits from engaging in PA than younger adults, particularly for EF (Hayes, Forman, & Verfaellie, 2016; Kirton & Dotson, 2016; Stern et al., 2019). However, it is not clear whether there is an age at which engaging in greater amounts of PA becomes substantially more beneficial. In fact, the recently released 2018 Physical Activity Guidelines for Americans could not conclude whether long-term PA is beneficial to cognitive functioning in young and middle-aged adults due to insufficient evidence (PAGAC, 2018), leaving a critical gap in our understanding. Since cognitive functioning earlier in life is a key predictor of function later in life (Dekhtyar et al., 2015; Plassman et al., 1995) and health factors likely have age-dependent effects on cognitive functioning (Kirton & Dotson, 2016), testing the relationship between PA engagement and EF during midlife could inform cognitive aging trajectories.

1.2.2 Physiological Mechanisms of Physical Activity

PA influences cognitive functioning and brain health through multiple cellular, molecular, and systems-level mechanisms (Cotman, Berchtold, & Christie, 2007; Ratey & Loehr, 2011; Wang & Holsinger, 2018). Engaging in PA increases central growth factor expression to modulate synaptic plasticity and increase neurogenesis and angiogenesis (Cotman & Berchtold, 2002). Cells in the endothelium (the membrane lining the blood vessels and heart) release brain derived neurotrophic factor (BDNF), a growth factor that stimulates neurogenesis, or the development of new neurons (Schmidt, Endres, Dimeo, & Jungehulsing, 2013). Increasing BDNF expression facilitates dendritic branching and synaptic plasticity, which facilitate long-term potentiation

(LTP) critical for learning (Ma, 2008) and make it a target for understanding how PA can induce changes in the brain (Cotman et al., 2007; Dishman et al., 2006; Ratey & Loehr, 2011). One key brain region where BDNF is expressed is in the hippocampus, and greater expression induces increased hippocampal volume, LTP, and subsequent improvements in performance on memory tasks (Wang & Holsinger, 2018). Increased serum levels of BDNF are also associated with enhanced EF task performance (Leckie et al., 2014) and enhanced BDNF gene expression is associated with slower overall cognitive decline (Buchman et al., 2016), suggesting that this neurotrophic factor has widespread effects on the brain and related cognition.

Increased angiogenesis, or the development of new blood vessels, is also associated with PA and leads to better cerebrovascular perfusion (Schmidt et al., 2013). During exercise, blood flow through carotid and vertebral arteries and total cerebral blood volume change as a function of physical exertion (Sato, Ogoh, Hirasawa, Oue, & Sadamoto, 2011; Timinkul et al., 2008). Greater blood flow in the brain provides more nutrients, glucose, and oxygen, all of which are needed for energy consumption (Licht & Keshet, 2015). Without sufficient cerebral blood flow, the brain is more susceptible to dysfunction; with more blood flowing to the brain, there are more resources available for cognitive functioning. Better cerebrovascular perfusion further reduces the risk of future cerebrovascular disease (Tarumi & Zhang, 2018), which is characterized by executive dysfunction, and limits the potential burden of cognitive impairment later in life.

Despite an understanding that PA promotes brain health through multiple pathways, there is limited research on the features, or parameters, of PA that may be most effective for inducing these physiological changes. Specifically, PA parameters can reference the total volume of activity, the intensity of activity, or the pattern in which activity is accumulated throughout the day. It is possible, and likely, that multiple parameters work in concert to improve cognitive

functioning. However, no studies have examined a range of objectively monitored PA parameters within a single PA index or compared these parameters to each other, opting rather to utilize one parameter (e.g., total minutes of activity) or categorical (e.g., yes or no) PA participation to determine associations (or lack thereof) with cognitive function. One aim of the current project was to evaluate the relative contributions of various PA parameters in any association with EF to better determine amounts and types needed to optimize its effects.

1.3 Parameters of Physical Activity

Multiple parameters of PA can be measured with monitoring devices or through self-report, though it is difficult to quantify PA precisely (Lamonte & Ainsworth, 2001). Current research has focused almost exclusively on frequency, intensity, time, and type of activity using the F.I.T.T. Principle (ACSM, 2017), partly because these are relatively straightforward to evaluate. The *frequency*, or how often an individual engages in an activity, is often quantified with regard to weekly or monthly activity – e.g., how many times someone plays a round of golf per month. The *intensity* quantifies the physical exertion during an activity. For example, sprinting is PA at a higher intensity than jogging – both of which are activities at higher intensities than walking. The *time* associated with an activity can be measured as total volume or duration of PA engagement. The total volume of activity is the sum of all PA in a given time period and it is typically recorded in minutes per week or per day. The duration of activity is also often quantified in minutes and describes the length of time during which an individual has engaged in PA. The *type*, or modality, describes the specific form of activity, such as cycling, playing tennis, or resistance training. Frequency and time of activity can be measured for any movement, based on a specific type of

movement, or based on specific intensities (e.g., how often an individual participates in light or vigorous PA).

One way to estimate the *intensity* of an activity is by measuring heart rate during activity relative to rest. Another way is through the metabolic equivalent of the task (MET), or the energy expended during that activity. One MET is the rate of energy an individual expends while seated at rest. Higher METs are proportionate to expending as much additional energy given the specific activity. METs are calculated based on an individual's demographics and body composition. PA can be categorized based on METs, and these categorizations can be determined by age (see Table 1 for details; (ACSM, 2017). For instance, taking a brisk walk may achieve a MET level that is categorized as moderate intensity activity, while sprinting in a race may achieve vigorous intensity. Spending one minute engaging in vigorous PA is approximately equivalent to spending two minutes engaging in moderate PA, despite a non-linear increase in METs (Powell, Paluch, & Blair, 2011). Current research is limited in understanding how different PA intensities vary in their physiological outcomes.

Table 1 Estimating Physical Activity Intensity Level Thresholds

All thresholds are reported in METs. Adapted from *ACSM's Guidelines for Exercise Testing and Prescription* (p. 165) by American College of Sports Medicine, 2017, Philadelphia, PA: Wolters Kluwer. METs = metabolic equivalents (1.0 METs = exertion at rest).

	Absolute Threshold	**Age-Specific Thresholds**		
Intensity Category		**Young (20-39 years)**	**Middle Age (40-64 years)**	**Older (≥ 65 years)**
Sedentary/Very Light	< 2.0	< 2.4	< 2.0	< 1.6
Light	2.0 - < 3.0	2.5 - < 4.8	2.0 - < 4.0	1.6 - < 3.2
Moderate	3.0 - < 6.0	4.8 - < 7.2	4.0 - < 6.0	3.2 - < 4.8
Vigorous +	6.0 +	7.2 +	6.0 +	4.8 +

METs can be converted into energy expenditure in kilocalories, which quantifies the energy cost of an activity. Active energy expenditure (AEE) quantifies the energy cost of any activity above resting levels. AEE is also dependent on demographics and body composition, in addition to the environment (Ainsworth et al., 2000). For instance, an individual jogging at higher altitude will have higher AEE than the same individual jogging at sea level. As another example, a person who weighs 200 pounds and a person who weighs 100 pounds can both exercise at a MET level of 4.0, but the person who weighs 200 pounds will have greater AEE because they burn more total calories. Thus, both METs and AEE vary by activity and by person.

Moderate-to-vigorous PA (MVPA) has been considered the most important category of PA due to its ability to induce the physiological changes described above. While research is expanding to examine the effects of light PA on health and cognitive functioning, much of the evidence focuses exclusively on MVPA. Prior recommendations for PA have included specifications about accumulating minutes of MVPA in bouts of at least 10 minutes (Haskell et al., 2007). Newer

guidelines suggest that, as long as individuals are accumulating at least 150 minutes per week of MVPA, bout duration is unlikely to influence the benefits to health outcomes, such as lower incidence of cardiometabolic disorders (PAGAC, 2018). As it is unlikely that an individual would only begin to reap the benefits of PA after attaining a certain threshold (Blair, Kohl, Gordon, & Paffenbarger, 1992; Powell et al., 2011), these newer recommendations allow the general public to consider all durations of activity as advantageous as long as they total the recommended 150 minutes per week. Despite a general understanding that engaging in PA is beneficial to reduce all-cause mortality (Arem et al., 2015; Warburton et al., 2006), cardiometabolic disorders (Daskalopoulou et al., 2017; Sattelmair et al., 2011), and incidence of dementia (Xu et al., 2017), the relationships between cognitive functioning and distinct PA parameters are not clear. As such, an integral goal of the current study was to understand the influence of individual parameters of PA on EF.

1.3.1 Intensity

Few studies have focused on the associations between PA intensity and cognitive outcomes. Research examining health outcomes, such as cardiometabolic conditions, may provide some insight regarding differential effects of PA intensities. Most research focuses on MVPA, as this is the intensity threshold most frequently associated with intentional exercise. Relatively little work has examined the effects of light PA on EF, although it is the intensity of PA accumulated in the greatest volume throughout the day (Berkemeyer et al., 2016). Across healthy and patient populations, greater engagement in light PA is associated with better health outcomes. For example, in breast cancer survivors, greater accumulation of light PA minutes was associated with lower body mass index (BMI), waist circumference, and C-reactive protein (CRP) independently

from MVPA minutes or sedentary time (Lynch et al., 2011). In healthy participants, similar patterns are observed: greater engagement in light intensity PA measured by accelerometry was associated with lower BMI, waist circumference, circulating CRP, insulin resistance, and diastolic blood pressure (BP) (Loprinzi, Fitzgerald, Woekel, & Cardinal, 2013; Loprinzi, Lee, & Cardinal, 2015; Riou et al., 2014). Further, engaging in less light PA was associated with a 1.18 times greater rate of having a comorbid chronic disease (Loprinzi et al., 2015). Although research on light PA is in its infancy, considerable evidence suggests that accumulating time in lower-intensity activities is still beneficial to cardiometabolic health.

In younger samples, it is not clear whether PA intensity has a dose-response effect on various health outcomes. A recent study using device-monitored (i.e., accelerometry) PA assessments on 29,734 children indicated that participants who accumulated higher volumes of activity had reduced cardiometabolic risk scores, regardless of activity intensity (Tarp et al., 2018). Superficially, these findings suggest that the overall volume of activity achieved is more important for health than the intensity of those activities because engaging in more overall activity was associated with better cardiometabolic outcomes. However, additional evaluation within this sample showed that only more time spent in higher-intensity PA was associated with lower cardiometabolic risk scores after controlling for total PA volume, suggesting that there is something unique about higher-intensity exercise that exerts greater benefits for cardiometabolic health (Tarp et al., 2018). In contrast, an earlier study of 52 adolescents (mean age of 14.5 years old) showed that more time spent in MVPA as compared with vigorous PA alone was associated with lower systolic BP (Radtke, Kriemler, Eser, Saner, & Wilhelm, 2013). Together, these mixed results suggest that we do not yet understand how intensity of PA influences various health outcomes or whether any associations are contingent upon some factor, such as age.

High intensity interval training (HIIT) has been implicated in improvements in several outcomes to a greater degree than continuous, moderate-intensity PA. In general, high intensity, intermittent PA has beneficial effects on endothelial function and reduces BP, low-density lipoprotein levels, and circulating pro-inflammatory cytokines (Cooper, Dring, & Nevill, 2016; Gibala, Little, Macdonald, & Hawley, 2012; Metcalfe, Babraj, Fawkner, & Vollaard, 2012). A recent meta-analysis examined the effects of HIIT interventions on cardiometabolic risk in children and adolescents and revealed that high intensity PA groups had a significant reduction in systolic BP and increase in CRF when compared with other forms of exercise (Garcia-Hermoso et al., 2016). However, there were no effects of PA on other metrics of body composition, lipoprotein levels, or insulin resistance. In 44 normotensive women between 20-30 years old, only aerobic HIIT was effective at reducing resting BP and plasma markers of vascular functioning (i.e., endothelin-1, nitric oxide availability) when compared with continuous, moderate intensity exercise after a four-month intervention (Ciolac et al., 2010). Even in the context of acute exercise, just one 20-minute bout of HIIT reduced ambulatory BP for 24 hours following exercise engagement (Sosner et al., 2016). Together, these studies suggest that higher intensity PA is effective at improving cardiometabolic health outcomes. In contrast, there is also evidence suggesting that continuous, moderate activity is better for health than intermittent, vigorous exercise. For example, one moderate intensity, continuous PA intervention reduced BP in midlife adults (average age of 42 years old) when compared with a HIIT intervention (Shepherd et al., 2015). A meta-analysis of 10 intervention studies at least four weeks in duration in midlife and older adults revealed that HIIT increased CRF but was not as effective as moderate, continuous exercise at reducing BP (Liou, Ho, Fildes, & Ooi, 2016). The mixed evidence regarding the

intensity of PA best suited to improve health outcomes highlights the limited understanding of how PA can invoke long-term health benefits.

In contrast to the studies described above, there is also evidence suggesting that there are limited additional benefits of PA above a moderate intensity threshold. Multiple studies demonstrated that increasing PA intensity above moderate levels had only a marginal influence on reducing BP, circulating levels of pro-inflammatory cytokines, and overall cardiovascular disease risk (Curtis et al., 2017; Humphreys, McLeod, & Ruseski, 2014; D. H. Lee et al., 2019). Across PA interventions, there are not consistent intensity-dependent influences on cardiometabolic markers. In 106 overweight children and adolescents (average age of 15 years old), six months of either moderate or vigorous intensity aerobic exercise reduced markers of Type 2 Diabetes Mellitus without significant differences between groups (Hay et al., 2016). A previously discussed intervention with young adults showed differences in clinical BP as a function of exercise intensity, but no differences in ambulatory BP. That is, there were no differences in multiple measurements of BP throughout the day, but there were group differences in the sole laboratory BP measurement (Ciolac et al., 2010). The lack of group differences in these interventions suggests that adding any PA is better than remaining sedentary but that the intensity of the activity may not strongly influence cardiometabolic health. Additional evidence indicates that greater engagement in both light PA and MVPA in midlife and older adults can reduce cardiometabolic risk factors and diseases, such as waist circumference, resting BP, BMI, and the presence and severity of the Metabolic Syndrome (Ekblom et al., 2015; LaMonte et al., 2017; Ramos et al., 2017). Recent physical activity guidelines describe that the cardiometabolic health benefits from continuous, moderate-intensity activity are comparable to the benefits incurred from HIIT (PAGAC, 2018).

Thus, while intensity may be an important, modifiable PA parameter to maintain or improve health, any potentially distinct effects of PA intensities on health are not yet fully understood.

Only recently has this research on PA intensity expanded to the realm of brain health and cognitive functioning. Of the studies that exist, evidence is mixed. In a non-controlled intervention with 110 older adults, the 75 individuals participating in up to two years of light PA calisthenics showed preserved bilateral PFC volume and improved attentional task performance when compared with the non-exercise group (Tamura et al., 2015). Notably, these effects were no longer significant at a six-month follow-up, indicating that light PA may only benefit brain health while individuals are habitually engaging in activity. Other studies have shown opposite effects, in that only PA engagement reaching at least moderate intensity was associated with better cognitive functioning. In 310 older adults ≥65 years old with MCI, device-monitored time spent engaging in moderate PA, but not light or total PA, was associated with greater hippocampal volume (Makizako et al., 2015). In this sample, greater hippocampal volume mediated the relationship between moderate PA and memory task performance and suggests that moderate intensity may uniquely contribute to conferring the benefits of PA. These results highlight the interconnected relationships between health behaviors, brain health, and cognitive functioning.

Interventions in healthy older adults have demonstrated that MVPA preserves or improves cognitive abilities, particularly in EF, memory, and overall cognitive functioning (Anderson-Hanley et al., 2018; Erickson et al., 2011; Jonasson et al., 2016; Leckie et al., 2014; Scherder et al., 2014). One meta-analysis of eight walking RCTs (ranging from four weeks to one year in duration) in sedentary older adults demonstrated that engagement in aerobic PA improved shifting and inhibitory control only in participants without baseline cognitive impairment (Scherder et al., 2014). Increasing aerobic activity after the onset of cognitive impairment did not improve EF,

which suggests that PA cannot reverse the burden of cognitive decline. However, it may also suggest that engaging in positive health behaviors (e.g., PA) earlier in life could delay or prevent a decline in cognitive abilities. A recent six-month intervention randomized 14 participants to aerobic cycling with either high or low additional cognitive load (i.e., playing a video game or viewing scenery) or cognitive training only, and tested multiple subdomains of EF (Anderson-Hanley et al., 2018). Following the intervention, all participants improved inhibitory control task performance, but not working memory or shifting. These findings indicate that aerobic PA training may improve specific cognitive processes, leading to the question of whether certain subdomains of EF are more sensitive to PA than others. However, the previously described studies did not examine whether improvements in cognitive functioning, and specifically EF, varied as a function of different PA intensities, leaving a gap in our understanding.

It is not clear whether greater exercise intensity is associated with benefits to cognition independently of other parameters of exercise. For instance, higher intensities of exercise might also be related to reduced frequency and/or shorter duration of activity. Individuals engaging in vigorous PA may engage in fewer exercise sessions during the week due to fatigue or muscle soreness. It is not clear whether less frequent bouts of vigorous PA are similarly related to EF as more frequent bouts of moderate PA. It is currently unknown whether the effects of exercise intensity on cognitive functioning can be distinguished from other parameters, including frequency or duration of activity. Understanding the associations between patterns of PA engagement and EF may help to further delineate how to use PA as a prescription to prevent cognitive decline.

1.3.2 Pattern of Activity

Beyond frequency, intensity, duration, and volume of activity, the pattern of PA accumulated throughout the day may influence its beneficial effects. Research on sedentary behavior suggests that more time spent inactive is associated with increased rates of cardiometabolic disorders and all-cause mortality (Ekelund et al., 2016; Loprinzi et al., 2015; Lynch et al., 2011) and greater risk of cognitive impairment and dementia (Falck et al., 2017). However, engaging in more PA may reduce these risks for reasons beyond increasing active time. For example, one group conducted several meta-analyses and demonstrated that greater PA volume and intensity can counteract even large amounts of sedentary time (Ekelund et al., 2018; Ekelund et al., 2016). Specifically, individuals engaging in the highest volume and highest intensity activities do not show an increased risk of cancer-related or cardiovascular disease-related mortality even with increasing sedentary time, likely due to the health benefits of engaging in regular PA. These findings suggest greater amounts of PA may offset the deleterious effects of sedentary behavior, particularly at higher levels of engagement than are currently recommended (i.e., 150 minutes of moderate activity per week). One remaining question is whether the risks associated with sedentary behaviors are mitigated by the way in which PA is accumulated throughout the day or solely the total volume of PA.

A ‘bout’ of PA is any consecutive amount of time engaging in activity (typically MVPA). Bouts are often defined as at least 10 minutes in length, although the minimal time for a bout in the literature ranges from two to 15 minutes. In the context of health outcomes, some studies suggest that only MVPA accumulated in bouts greater than 10 minutes improves cardiometabolic outcomes, such as incidence of obesity, hypertension, or insulin sensitivity, after controlling for total MVPA or non-bout MVPA minutes (Di Blasio et al., 2014; Strath, Holleman, Ronis, Swartz,

& Richardson, 2008; Yap, Balasekaran, & Burns, 2015). Others have found that MVPA accumulated in bouts shorter than 10 minutes are effective for reducing BP, insulin sensitivity, and incidence of Metabolic Syndrome after controlling for total MVPA (Ayabe et al., 2012; Ayabe et al., 2013; Gay, Buchner, & Schmidt, 2016; Glazer et al., 2013; White, Gabriel, Kim, Lewis, & Stemfeld, 2015; Wolff-Hughes, Fitzhugh, Bassett, & Churilla, 2015). In contrast, a meta-analysis on PA interventions in cancer survivors revealed that short bouts of vigorous PA (up to four minutes) were more effective than longer bouts of continuous, moderate PA for weight reduction and increased lean mass, CRF, and strength (Toohey, Pumpa, McKune, Cooke, & Semple, 2018). Whether the pattern of accumulated activity is related to cognitive functioning is especially important for individuals who may not be able to engage in longer PA bouts, such as older adults or those with physical limitations. With discrepancies in the current evidence, investigating whether there is a relationship between the pattern of PA and cognitive functioning is an important step in prescribing PA as prevention or treatment for cognitive decline.

Some research has also shown no differences in the effects of bout length (i.e., less or greater than 10 minutes) on various health-related outcomes. Multiple studies show that greater total accumulation of PA is associated with lower cardiovascular disease risk and mortality, regardless of bout length (Curtis et al., 2017; Loprinzi, 2015; Saint-Maurice, Troiano, Matthews, & Kraus, 2018). A recent systematic review summarized the 27 cross-sectional, longitudinal, and RCT studies on bouts and health outcomes and showed no differences in associations between bout length and BP, weight, incidence of obesity, low-density lipoprotein levels, fasting glucose, fasting insulin, CRP, or all-cause mortality (Jakicic et al., 2019). This review concluded that, although there are discrepancies across studies, engaging in *any* PA is associated with better health

outcomes and the pattern of PA accumulation is less important than the total volume of activity accumulated.

Most importantly for the current study, there is a lack of published evidence describing a relationship between the length of PA bouts and cognitive functioning. The question remains unanswered whether shorter bouts of activity throughout the day are differently beneficial to cognitive functioning when compared with only one daily longer bout of activity (i.e., an intentional exercise session). To date, three studies have examined this relationship and showed mixed results across populations. The earliest study aimed to understand the effects of acute bouts of moderate intensity PA on selective attention in children aged between 10-13 years. The authors randomly assigned 56 student participants to one of three conditions: 1) sitting all morning; 2) sitting for 90 minutes, engaging in one 20-minute bout of moderate PA, resuming sitting; 3) engaging in one 20-minute bout of moderate PA, sitting for 90-minutes, engaging in another bout of activity, resuming sitting. They found that the children who participated in two bouts of moderate intensity PA performed better on a test of selective attention compared to the children who remained seated all morning or those who only participated in one bout (Altenburg, Chinapaw, & Singh, 2016). These results suggest that more frequent PA engagement yields better selective attention performance but do not provide sufficient evidence regarding whether this is related to the timing of activity or simply the greater accumulation of active time and reduction in sedentary time.

The second study examined whether the accumulation of MVPA in greater or less than 10-minute bouts was differentially related to EF than total MVPA accumulation in adults between 55-86 years old. PA was measured with accelerometry over an average of 6.5 days and EF was quantified through two tests of inhibitory control. The authors showed that greater total MVPA

accumulation was related to better EF and that activity accumulated in bouts greater or less than 10-minutes in duration did not affect performance above and beyond total activity (Peven, Grove, Jakicic, Alessi, & Erickson, 2018). However, this study did not examine whether equivalent MVPA accumulation through one long bout (e.g., briskly walking for one hour) versus many shorter bouts (e.g., taking multiple brisk walks throughout the day) was differentially associated with EF.

The third study to examine bouts in the context of cognitive functioning included only 12 older adults in a randomized crossover trial that utilized three conditions: 1) prolonged sitting for eight hours; 2) sitting for one hour, walking at moderate intensity for 30 minutes, and then prolonged sitting for 6.5 hours; 3) sitting for one hour, walking at moderate intensity for 30 minutes, and then sitting for 6.5 hours with three-minute, light intensity walking breaks every 30 minutes. Only participating in the third condition (taking short breaks every 30 minutes) resulted in improved working memory task performance compared with the other two conditions (Wheeler et al., 2019). This suggests that breaking up periods of prolonged sitting with light intensity PA was beneficial to this EF subdomain, although it is not clear whether this was due to a reduction in sedentary time (i.e., higher volume of total PA) or if a short bout of light PA had other physiological benefits to brain health. Together, the ways in which different patterns of PA are related to cognitive functioning remain unclear, leaving a gap in the literature that the current study sought to fill.

1.4 Demographic Moderators of Physical Activity and Executive Functioning

1.4.1 Age

PA decreases with age (Carlson, Densmore, Fulton, Yore, & Kohl, 2009; Pollard & Wagnild, 2017; Troiano et al., 2008), making it an important factor in PA research. It is possible that this reduction in activity is related to functional impairments, such as reduced mobility or risk of falling. It is also likely that reduced PA and age-related cognitive decline are related, as dementia patients engage in less activity than healthy controls, possibly due to reduced cognitive capacity to be motivated to engage in or follow through with PA (Hartman, Karssemeijer, van Diepen, Olde Rikkert, & Thijssen, 2018; Lu, Harris, Shiroma, Leung, & Kwok, 2018). The relationship between advanced age and reduced PA engagement is therefore a notable factor to consider when evaluating cognitive functioning.

Overall cognitive abilities begin to decline as early as the third decade of life, with initial decrements in reasoning, memory, and visuospatial abilities (Salthouse, 2010). Advanced age is associated with lower baseline performance across most cognitive domains when compared with younger adults (Goh, An, & Resnick, 2012; McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016), indicating that overall abilities decline through the aging process. This is consistent with longitudinal work that suggests steeper declines over time in EF, processing speed, and memory – cognitive domains that are highly sensitive to the effects of aging (McCarrey et al., 2016; Verhaeghen & Salthouse, 1997). For instance, one study of 148 adults aged between 56-86 years old at baseline followed participants over a maximum period of 14 years. The authors showed longitudinal declines in switching, inhibition, manipulation, memory, semantic retrieval, and visual processing despite all participants being cognitively normal at baseline (Goh et al., 2012).

These may be the cognitive processes that are particularly susceptible to aging, although there was considerable variability in the rate of cognitive decline within participants. Given that all participants, regardless of baseline age, showed decline in their cognitive abilities, age is an important potential moderator of the relationship between PA and cognitive functioning. Further, with worsening health later in life (Arbeev et al., 2011; Kulminski et al., 2007; Mitnitski, Song, & Rockwood, 2013), age may confound the relationships between cognitive functioning and health-related behaviors, such as PA.

It is possible that the influence of PA on cognitive functioning may vary by age, but little work has explored these relationships throughout the lifespan. Instead, most work has been conducted in either children or older adults. In children, meta-analyses suggest that participating in aerobic PA interventions improve EF including inhibitory control, working memory, planning, and cognitive flexibility (de Greeff et al., 2018). A meta-analysis of RCTs that enrolled adults indicated that engaging in aerobic PA improves EF (Smith et al., 2010); however, most of the studies included in this meta-analysis used samples of older adults. In fact, only seven of the 29 included studies enrolled any participants under the age of 50 and five of these seven studies were conducted in patient populations (e.g., fibromyalgia, multiple sclerosis). With only two RCTs of healthy adults that included participants younger than 50 years old, our understanding of how PA is related to cognitive functioning in midlife is limited. Further, studies of older adults suggest that engaging in PA may only improve specific executive processes, such as inhibitory control or switching, only prior to the onset of cognitive impairment (Scherder et al., 2014). Thus, while it appears that PA benefits EF in children and late adulthood, it is not clear whether such a relationship exists during midlife.

1.4.2 Sex

Sex differences in the association between PA and cognitive functioning have been well-studied over the past several decades. Across the lifespan, men are more active and more likely to meet the recommended PA guidelines than women (Belcher et al., 2010; Carlson et al., 2009; Troiano et al., 2008). These differences may be due to men engaging in more leisure-time sports or occupational PA, while women tend to participate in more sedentary or light intensity activities, such as household chores (Jones et al., 1998; Y. S. Lee, 2005). It is possible that women achieve greater levels of light PA when compared with men, and this would result in fewer women achieving the amount of MVPA recommended for health benefits (Piercy et al., 2018). Whether there are sex differences in PA intensity or pattern of accumulation that further relate to cognitive outcomes has yet to be determined.

Sex differences in cognitive functioning generally reflect an advantage for women on verbal tasks and an advantage for men on nonverbal tasks: Women outperform men on tests of learning, memory, and EF , while men perform better on tests of processing speed and visuospatial processing (Gur & Gur, 2017; McCarrey et al., 2016; Sundermann et al., 2016). These differences may confound the effects of PA on cognitive functioning and prior work suggests that women experience greater cognitive benefits from PA than men, particularly in EF and memory (Barha, Hsiung, et al., 2017; Colcombe & Kramer, 2003; Liu-Ambrose, Barha, & Best, 2018). Given that PA is known to benefit EF and memory task performance disproportionately relative to other cognitive domains, it may not be surprising that women show greater improvements in these cognitive processes. Meta-analytic findings indicate that women's EF abilities improve more from PA interventions, as shown by larger effect sizes in interventions with greater proportions of female participants (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017). These findings may

be due to physiological differences between males and females, such as differences in CRF or vascular functioning (Barnes & Fu, 2018; Morita & Okita, 2013). As women generally have lower CRF than men, it is possible that greater increases in CRF through PA interventions for women have substantially greater benefits to their cognitive performance (Liu-Ambrose et al., 2018). With well-documented sex differences in both cognitive task performance and PA engagement, it is important to consider sex as one potential moderator of any relationship between PA and cognitive functioning.

1.5 Gaps in the Existing Literature

In sum, there are several gaps in the current literature on the relationship between PA and EF. First, while some work has explored individual parameters of PA (e.g., frequency, intensity, duration) in the context cognitive functioning, few studies have examined multiple parameters within the same sample by creating a latent factor of PA to evaluate how overall PA engagement is related to cognitive functioning. Second, there is a limited understanding of the distinct PA parameters (e.g., volume, intensity, pattern of activity) that are related to overall EF and specific executive processes. Third, the moderating influences of sex and age on these relationships are currently unknown. To address these gaps, the current study had the following aims:

1. Determine whether PA is associated with EF in a well-characterized midlife sample.
   Hypothesis 1a: Greater overall PA engagement (i.e., latent scores of PA) will be associated with better EF (also derived from latent scores).
   Hypothesis 1b: The shared variance captured by a PA factor will better account for the differences in EF abilities relative to any individual parameter. In other words, individual

PA parameters will not capture as much of the variance in midlife EF as a latent factor of PA.

Hypothesis 1c: Individual parameters of PA will have different, but related, associations with EF. Specifically, the associations between EF and intensity, active energy expenditure, and volume of MVPA will be stronger than the associations between EF and pattern of activity and total PA.

2. Examine the possible moderating effects of sex and age on the relationships between PA engagement and EF.

Hypothesis 2a: Age will moderate the relationship between PA and EF, such that greater PA engagement will be associated with better EF only for the oldest participants. Older participants will engage in less PA and have lower EF scores relative to younger participants, indicating a main effect of age.

Hypothesis 2b: Sex will moderate the relationship between PA and EF, such that males engaging in the least PA will have lower EF scores than females and females engaging in the most PA will have the highest EF scores.

The current research examined the relationships between PA parameters and EF as both unitary and diverse concepts. There is minimal understanding of which parameters of PA are related to cognitive functioning beyond the volume of accumulated activity. By teasing apart additional components of PA (intensity, energy expenditure during exercise, and pattern of activity), it may be possible to identify specific recommendations for PA to maximize cognitive functioning. The current research sought to characterize the relationships between PA (and its distinct parameters) and EF (and its subdomains) in healthy midlife adults.

2.0 Methods

2.1 Participants

Participants were drawn from the Adult Health and Behavior Project – Phase II (AHAB-II). Participants were recruited between 2008-2011 through mass-mailing advertisements in Western Pennsylvania to participate in an epidemiological registry of the biobehavioral correlates of cardiovascular disease risk in midlife adults. Inclusion criteria included being between 30-54 years of age, being in good health, and working at least 25 hours per week outside the home. Exclusion criteria could be grouped into several categories and included: general and mental health (i.e., history or presence of cardiovascular disease, schizophrenia, bipolar disorder, chronic hepatitis, renal failure, major neurological disorder, chronic lung disease, Stage 2 hypertension (BP $\geq$160/100 mmHg)), alcohol intake (i.e., report of consuming $\geq$35 drinks per week), specific prescribed medication use (i.e., antihypertensive, anti-arrhythmic, lipid-lowering, insulin, glucocorticoid, psychotropic, weight loss), taking fish oil supplements, lower than 8th grade reading ability, being a shift worker, being pregnant or lactating, or preclusion to magnetic resonance imaging (MRI) (i.e., claustrophobia, presence of permanent metal in the body (devices, implants), tattooed makeup, body status prohibitive of MR scanning).

2.2 Procedures

Prior to participating in any study procedures, participants provided informed consent in accordance with the Institutional Review Board at the University of Pittsburgh and with the Declaration of Helsinki. Participants came to a laboratory facility at the University of Pittsburgh over eight visits for assessment of demographic information, health information, neuropsychological testing, and to obtain and return the PA monitoring device. Demographic and health information were obtained during Visit 1. The devices to monitor PA were distributed at Visit 2 and collected at Visit 3 one week later. Participants were also given ambulatory BP monitors at Visit 2, which were worn during at least four of the seven days between Visits 2 and 3. Participants were instructed to wear the devices on at least two workdays and at least one non-workday. If participants did not achieve sufficient wear-time of the ambulatory BP monitors, they were asked to continue wearing all devices, including the SenseWear armbands, for additional days. All available SenseWear data were utilized for each participant included in the current study.

Participants also completed a comprehensive neuropsychological test battery to assess EF, attention, learning and memory, visuospatial functioning, and language. The assessments used for the current study are described below. Neuropsychological testing was completed during Visits 4 and 6 so as to avoid fatigue that may have influenced cognitive testing results.

2.2.1 Assessments

2.2.1.1 Demographic and Health Information

Participants provided self-reported demographic information that included age, sex, race, and level of formal education. They were also asked to report their smoking status (i.e., never smoker, history of smoking, current smoker, other tobacco user).

Participants' height and weight were measured during the first baseline assessment visit to calculate BMI. They underwent measurements of waist-to-hip ratio, BP, cholesterol levels, triglyceride levels, and fasting blood glucose to quantify criteria for Metabolic Syndrome using the National Cholesterol Education Program (NCEP)'s guidelines from the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2002). Meeting criteria for Metabolic Syndrome, while not comprehensive, is one way to integrate the related detriments of poor health (Huang, 2009). Self-reported information about age and smoking status were combined with measured total cholesterol, high-density lipoprotein level, and systolic BP were used to calculate participants' 10-year risk of a coronary heart disease (CHD) event (ATP-III, 2001).

2.2.1.2 Cognitive Functioning

Participants underwent a comprehensive neuropsychological evaluation to assess multiple domains of cognitive functioning. Neuropsychological tests designed to measure different components of EF and attention were used for the current study. These included working memory (i.e., Digit Span Backward, Spatial Span Backward), switching (i.e., Trail Making Test (TMT) Part B – Part A), inhibitory control (i.e., Stroop Color-Word condition), abstract reasoning (i.e.,

Matrix Reasoning, Similarities), and processing speed (i.e., Stroop Color and Word conditions, TMT Part A). The details of these tests are described below.

All neuropsychological test scores were converted to z-scores and inverted, where appropriate, such that higher scores reflected better performance (i.e., TMT time to completion where longer time would indicate poorer performance). Z-scores were selected to mitigate any differences in scoring across measures (i.e., total correct versus time to completion). For any neuropsychological tests that showed significant skew after standardization, z-scores were log-transformed (base 10) prior to inclusion in analyses. The z-scores were then used in subsequent factor analyses.

2.2.1.2.1 Digit Span Subtest

The Digit Span subtest of the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) consists of two conditions during which participants are asked to repeat strings of digits either forward or backward (Wechsler, 1997a). During each of the conditions, participants are asked to repeat progressively longer strings of digits. The forward condition measures simple and sustained verbal attention, in addition to short-term memory; the backward condition measures working memory. The z-scores of the total number of digit spans completed correctly (either forward or backward) were used in all analyses.

2.2.1.2.2 Spatial Span Subtest

The Spatial Span subtest of the Wechsler Memory Scale – 3rd Edition (WMS-III) is a visuospatial analog of the Digit Span subtest. It consists of two conditions where participants are asked to tap blocks arranged in an unstructured array either in forward or backward order (Wechsler, 1997b). During each of the conditions, the strings of block patterns become progressively longer. The task measures simple and sustained visuospatial attention, in addition to short-term memory, in the forward condition and working memory in the backward condition. The z-scores of the total number of spatial spans completed correctly (either forward or backward) were used in all analyses.

2.2.1.2.3 Trail Making Test

The Trail Making Test (TMT) consists of two parts that require participants to connect circles with either numbers or letters inside (Reitan & Wolfson, 1985). Part A contains only numbers and measures simple attention, processing speed, and psychomotor speed. Part B consists of numbers and letters, and participants are required to alternate sequencing between them (e.g., 1-A-2-B-3, etc.). Part B measures switching and, to a lesser extent, inhibitory control. The difference between TMT Part A and B (i.e., TMT Part B – TMT Part A; TMT B-A) quantifies the time required for switching and inhibiting above and beyond psychomotor speed. The inverted z-scores of total time to completion (Part A) and difference between times to completion (TMT B-A) were used in all analyses to reflect better performance.

2.2.1.2.4 Stroop Task

The Stroop task contains three conditions (i.e., Color (C), Word (W), Color-Word (CW)) that require participants to complete distinct tasks. In the Color condition, participants are shown rows of color blocks (i.e., red, green, blue) and asked to name the colors as quickly as possible. In the Word condition, participants are shown rows of color words (i.e., "red", "green", "blue") printed in black ink and asked to read the words as quickly as possible. Each of these conditions measures simple attention and processing speed. In the CW condition, participants are shown rows of color words printed in a different colored ink (i.e., "red" printed in green ink). In this condition, they are instructed to name the color of the ink, not read the word. Here, participants are instructed to inhibit an automatic response (i.e., reading) in favor of engaging in an effortful response (i.e., naming colors). The CW condition measures inhibitory control and selective attention. For each condition, the number of items correctly named or read in 45 seconds was the total score.

An interference score was calculated by subtracting a predicted CW score from the obtained CW score. To calculate the predicted CW score, the following equation was used: (((216 – W) x C) / ((216 – W) + C)). This calculation of the predicted CW score was selected because it accounts for the time required to *suppress* word reading during the CW condition, rather than assuming that the time required to complete the CW task is simply the sum of the time it takes to read a word and name a color. Therefore, this calculation is the sum of the time it takes to suppress word reading plus the time it takes to name a color (Chafetz & Matthews, 2004). With this interference score, positive scores indicate better-than-predicted performance and negative scores indicate poorer-than-predicted performance. Z-scores of the total number of items correctly identified or the interference score were used in all analyses.

2.2.1.2.5 Matrix Reasoning Subtest

The Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) consists of arrays of figures with one component missing (Corporation, 1999). Participants are instructed to choose one of five figures presented at the bottom of the stimulus page that would complete the image. The items become progressively more difficult and require nonverbal abstract reasoning to complete correctly. The z-score of the total number of correct items was used in all analyses.

2.2.1.2.6 Similarities Subtest

The Similarities subtest of the WASI requires that participants verbally explain the conceptual similarities between two presented words (Corporation, 1999). Responses are scored as incorrect (zero points), correct in a concrete understanding (one point), or correct in an abstract understanding (two points). The items become progressively more difficult throughout the subtest. The z-score of the total points earned was used in all analyses.

2.2.1.3 Physical Activity

PA was measured with SenseWear armband monitoring devices (Body Media, Pittsburgh, PA; SenseWear Pro3) worn during awake time over a seven-day period. SenseWear devices were distributed at Visit 2 and participants were instructed to return them one week later at Visit 3. The devices were worn around the bicep of the non-dominant arm during all awake time. Participants were instructed only to remove the devices if they were participating in an activity that could

damage the device (e.g., showering) or during sleep. Only participants with at least three days of SenseWear data were included in the current study. Although longer wear-time of monitoring devices likely leads to more reliable estimates of habitual activity, increasing the inclusion requirements for wear-time decreases a study's sample size and power (Migueles et al., 2017). Thus, participants were included in the current study if they had armband data for at least 60% of the time they wore the device. Due to the study protocol requiring participants to wear the armband only while awake, the 60% wear-time threshold was applied to 16 hours of awake time, presuming that participants were asleep or in bed for eight hours each night. With this threshold, participants were included only if they had an average of at least 576 minutes of armband data for each day they wore the SenseWear device.

SenseWear armband monitors calculate PA parameters using proprietary algorithms (SenseWear Body Media, Pittsburgh, PA) in one-minute epochs using data from a biaxial accelerometer, heat flux sensor, galvanic skin response, skin temperature sensor, and a near-body temperature sensor that are all contained within the device (Mackey et al., 2011). SenseWear devices have been validated in several samples (Calabro, Stewart, & Welk, 2013; Casiraghi et al., 2013) to show their sensitivity to activity type and intensity. All PA metrics calculated from SenseWear devices account for age, sex, height, and weight. Operationalization of PA parameters are described below.

For all PA metrics, raw values were divided by the total number of minutes each participant wore the SenseWear armband device. Since participants wore the armbands for different amounts of time (i.e., different number of days and number of minutes per day), dividing by the total number of armband minutes allowed for between-subject comparisons. For any PA metrics that showed significant skew, raw values were log-transformed (base 10) prior to inclusion in any analyses.

2.2.1.3.1 Intensity

PA intensity was operationalized in two ways: 1) average daily intensity in METs and 2) average measured active energy expenditure (AEE) in kilocalories. The metabolic equivalents (METs) of each one-minute epoch during the monitoring period were recorded by the SenseWear armband device. The American College of Sports Medicine (ACSM) guidelines for exercise testing describe two thresholds for METs that define activity categories: absolute and age-specific (ACSM, 2017). *Absolute* thresholds utilize a moderate-intensity threshold of 3.0 METs and do not consider age, CRF level, or any other potential influences (Piercy et al., 2018). *Age-specific* thresholds attempt not to over- or under-capture PA engagement by considering the relative capacity of each age group. For example, a midlife adult (i.e., aged 40-64 years) taking a brisk walk might achieve a MET level of 3.5, which would be considered moderate intensity using absolute thresholds but only light activity using age-specific thresholds. However, despite an understanding that absolute thresholds over-capture PA engagement for individuals who are younger or more fit and may under-capture PA for individuals who are older or less fit, there is debate in the field regarding the cut-points for any relative thresholds (Barnett, van den Hoek, Barnett, & Cerin, 2016; Gil-Rey, Maldonado-Martín, & Gorostiaga, 2019; Mendes et al., 2018). For reasons described below, absolute thresholds were primarily utilized in the current study. The ACSM categorizations of PA intensity for both absolute and age-specific thresholds can be found in Table 1.

AEE during MVPA is the kilocalorie (kcal) conversion of METs that considers age, sex, and body size (i.e., height, weight). Using AEE provided a marker of PA engagement independent from sedentary time. In summary:

1. *Daily intensity* was operationalized as the average daily METs, which is calculated by the SenseWear device.
2. *Measured AEE* was calculated as the average energy expenditure during all one-minute epochs when MET levels were at least 3.0, indicating engagement in MVPA.

2.2.1.3.2 Volume

The volumes of MVPA and light PA were calculated as the number of minutes a participant spent engaging in at least moderate-intensity activity or in light-intensity activity. MET thresholds for activity intensities were set either at an absolute threshold ($\geq$3.0 for MVPA, 1.5-2.9 for light PA) or at age-specific thresholds (see Table 1). The presented results primarily rely on the absolute thresholds, which is consistent with most published work in this field. The total volume of activity was calculated as the sum of MVPA and light PA (Bassett, Troiano, McClain, & Wolff, 2015). Given that all raw PA metrics were divided by the number of minutes each participant wore the SenseWear armband device, the volumes of MVPA and total PA could be compared between participants. In summary:

1. *MVPA minutes* were operationalized as the number of minutes spent engaging in MVPA.
2. *Total PA minutes* were operationalized as the number of minutes spent engaging in any activity (i.e., not sedentary time).

2.2.1.3.3 Pattern of Activity

The pattern of activity throughout the day was operationalized as a ratio of the minutes spent engaging in MVPA to the number of MVPA bouts. A bout was defined as at least one-minute engaging in MVPA. If an individual only engaged in one-minute bouts of MVPA, their Bouts Ratio would be 1.0 because the number of minutes spent engaging in MVPA would be equal to the number of MVPA bouts accumulated. Individuals engaging in shorter bouts of activity would have a Bouts Ratio closer to 1, while those engaging in longer bouts of activity would have Bouts Ratios that were increasingly larger. In other words, the Bouts Ratio was the average number of minutes spent in a bout of MVPA. Higher Bouts Ratios may indicate that an individual spent more time engaging in planned exercise, as opposed to shorter, intermittent activity throughout the day.

2.3 Statistical Analyses

Statistical analyses were run in SPSS 26.0 (IBM Corporation) and RStudio version 1.2.5033 (Team, 2019). Bivariate Pearson product-moment correlations examined the associations between demographic features (i.e., age, sex, race, education), health features (i.e., BMI, smoking status), disease outcomes (i.e., Metabolic Syndrome criteria, 10-year risk of a CHD event), PA, and EF. Statistically significant associations with PA and/or EF resulted in the potential inclusion of that demographic or health variable as a covariate in subsequent analyses. One-way analysis of variance (ANOVA) and Chi-squared tests examined any differences between participants with complete cognitive functioning data and those with missing data on demographic, health, disease, and PA characteristics.

2.3.1 Factor Analyses

2.3.1.1 Physical Activity

Exploratory factor analyses were used to determine latent factors of PA from the individual parameters described above. Two separate factor analyses were conducted that included: 1) METs, measured AEE, Bouts Ratio, MVPA minutes, and 2) METs, measured AEE, Bouts Ratio, total PA minutes. The distinction in these analyses was intended to allow for comparison between all PA engagement versus only MVPA engagement. Variables were entered into the exploratory factor analyses using pairwise deletion and only factors with an Eigenvalue of at least 1.0 were extracted. A latent factor was considered to be derived from any PA parameters with factor loadings of at least 0.4. The Scree plot was examined to identify the inflection point for relevant latent factors. If appropriate, an Oblimin rotation was used, given that all of the PA metrics included in this study were inherently dependent upon one another. The emergent latent factor was then used as a PA index in subsequent analyses as a primary variable of interest.

Secondary analyses investigated the relationships between distinct PA parameters (i.e., volume of activity, average intensity, measured AEE, pattern of activity) and EF for all parameters that met significance within the exploratory factor analyses. These secondary analyses examined whether any individual PA parameters could be sufficient to predict cognitive functioning, relative to the creation of a PA index.

2.3.1.2 Executive Functioning

An exploratory factor analysis was used to determine the latent factor(s) of EF using all six neuropsychological tests and subtests described above. Z-scores, inverted where appropriate, were entered into the exploratory factor analysis using pairwise deletion and reliance on an eigenvalue

of at least 1.0. A factor was considered to be derived from any test scores with factor loadings of at least 0.4. The Scree plot was examined to identify the inflection point for relevant factors. If appropriate, an Oblimin rotation was utilized, given that all neuropsychological test scores were highly correlated with at least one other test. The resulting EF latent factor was used in all subsequent analyses as the primary outcome of interest.

Secondary analyses investigated the subdomains of EF using confirmatory principle component analyses (PCA) guided by *a priori* theory about executive processes and previously published work with the AHAB-II sample (Marsland et al., 2015). Specifically, a working memory component was derived from z-scores of the WAIS-III Digit Span Forward and Backward subtests and the WMS-III Spatial Span Forward and Backward subtests. An inhibitory control component was derived from z-scores of the TMTB-A difference score, Stroop CW, and Stroop interference score. An abstraction component was derived from the WASI Matrix Reasoning and Similarities subtests. Additionally, given the reliance of executive functions on intact attentional capacity (McCabe et al., 2011; Zelazo et al., 2013), a processing speed component was derived from z-scores of TMT-A time to completion, Stroop Color, and Stroop Word. See Figure 1 for details about the tests included in the EF factor analyses.

Principle Components	**Executive Functioning Exploratory Factor** (n = 412)			
Abstraction (n = 456)	Similarities	Matrix Reasoning		
Working Memory (n = 426)	Digit Span Backward	Spatial Span Backward	Digit Span Forward	Spatial Span Forward
Inhibitory Control (n = 413)	Trail Making Test B-A	Stroop Interference	Stroop Color-Word	
Processing Speed (n = 415)	Trail Making Test Part A	Stroop Color	Stroop Word	

Figure 1 Neuropsychological Subtests or Calculated Scores that Derive Factor Scores Through EFA or PCA

Neuropsychological measures included in the EFA of executive functioning are shaded in green.

Neuropsychological measures included in each cognitive component derived from PCA can be read across each row.

2.3.1.3 Relationships Between Physical Activity and Executive Functioning

Ordinary least squares hierarchical regression models were used to test the associations between PA and EF. First, the PA and the EF latent factors were entered into a model to determine whether habitual PA was related to overall EF. Secondary EF components confirmed by PCAs were then entered into separate models with the PA latent factor. False discovery rate (FDR) was used to correct for multiple comparisons between PA and each of the cognitive component scores. The general regression model is displayed below:

$$\hat{Y} = \beta_0 + \beta_{Age} + \beta_{Sex} + \beta_{AgexSex} + \beta_{Education} + \beta_{Smoking} + \beta_{MetabolicSyndrome} + \beta_{CHDRisk} + \beta_{PA} + \beta_{PAxAge} + \beta_{PAxSex}$$

Next, distinct PA parameters that met statistical significance in the PA exploratory factor analyses were entered into separate regression models to test the strength of their independent associations with EF. Comparing the strength of these individual PA parameter associations with those of the EF factor scores tested whether a PA index was better than any individual PA metric in predicting cognitive functioning. Additionally, all other parameters of interest were included as covariates to test whether any one parameter explained variance in EF above and beyond the others. FDR was used to correct for multiple comparisons between individual PA parameters' relationships with EF. Finally, Fisher's r to z transformations were used to test for statistically significant differences in the strength of the associations between the PA index score versus individual PA parameters on the EF factor score or the cognitive component scores.

For any significant interactions in regression models, Johnson-Neyman intervals were calculated to determine the range of significant values of the moderator using a significance level of $p < 0.05$. In the case where sex was a significant moderator, due to mean centering, a Johnson-Neyman interval that did not contain -0.47 was indicative of significant effects for males and an interval that did not contain 0.53 was indicative of significant effects for females.

For sensitivity analyses, all regression models were re-run after removing highly influential data as estimated by Cook's Distance. Data points were identified as highly influential if they exceeded a threshold of 4/n for each model. A change in model significance indicated that the

influential data points were erroneously altering the model residuals to reflect the effects of extreme values, rather than the true relationship between independent and dependent variables. Since each regression analysis included a different subsample of participants due to missing cognitive data, Cook's Distance analyses were conducted for each regression model that included PA and EF factor scores.

2.3.2 Covariates

Potential covariates were determined from theoretical rationale and confirmed by significant bivariate associations with the PA and/or cognitive factor scores. Several demographic characteristics were included as covariates in all analyses. Age was included as a covariate due to the well documented effects of increasing age on lower PA engagement (Barnes & Fu, 2018) and poorer cognitive functioning (Goh et al., 2012; Verhaeghen & Salthouse, 1997). Sex was included as a covariate due to similarly well documented effects on PA engagement (Chen, Li, & Yen, 2015; Pollard & Wagnild, 2017) and cognitive functioning, particularly with women out-performing men on tasks of abstraction and mental flexibility (Gur & Gur, 2017). Notably, there are age-by-sex differences in both PA engagement and cognitive functioning. While younger women may be more active than younger men, several studies have demonstrated that older women are less active than older men (Cohen-Mansfield, Shmotkin, & Goldberg, 2010; Pollard & Wagnild, 2017). With a midlife sample spanning from 30-55 years, it is possible that the current sample could show age-by-sex differences in PA engagement. Further, some studies suggest that postmenopausal women show declines in working memory, phonemic verbal fluency, and delayed memory (Greendale et al., 2009; Weber, Maki, & McDermott, 2014). With some female participants in the sample in an appropriate age range for perimenopause, there may be cognitive

changes related to these biological changes. Thus, an age x sex interaction was used as a covariate that may have influenced potential relationships between PA and EF.

Higher education is associated with better cognitive functioning and better cognitive outcomes later in life (Ardila, Ostrosky-Solis, Rosselli, & Gomez, 2000), so level of education (i.e., no high school diploma, GED, high school diploma, technical training, some college, Associate's degree, Bachelor's degree, Master's degree, or Doctorate degree) was transformed into years and included as a covariate. Racial minorities participate in less PA and fewer beneficial health behaviors relative to Caucasians, particularly in midlife (August & Sorkin, 2011). However, evidence suggests that race-related differences in EF abilities, which may reflect health, socioeconomic, and education disparities, rather than true, racially driven differences (Castora-Binkley, Peronto, Edwards, & Small, 2015; Proctor & Zhang, 2008; Zahodne, Manly, Azar, Brickman, & Glymour, 2016). Therefore, sensitivity analyses investigated differences in PA or EF in White versus non-White participants to determine whether race would be included as a covariate.

Several health characteristics were also included as covariates in all analyses to account for potential confounds that affect PA engagement and/or cognitive functioning. Although the evidence is limited, smoking status (i.e., non-smoker, ex-smoker, current smoker, other tobacco user) has been associated with detriments certain cognitive domains. Specifically, history of heavy smoking and current smoking have been linked to poorer EF and verbal memory task performance (Paul et al., 2006; Razani, Boone, Lesser, & Weiss, 2004) but no detriments in other areas of cognition. Therefore, smoking status was considered as a potential covariate and included following significant association with the abstraction component.

Disease outcome variables were included as covariates because of the bidirectional association between lower PA engagement and higher disease risk. Specifically, lower PA engagement results in poorer health and individuals with higher disease markers tend to engage in less PA. The number of Metabolic Syndrome criteria and the 10-year risk of a CHD event were included as covariates to account for distinct disease outcomes. Utilizing these composite metrics captures many related aspects of poor health that likely share some of the variance they account for in the relationship between PA and EF. Meeting criteria for Metabolic Syndrome is associated with poorer EF (Bird & Hawley, 2016; Muller et al., 2010) and is related to lower PA engagement (Zhang et al., 2017), so it was considered as a potential covariate. The 10-year risk of a CHD event (ATP-III, 2001) was included because it accounts for several cardiovascular risk factors that are associated with reduced EF task performance and greater risk for future cerebrovascular disease. Including two composite metrics of health outcomes accounted for the contributions of two distinct disease processes that might have affected cognitive functioning.

Bivariate correlations between PA, EF, and any possible covariates confirmed the inclusion of potentially confounding variables. Only possible covariates that were significantly associated with PA or EF were included (see Results below). Ultimately, all statistical analyses controlled for age, sex, age x sex, education, smoking status, number of Metabolic Syndrome criteria, and 10-year risk of a CHD event. In secondary analyses that tested the effects of individual PA parameters, the three remaining parameters were included as additional covariates.

2.3.3 Moderators

As previously described, there are several demographic and health characteristics that are related either to PA engagement, EF, or both. Age and sex are two such characteristics with well-

documented influences on both PA and EF that led them to be considered as potential moderators in the current study.

2.3.3.1 Age

As previously described, EF is sensitive to aging and age-related health concerns (Jurado & Rosselli, 2007; Salthouse, 2010; Verhaeghen & Salthouse, 1997). The age discrepancy in executive abilities can be stark, with younger adults outperforming older adults across a variety of executive tasks including inhibitory control, working memory, and planning (Brennan, Welsh, & Fisher, 1997; Jarjat, Portrat, & Hot, 2019; Scuteri, Palmieri, Lo Noce, & Giampaoli, 2005). Within adults aged at least 55 years, one longitudinal study demonstrated that some EFs (i.e., inhibition, switching, manipulation) showed considerable decline over a 14-year follow-up, highlighting age-dependent cognitive changes (Goh et al., 2012). Poorer health can exacerbate detriments in EF (Debette et al., 2011), and health integrity and behaviors tend to decline with increasing age (Cohen-Mansfield et al., 2010; Lu et al., 2018). Reduced PA engagement with advanced age even within relatively healthy populations may contribute to some of the decline in cognitive abilities, particularly EF (Barnes & Fu, 2018; Daly et al., 2014; Willey et al., 2016). However, the potential involvement of other non-modifiable factors, such as sex, must also be considered.

2.3.3.2 Sex

Sex differences across domains of cognitive functioning are well recognized, with longstanding documentation of females showing an advantage on verbal tests and those of EF, learning, and memory (Gur & Gur, 2017; McCarrey et al., 2016). Males tend to engage in greater volume and intensity of PA across the lifespan, particularly in the context of occupational activity or sports (Jones et al., 1998; Pollard & Wagnild, 2017). Notably, one meta-analysis of RCTs

suggested increasing PA engagement benefited females' EF abilities to a greater degree than for males (Barha, Davis, et al., 2017). With sex differences in cognitive functioning, PA, and the effects of PA on cognition, sex was an important moderator to consider in the relationship between midlife PA and EF.

2.3.4 Power Analyses

Cross-sectional studies examining the relationship between PA engagement and cognitive functioning have identified significant effects in sample sizes ranging from 52-18,766 with effect sizes ranging from 0-0.5. At a significance threshold of $p < 0.01$, obtained effect sizes between |0-0.4|, and with a sample size of 412 (at minimum), the current study achieved 99.99% power, which was sufficient to test the previously described aims.

3.0 Results

3.1 Participants

A total of 483 participants had neuropsychological assessment and SenseWear armband data that could be analyzed. Of these, 20 did not have sufficient SenseWear armband data to be included in analyses (i.e., less than 60% of awake time wearing armband = 18, less than three days of data = 2). Seven had estimated full-scale intelligence quotients (IQ) in the borderline range (i.e., below 80 on a standardized scale) and were excluded from analyses. This left 456 participants with complete PA data. Finally, 44 participants had incomplete cognitive data and were excluded from some analyses (specific participant counts for analyses with cognitive factors are included in Table 5). Thus, the final sample included between 412-456 participants, specific to each analysis.

Participants' ages ranged from 30-55 years, with an average of 43 years old (43.03 $\pm$ 7.25 years). Although participants were required to be 30-54 years old to be enrolled in AHAB-II, two participants turned 55 while completing the assessments. Of the 456 with complete PA data, 240 (52.6%) were female and 377 (82.7%) were White; of the remaining 79 participants, 70 were Black (15.4%), six were Asian (1.3%), and three were multi-racial (0.6%). The racial makeup of this sample included more White participants and fewer Black participants than the general Pittsburgh area (Pittsburgh, 2011). See Table 2 for full demographic details. There were no differences in PA engagement or EF between White and non-White participants (all p-values $\geq$ 0.160), and so race was not included as a covariate in subsequent analyses.

Participants were highly educated with an average of 16 years of formal education (15.92 $\pm$ 1.48 years), or having almost completed a Bachelor's degree. Participants' average full-scale IQ,

as estimated from performance on the four WASI subtests, fell within the high end of the average range (mean Standard Score = 113.52 $\pm$ 11.96, range = 80-140). 44 participants did not have complete cognitive data; however, there were no differences between these participants and those who had complete cognitive data on any demographic characteristics or PA engagement (all *p*-values $\geq$ 0.095, see Appendix Table 1).

Seventy-two participants (15.7%) met criteria for Metabolic Syndrome using the NCEP guidelines (2002). Overall, participants were generally healthy without considerable risk for experiencing a CHD event in the next 10 years (average risk = 1.94 $\pm$ 3.44%) (ATP-III, 2001). Additionally, 22 participants (4.8%) reported having been diagnosed with a concussion at some point in their lives. None of the participants reporting a history of concussion also reported cognitive-related sequelae. Participants with and without histories of concussion did not differ on any demographic or health characteristics (all *p*-values > 0.070), PA engagement (all *p*-values > 0.350), or cognitive functioning (all *p*-values > 0.180) (see Appendix Table 2).

Table 2 Participant Demographic Information

Note: **SD, standard deviation; BMI, body mass index; KG, kilogram; M, meter; METAB. SYNDR., Metabolic Syndrome; NCEP, National Cholesterol Education Program; WASI, Wechsler Adult Scale of Intelligence; IQ, intelligence quotient; SS, standard score**

N = 456	MEAN (SD) OR N (%)
AGE	43.03 (7.25)
SEX (FEMALE)	240 (52.6%)
RACE (WHITE : NON-WHITE)	377 (82.7%) : 79 (17.3%)
EDUCATION (YEARS)	15.92 (1.48)
BMI (KG/M^2)	26.74 (5.08)
METAB. SYNDR. CRITERIA (NCEP)	1.25 (1.20)
WASI IQ SS – 4 SUBTESTS	113.52 (11.96)
CONCUSSION HISTORY	22 (4.8%)

3.2 Physical Activity

3.2.1 Characterizing the Sample

All details described below utilized the absolute MET thresholds to categorize PA intensity. On average, participants wore the SenseWear armband on seven days (mean = 7.13 $\pm$ 1.26, range = 3-14 days) with 782 minutes of data acquired for each day of wear (mean = 782.16 $\pm$ 94.56, range = 577-1080 minutes). Participants were relatively sedentary with an average of 1.63 METs (1.63 $\pm$ 0.29) and 379 kcal burned (378.91 $\pm$ 241.75) during at least moderate activity per day. Across all days wearing the SenseWear device, participants engaged in an average of 282 total active minutes (i.e., at least light PA; 281.56 $\pm$ 85.01) and 76 MVPA minutes (76.10 $\pm$ 49.44)

(see Figure 2). The average Bouts Ratio was 2.6 (2.60 $\pm$ 0.96), indicating that the average length of an MVPA bout was 2.6 minutes in duration (see Table 3 for details).

Participants with complete cognitive data wore the SenseWear armband devices for more total minutes (5638.44 $\pm$ 1266.97 minutes) than those without complete cognitive data (5101.77 $\pm$ 1135.56 minutes), $F(1,454) = 7.268$, $p = 0.007$. The same pattern was present across the total days the devices were worn (complete cognitive data: 7.20 $\pm$ 1.27 days, incomplete cognitive data: .52 $\pm$ 1.02 days), $F(1,454) = 11.575$, $p = 0.001$. Participants with complete cognitive data had lower Bouts Ratios per armband minute than participants with incomplete data, $F(1,454) = 7.891$, $p = 0.005$ (see Appendix Table 1 for details). No other differences on PA metrics, including the PA latent factors, were found between participants with and without complete cognitive data (all *p*-values $\geq$ 0.169).

Prior to entry into analyses, all PA metrics were summed across armband wear days and then divided by the number of armband minutes to allow for between-participant comparisons without the confound of unequal armband wear-time. Also prior to entry into all analyses, all PA metrics were examined for skewness. Measured AEE, MVPA minutes, and Bouts Ratio were significantly skewed and subsequently log-transformed.

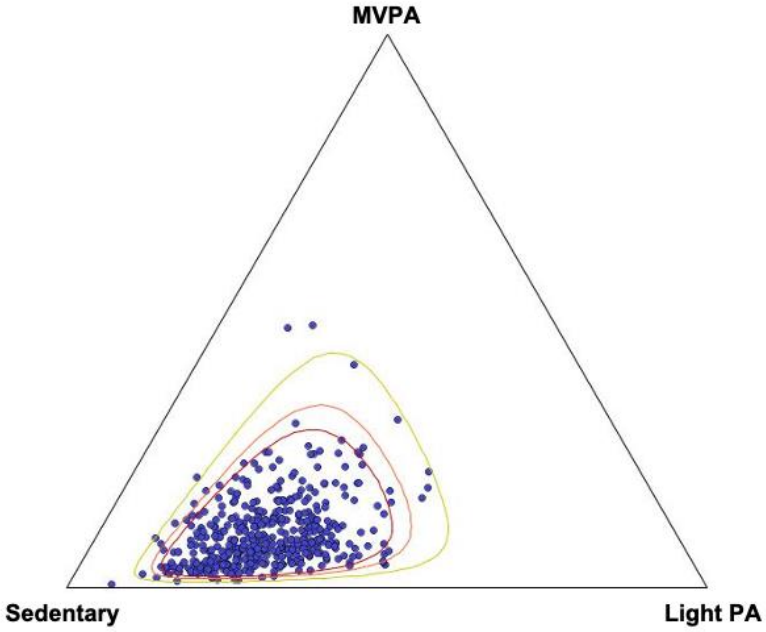


Figure 2 Proportion of the Time Participants Spent in Categories of Physical Activity

Lines represent the normal distribution of data at 90% (red/inner), 95% (orange/middle), and 99% (gold/outer).

Table 3 Physical Activity Characteristics Using the Absolute MET Thresholds

Note: **SD, standard deviation; PA, physical activity; MVPA, moderate-to-vigorous physical activity; METs, metabolic equivalents; AEE, active energy expenditure; KCAL, kilocalories; #, number.**

N = 456	MEAN (SD)
DAYS WITH ARMBAND DATA	7.13 (1.26)
TOTAL MINUTES OF ARMBAND DATA	5586.66 (1263.73)
AVERAGE ARMBAND MINUTES/DAY	782.16 (94.56)
SEDENTARY MINUTES/DAY	500.60 (96.69)
LIGHT PA MINUTES/DAY	205.45 (66.41)
MVPA MINUTES/DAY	76.10 (49.44)
TOTAL PA MINUTES/DAY	281.56 (85.01)
AVERAGE METS/DAY	1.63 (0.29)
MEASURED AEE/DAY (KCAL)*	378.91 (241.75)
# MVPA BOUTS	200.82 (93.89)
# MVPA BOUTS ≥10 MINUTES	8.22 (9.88)
# MVPA BOUTS <10 MINUTES	192.60 (88.97)
BOUTS RATIO	2.60 (0.96)
NUMBER OF MVPA BOUTS/DAY	28.11 (11.55)

3.2.2 Exploratory Factor Analyses

As described above, METs, measured AEE, and Bouts Ratio were entered into all exploratory factor analyses. Two separate analyses were conducted using the volume of MVPA minutes (MVPA factor) and the volume of total PA minutes (Total PA factor) to evaluate potential differences in the relationship between PA and EF based on PA intensity. An initial exploratory factor analysis that included both MVPA minutes and light PA minutes resulted in communality

that was too high to extract variable loadings. Thus, the total PA minutes variable was created by summing the MVPA minutes with the light PA minutes. Then, MVPA and total PA minutes were entered with the other previously described variables into separate factor analyses. Details about the derived latent factors can be found in Table 4.

3.2.2.1 MVPA Factor

One latent factor was derived from METs, measured AEE, Bouts Ratio, and MVPA minutes with factor loadings between 0.73-0.99 (see Table 4, Figure 2). This MVPA factor explained 77.49% of the variance shared between the variables and achieved an eigenvalue of 3.100. The Cronbach's α for this factor was 0.799, indicating good internal consistency between measures and confirming that this factor represented a unidimensional construct of PA.

3.2.2.2 Total PA Factor

One latent factor was derived from METs, measured AEE, Bouts Ratio, and total PA minutes with factor loadings between 0.61-0.90 (see Table 4). This Total PA factor explained 65.89% of the shared variance and achieved an eigenvalue of 2.636. The Cronbach's α for this factor was 0.617, indicating questionable internal consistency between measures. The lower internal consistency for this factor suggests that it may not have represented a unidimensional construct of PA, or at least not to the degree of the MVPA factor.

Table 4 Physical Activity Latent Factor Characteristics

Factors derived from exploratory factor analyses using absolute MET thresholds.

FACTOR	N	PARAMETERS	FACTOR LOADING	EIGENVALUE	% VARIANCE EXPLAINED	CRONBACH'S α
MVPA	456	METs Measured AEE Bouts Ratio MVPA Minutes	.730 .895 .735 .985	3.100	77.489	.799
TOTAL PA	456	METs Measured AEE Bouts Ratio Total PA Minutes	.889 .800 .660 .605	2.636	65.891	.617

Significant challenges arose when attempting to derive additional PA factors using age-specific MET thresholds for PA intensity category, which prohibited their use in subsequent analyses. The individual PA parameters calculated using these age-specific thresholds (i.e., MVPA minutes, total PA minutes, and Bouts Ratio) revealed no significant main or interaction effects on any EF factor score. Therefore, these age-specific thresholds and the PA parameters calculated from them are not discussed in this document.

Details about supplementary PA factor analyses can be found in the Appendix.

3.3 Executive Functioning

3.3.1 Characterizing the Sample

As previously described, 44 participants did not have complete cognitive data. However, given the use of component scores for specific cognitive domains, some of those 44 participants

were included in specific analyses. The exact number of participants with data for each of the neuropsychological tests and subtests used in the current study are included in Table 5.

All neuropsychological measures included were highly correlated (all *p*-values ≤ 0.023) (see Figure 3). Prior to entry into factor analyses, all neuropsychological test variables were examined for skewness. All components of the TMT (i.e., Part A, Part B, the difference score between Parts A and B) exhibited significant skew (≥1.76) and the z-scores were log-transformed. No other z-scores required transformation.

Table 5 Cognitive Test Characteristics

Values are presented as raw values or calculated scores. *Note:* SD, standard deviation; MIN., minimum; MAX., maximum; SEC, seconds.

	N	MEAN (SD)	RAW SCORES (MIN. – MAX.)
SIMILARITIES TOTAL	456	39.39 (4.14)	23 – 48
MATRIX REASONING TOTAL	456	27.16 (4.05)	8 – 35
SPATIAL SPAN FORWARD TOTAL	426	8.28 (1.80)	3 – 14
SPATIAL SPAN BACKWARD TOTAL	426	7.76 (1.68)	2 – 12
DIGIT SPAN FORWARD TOTAL	426	10.77 (2.20)	5 – 16
DIGIT SPAN BACKWARD TOTAL	426	7.84 (2.47)	2 – 14
STROOP COLOR TOTAL	422	76.50 (12.22)	36 – 158
STROOP WORD TOTAL	422	103.76 (18.00)	45 – 116
STROOP COLOR-WORD TOTAL	425	44.65 (9.66)	19 – 90
STROOP INTERFERENCE SCORE	416	0.12 (9.06)	-23.97 – 51.33
TRAIL MAKING TEST PART A (SEC)	425	23.09 (7.14)	11 – 66.25
TRAIL MAKING TEST PART B (SEC)	426	52.85 (20.03)	25.20 – 200.00
TRAIL MAKING TEST B-A (SEC)	424	29.77 (17.50)	1.50 – 169.00

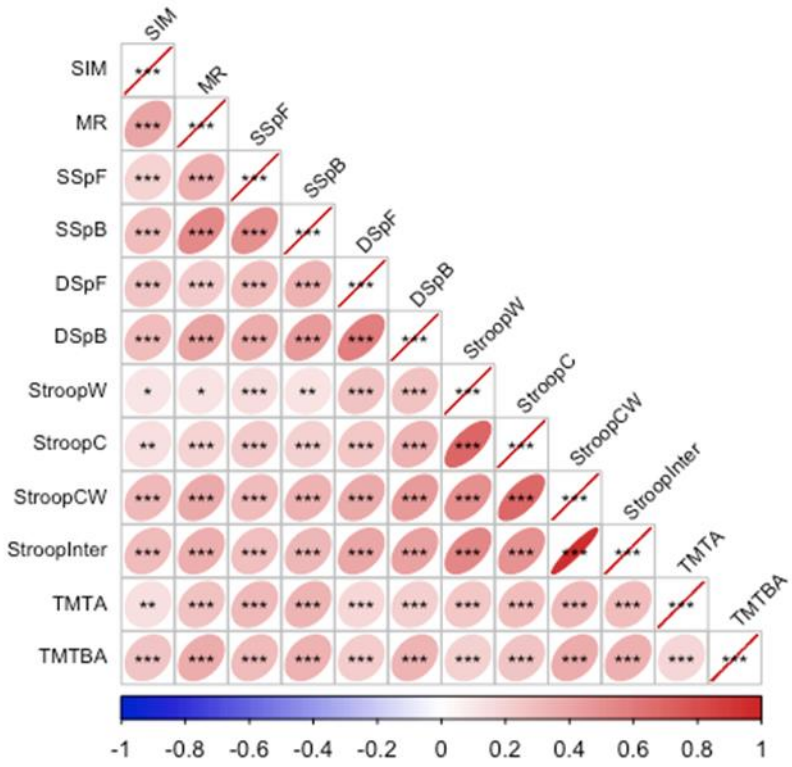


Figure 3 Correlation Plot of all Neuropsychological Measures

*** indicates p < 0.05; ** indicates p < 0.01; *** indicates p < 0.001. *Note:* SIM, WASI Similarities subtest; MR, WASI Matrix Reasoning subtest; SSpF, Spatial Span Forward subtest; SSpB, Spatial Span Backward subtest; DSpF, Digit Span Forward subtest; DSpB, Digit Span Backward subtest; StroopW, Stroop Word condition; StroopC, Stroop Color condition; StroopCW, Stroop Color-Word condition; StroopInter, Stroop Interference score; TMTA, Trail Making Test – Part A; TMTBA, Trail Making Test Part B – Part A**

3.3.2 Exploratory Factor Analyses

Only one latent factor was derived from TMTB-A, Stroop Interference score, and the Digit Span Backward, Spatial Span Backward, Matrix Reasoning, and Similarities subtests. All six variables had factor with loadings between 0.48-0.71 (see Table 6). The factor achieved an eigenvalue of 2.817 and explained 46.95% of the variance shared between neuropsychological

measures. The Cronbach's α for this factor was 0.770, indicating acceptable internal consistency between the six measures. Although internally consistent, the factor explaining only 47% of the shared variance suggests that it did not reflect a unidimensional construct (see Table 6, Figure 4).

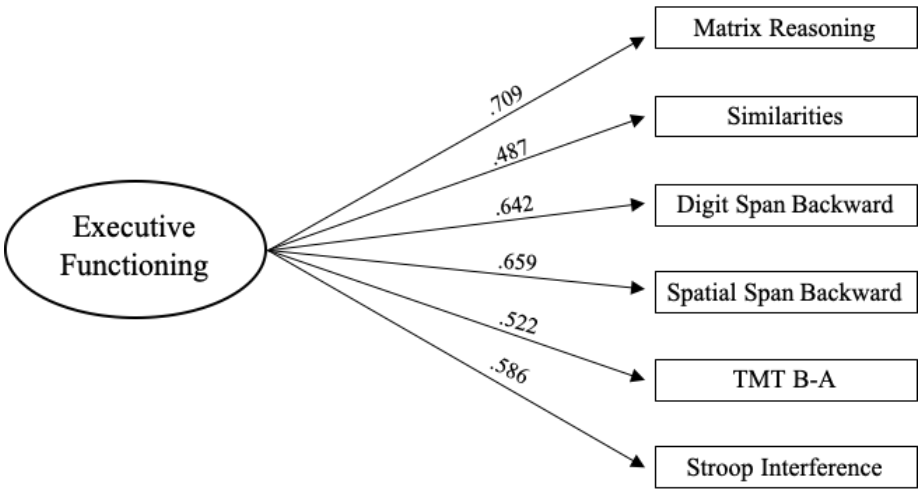


Figure 4 Variable Loadings from the EF Exploratory Factor

Although the neuropsychological measures all loaded onto one derived factor, suggesting an underlying EF domain, the variables included in this analysis were considered to map onto distinct, but related, cognitive processes. Examining the relationships between this exploratory latent factor and PA would provide information about EF as a whole but not any of the well-studied subdomains of EF. Therefore, secondary confirmatory PCAs parsed the EF measures apart into distinct cognitive processes that could further elucidate possible associations with PA engagement.

Table 6 Cognitive Factor Characteristics Derived from EFA and Confirmatory PCA

Note: **NEUROPSYCH, neuropsychological; EIGEN, eigenvalue; VAR. EXPL., variance explained; EFA, exploratory factor analysis; PCA, principle component analysis; TMTB-A, Trail Making Test Part B – Part A; TMT-A, Trail Making Test – Part A.**

FACTOR (ANALYSIS METHOD)	N	NEUROPSYCH MEASURES	FACTOR LOADING	EIGENV.	% VAR. EXPL.	CRONBACH'S α
EXECUTIVE FUNCTIONING (EFA)	412	Matrix Reasoning Similarities Digit Span Backward Spatial Span Backward TMTB-A Stroop Interference	.709 .487 .642 .659 .522 .586	2.817	46.950	.770
WORKING MEMORY (PCA)	426	Digit Span Forward Digit Span Backward Spatial Span Forward Spatial Span Backward	.738 .809 .705 .762	2.276	56.889	.746
INHIBITORY CONTROL (PCA)	413	TMTB-A Stroop Interference Stroop Color-Word	.629 .947 .954	2.202	73.384	.804
ABSTRACTION (PCA)	456	Matrix Reasoning Similarities	.837 .837	1.401	70.061	.573
PROCESSING SPEED (PCA)	415	TMT-A Stroop Color Stroop Word	.602 .883 .870	1.899	63.307	.698

3.3.3 Confirmatory Principle Component Analyses

3.3.3.1 Working Memory

The Forward and Backward conditions of the WAIS-III Digit Span subtest and WMS-III Spatial Span subtest were entered into a confirmatory PCA to capture working memory capacity. All four measures had loadings onto the component between 0.70-0.81, which explained 56.90% of the shared variance and achieved an eigenvalue of 2.276 (see Table 6, Figure 5a). The

Cronbach's α for this component was 0.746, indicating acceptable internal consistency between the four measures.

3.3.3.2 Inhibitory Control

TMTB-A time, Stroop Interference score, and Stroop Color-Word raw score were entered into a confirmatory PCA to capture inhibitory control. All three measures had loadings onto the component between 0.62-0.96 (see Table 6, Figure 5b). The component explained 73.38% of the shared variance and achieved an eigenvalue of 2.202. The Cronbach's α for this component was 0.804, indicating good internal consistency between the measures.

3.3.3.3 Abstraction

The Matrix Reasoning and Similarities subtests of the WASI were entered into a confirmatory PCA to capture abstraction. Both measures had loadings onto the component of 0.837, the component explained 70.06% of the shared variance, and it achieved an eigenvalue of 1.401 (see Table 6, Figure 5c). The Cronbach's α for this component was 0.573, indicating poor internal consistency between Matrix Reasoning and Similarities.

3.3.3.4 Processing Speed

Although not a direct subdomain of EF, processing speed is important for successful use of executive abilities (Albinet, Boucard, Bouquet, & Audiffren, 2012). TMT-A, Stroop Color, and Stroop Word were entered into confirmatory PCA to capture processing speed capacity. All three measures had loadings onto the component between 0.60-0.89. The component explained 63.31% of the shared variance and achieved an eigenvalue of 1.899 (see Table 6, Figure 5d). The

Cronbach's α for this component was 0.698, indicating marginally acceptable internal consistency between the three measures.

Details about supplementary EF factor analyses can be found in the Appendix.

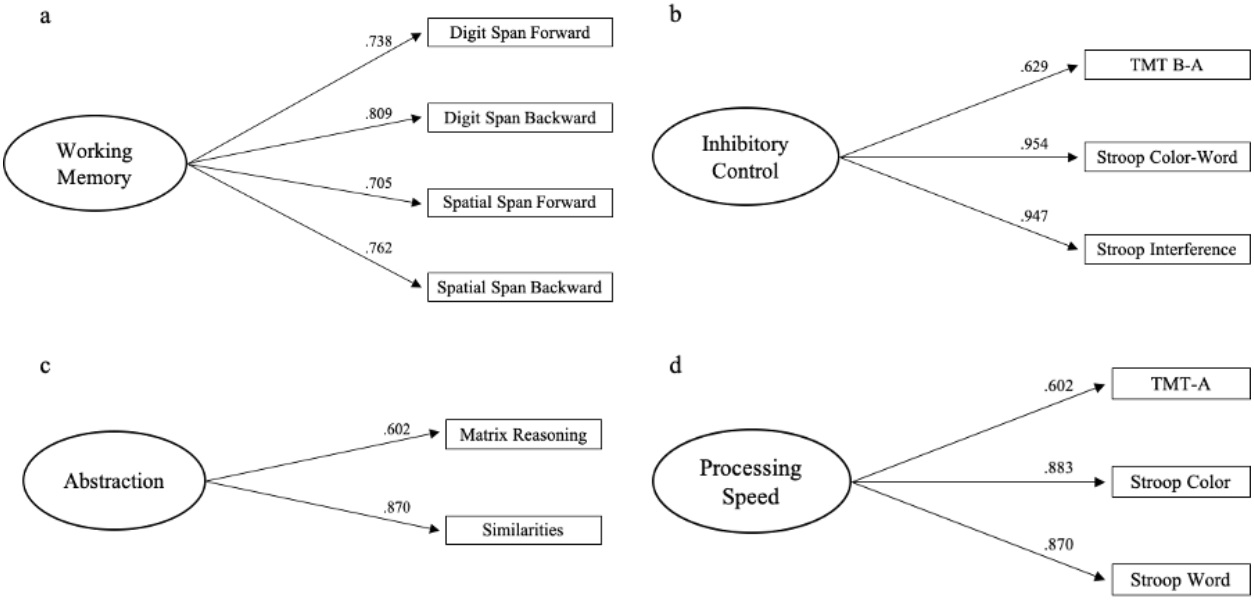


Figure 5 Neuropsychological Subtests or Calculated Scores that Derive the Factor Scores Through PCA

3.4 Physical Activity and Executive Functioning

3.4.1 MVPA Factor

3.4.1.1 Exploratory Executive Functioning Factor

In contrast with Hypothesis 1a that greater PA engagement would be associated with better EF, a bivariate correlation revealed no significant relationship between the MVPA factor and the exploratory EF factor, r(410) = -0.006, p = 0.901. After controlling for relevant covariates, the

overall regression model was not significant, $F(10, 368) = 1.643$, $R^2 = 0.043$, model $p = 0.093$. Again, in contrast with Hypothesis 1a, there was no main effect of the MVPA factor on EF. In contrast with Hypotheses 2a and 2b, nor were there any interaction effects between PA and age or sex (all $\beta < |0.02|$, all p-values ≥ 0.134).

Eighteen highly influential data points were removed following a Cook's Distance analysis as a sensitivity measure. Removing these participants resulted in a significant overall model, $F(10, 350) = 2.261$, $R^2 = 0.061$, model $p = 0.014$. In contrast with hypotheses, there was a trend toward a negative main effect of MVPA ($\beta = -0.113$, $p = 0.081$), suggesting that increased PA engagement may be related to poorer EF task performance (see Table 7, Figure 6 for details). Again, there were no significant interaction effects between PA and age or sex on EF (all $\beta \geq -0.07$, all p-values ≥ 0.448). Overall, the MVPA factor was not associated with EF in this sample.

Table 7 Regression Results Using the MVPA Factor on the EF Exploratory Factor

$^{\int}$ indicates $p < 0.10$; * indicates $p < 0.05$; ** indicates $p < 0.01$. *Note:* DIFF., difference; MET. SYNDR., Metabolic Syndrome; YR, year; CHD, Coronary Heart Disease; MVPA, moderate-to-vigorous physical activity.

PREDICTOR	β	CI (95%)	P	FIT	DIFF.
AGE	0.10	[-0.02, 0.22]	.113		
SEX	0.02	[-0.11, 0.15]	.753		
AGE X SEX	-0.04	[-0.16, 0.07]	.448		
EDUCATION	0.07	[-0.04, 0.17]	.213	R^2 = .030*	
SMOKING STATUS	-0.12*	[-0.23, -0.01]	.040		
MET. SYNDR. CRITERIA	-0.10$^{\int}$	[-0.21, 0.02]	.099		
10-YR CHD RISK	0.05	[-0.10, 0.20]	.535	R^2 = .046*	ΔR^2 = .016
MVPA FACTOR	-0.11$^{\int}$	[-0.25, -0.02]	.080	R^2 = .060**	ΔR^2 = .014
MVPA FACTOR X AGE	0.02	[-0.08, 0.13]	.635		
MVPA FACTOR X SEX	0.01	[-0.09, 0.12]	.837	R^2 = .061*	ΔR^2 = .001

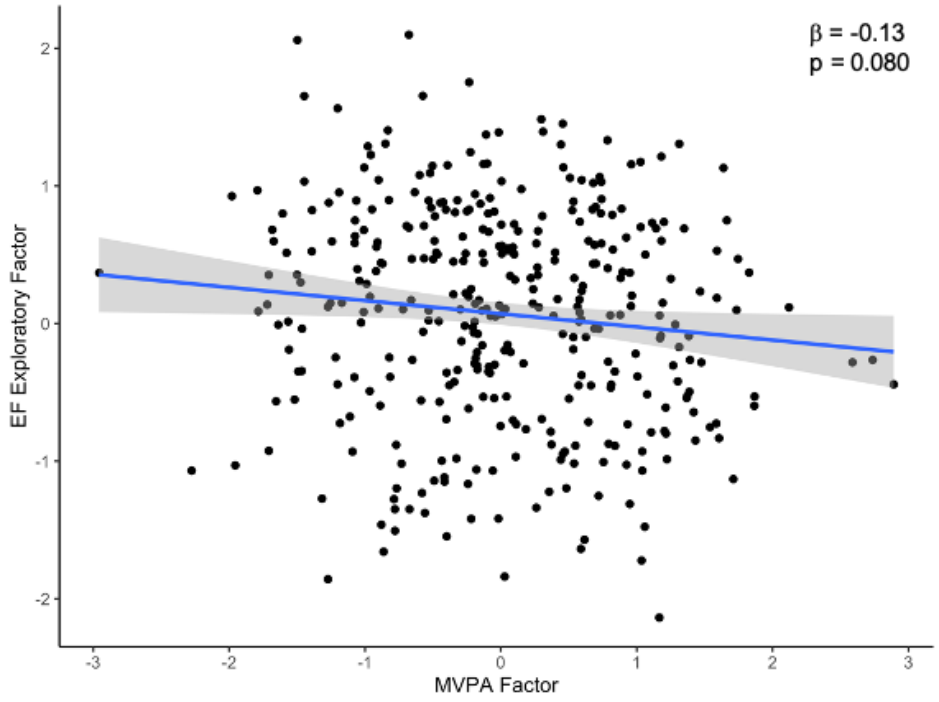


Figure 6 Main Effect of the MVPA Factor on the EF Exploratory Factor

Grey shading represents the 95% confidence interval.

3.4.1.2 Cognitive Components

3.4.1.2.1 Working Memory

After controlling for all relevant covariates, there were no significant relationships between the MVPA factor or any interaction terms and working memory (all $\beta \leq |0.079|$, all *p*-values $\geq$ 0.100), despite a significant overall model, $F(10, 392) = 5.648$, $R^2 = 0.126$, model $p < 0.001$. Removing 22 highly influential data points improved the model fit but did not change the significance, $F(10, 370) = 8.738$, $R^2 = 0.191$, model $p < 0.001$. In line with Hypothesis 2a, that higher PA factor scores would be associated with better EF in older participants, the updated model

revealed a significant MVPA factor x Age interaction (β = -0.104, $p = 0.019$). In this sample, greater MVPA engagement was associated with better working memory only for participants over the age of 51 (Johnson-Neyman age interval [26.42, 51.4]). Further, this interaction was only significant for the older participants engaging in the least amount of PA (Johnson-Neyman interval for MVPA factor score [1.17, 14.89]), suggesting that age-related differences in working memory may be ameliorated for participants engaging in the most activity (see Table 8, Figure 8A). There was no main effect or moderation by sex on working memory (Figures 7A, 9A). The interaction with age was trending toward statistical significance after correcting for multiple comparisons ($p = 0.076$, see Figure 8A). This suggested that more MVPA may be related to better working memory later in midlife, perhaps in an age range when cognitive functioning is beginning to decline and more sensitive to a modifiable lifestyle behavior.

3.4.1.2.2 Inhibitory Control

The regression model controlling for all relevant covariates was not significantly related to inhibitory control, $F(10, 369) = 0.761$, $R^2 = 0.020$, model $p = 0.668$. There were no significant associations with PA (all $\beta \leq |0.198|$, all p-values ≥ 0.088). Removing 18 highly influential data points did not change the overall lack of association between the model and inhibitory control, $F(10, 351) = 1.514$, $R^2 = 0.041$, model $p = 0.133$. However, it did yield a significant main effect of the MVPA factor score ($\beta = -0.219$, $p = 0.005$) and an MVPA factor x sex interaction that was only significant for males ($\beta = 0.232$, $p = 0.019$). In contrast to Hypothesis 1a, this main effect was such that greater PA engagement was related to poorer inhibitory control (see Table 8, Figure 7B). Age did not moderate this relationship (see Figure 8B). In contrast to Hypothesis 2b that males

engaging in the lowest PA would have the lowest EF scores, males with higher MVPA factor scores demonstrated poorer inhibitory control (see 9B). After correcting for multiple comparisons, only the main effect of the MVPA factor remained significant (p = 0.020), suggesting that sex differences were not meaningful in this relationship.

3.4.1.2.3 Abstraction

In contrast to Hypotheses 1a, 2a, and 2b, there were no significant main effects of the MVPA factor score or interactions with PA on abstraction component scores (all $\beta \leq |0.057|$, all p-values ≥ 0.527) after controlling for all relevant covariates, despite a significant overall model, $F(10, 408) = 14.895$, $R^2 = 0.267$, model $p < .001$. Removing 23 highly influential data points did not change these results, $F(10, 385) = 14.527$, $R^2 = 0.274$, model $p < 0.001$ (all PA $\beta \leq |0.082|$, all PA p-values ≥ 0.200) (see Table 8, Figures 7C, 8C, 9C), suggesting that the MVPA factor was not related to abstraction.

3.4.1.2.4 Processing Speed

In contrast to the Hypotheses 1a, 2a, and 2b, the model examining the relationship between the MVPA factor and processing speed was not significant after controlling for all relevant covariates, $F(10, 371) = 0.710$, $R^2 = 0.019$, model $p = 0.715$. There were no significant main effects or interactions with PA (all $\beta \leq |0.113|$, all p-values ≥ 0.174). Removing 21 highly influential data points resulted in a marginally significant model overall, $F(10, 350) = 1.663$, $R^2 = 0.045$, model $p = 0.088$. Removing these points also revealed a significant main effect of the MVPA factor score

(β = -0.156, p = 0.042) and an MVPA factor x sex interaction (β = 0.200, p = 0.043). In line with the pattern for inhibitory control, greater PA engagement was associated with slower processing speed for males only (see Table 8, Figures 7D, 8D, 9D). However, neither effect remained significant after correcting for multiple comparisons, suggesting that the MVPA factor was not be related to processing speed, regardless of sex.

Table 8 Standardized Regression Coefficients (β) for the Main and Interaction Effects of MVPA Factor Variables on Each of the Cognitive Factors

$^{\int}$ indicates p < 0.10; * indicates p < 0.05; ** indicates p < 0.01 – prior to correcting for multiple comparisons with FDR. *Note:* EXPLOR., exploratory; EF, executive functioning; ABSTRACT., abstraction; PROCESS., Processing; ME, main effect; MVPA, moderate-to-vigorous physical activity; METS, metabolic equivalents; MEAS., measured; AEE, active energy expenditure; MINS, minutes.

		EXPLOR. EF	WORKING MEMORY	INHIBITORY CONTROL	ABSTRACT.	PROCESS. SPEED
MVPA FACTOR	*ME*	-0.11$^{\int}$	0.03	-0.22**	0.05	-0.15*
	x Age	0.02	0.10*	0.01	0.05	-0.05
	x Sex	0.01	0.09	0.23*	-0.08	0.20*
METS	*ME*	.01	-.09	.06	-.13	-.13
	x Age	-.03	.13**	.00	.00	-.08$^{\int}$
	x Sex	-.11	.03	.00	.00	.19$^{\int}$
MEAS. AEE	*ME*	-.15	-.18	-.04	-.35*	-.11
	x Age	.07	.07	.02	.00	-.03
	x Sex	.05	.14	.21*	.01	.25*
BOUTS RATIO	*ME*	-.02	-.04	-.09	.21**	-.13
	x Age	-.05	.02	-.01	.00	-.04
	x Sex	-.01	.14	.08	-.02	.10
MVPA MINS	*ME*	-.01	.10	-.30$^{\int}$	.27$^{\int}$	-.11
	x Age	.01	.12**	.02	.03	-.04
	x Sex	.04	.08	.16	.00	.24*

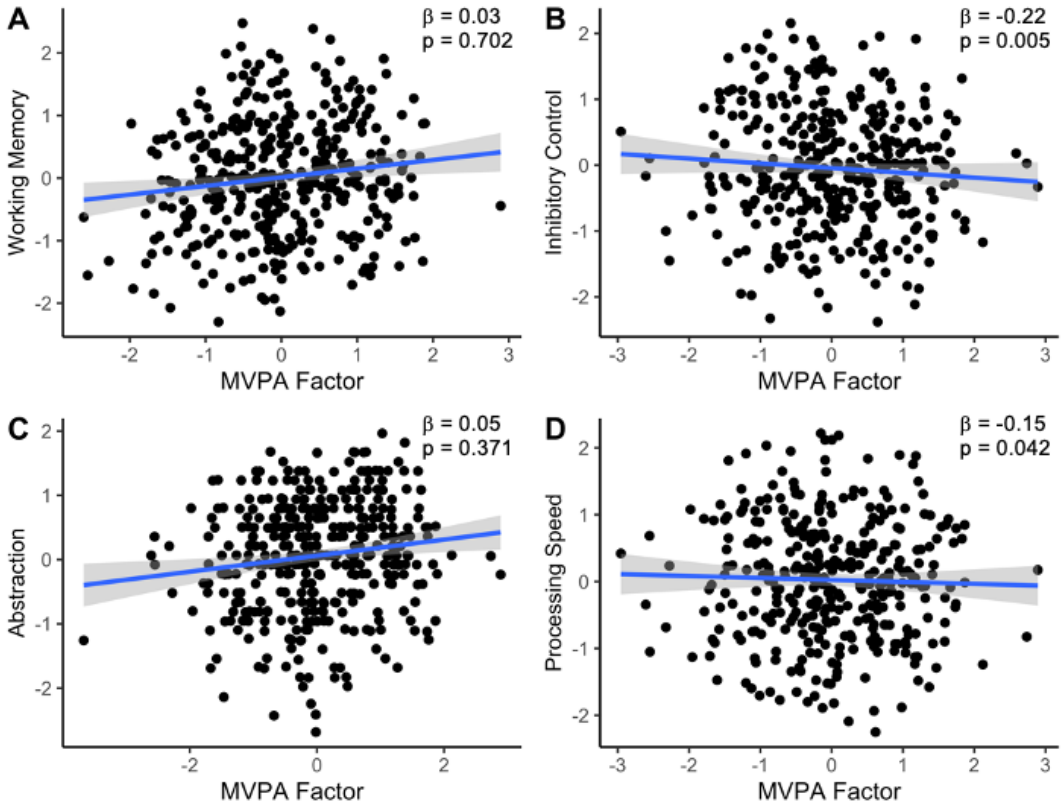


Figure 7 Main Effect of the MVPA Factor on Each of the Cognitive Component Scores

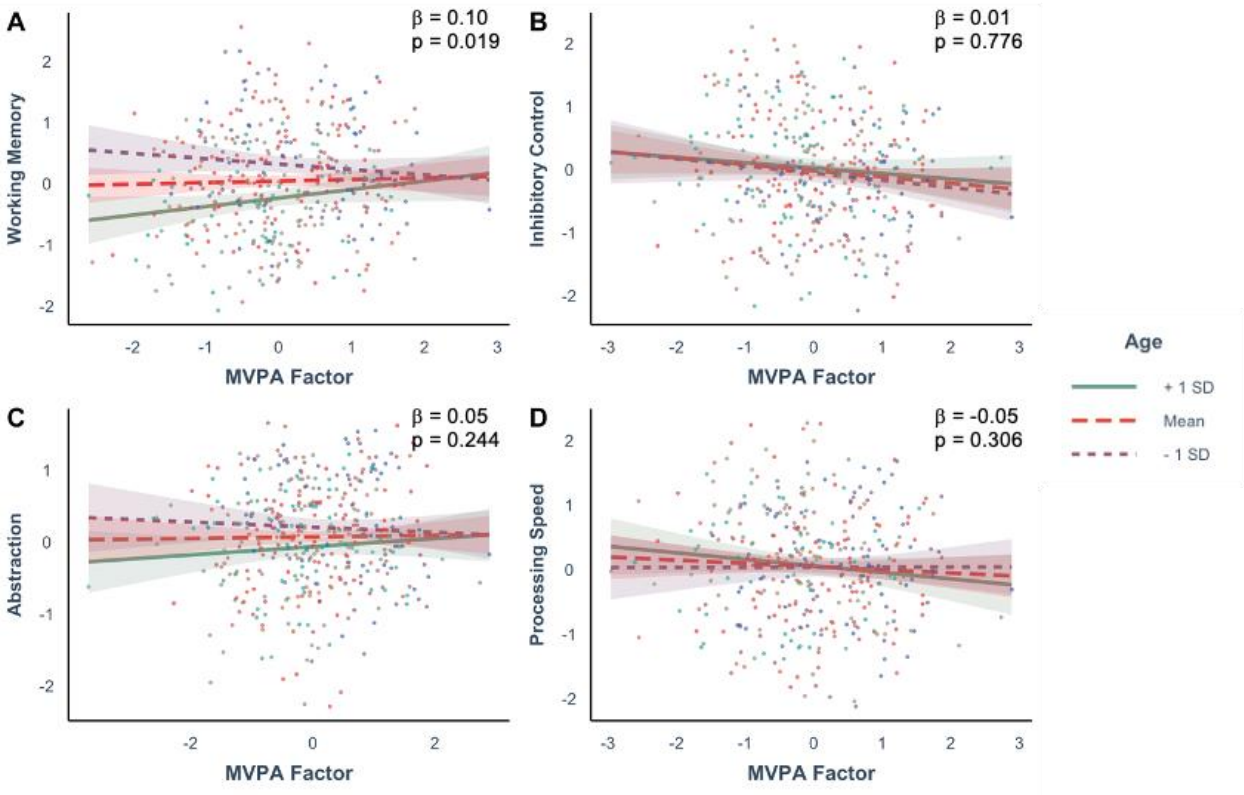


Figure 8 The MVPA Factor x Age Interactions on Each of the Cognitive Component Scores

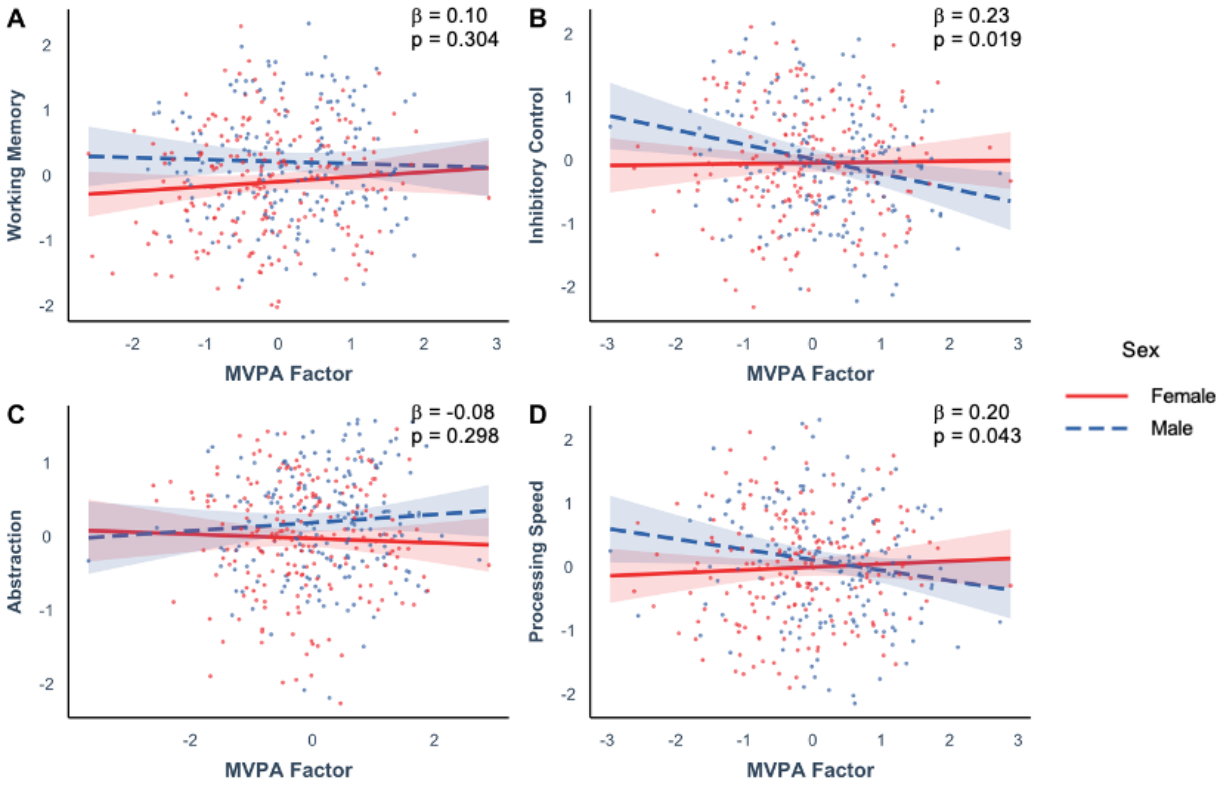


Figure 9 The MVPA Factor x Sex Interactions on Each of the Cognitive Component Scores

3.4.2 Total PA Factor

All previously described regression models were conducted again using the Total PA factor, which included total PA minutes, rather than only MVPA minutes. These models examined whether engagement in *any* activity was related to EF and the previously described subdomains.

3.4.2.1 Exploratory Executive Functioning Factor

In contrast with Hypothesis 1a that greater PA engagement would be associated with better EF, a bivariate correlation revealed no significant relationship between the Total PA factor and the exploratory EF factor, r(410) = 0.064, p = 0.195. After controlling for all relevant covariates, there was no significant relationship between the overall regression model and EF, F(10, 368) = 1.575,

R^2 = 0.041, model p = 0.112. There was no main effect of total PA engagement, nor were there any interaction effects between PA and age or sex (all $\beta < |0.116|$, all p-values ≥ 0.235).

Fourteen highly influential data points were removed following a Cook's Distance sensitivity analysis. Removing these data points resulted in a marginally significant overall model, $F(10, 354) = 1.723$, $R^2 = 0.046$, model $p = 0.074$. Again in contrast with Hypotheses 1a, 2a, and 2b, there were no main or interaction effects of the Total PA factor on EF (all $\beta \leq 0.064$, all p-values ≥ 0.186), suggesting that total PA engagement was not related to EF in this sample (see Table 9, Figure 10 for details).

Table 9 Regression Results Using the Total PA factor on the EF Exploratory Factor

$^{\int}$ indicates p < 0.10; * indicates *p* < 0.05; ** indicates *p* < 0.01. *Note:* DIFF., difference; MET. SYNDR., Metabolic Syndrome; YR, year; CHD, Coronary Heart Disease; PA, physical activity.

PREDICTOR	β	CI (95%)	P	FIT	DIFF
AGE	0.10$^{\int}$	[-0.02, 0.22]	.086		
SEX	0.04	[-0.09, 0.16]	.552		
AGE X SEX	-0.06	[-0.18, 0.05]	.260		
EDUCATION	0.05	[-0.05, 0.16]	.336	R^2 = .025	
SMOKING STATUS	-0.10$^{\int}$	[-0.22, 0.01]	.078		
MET. SYNDR. CRITERIA	-0.08	[-0.19, 0.03]	.140		
10-YR CHD RISK	0.02	[-0.13, 0.17]	.827	R^2 = .039*	ΔR^2 = .014
TOTAL PA	0.06	[-0.05, 0.16]	.329	R^2 = .042	ΔR^2 = .003
TOTAL PA X AGE	0.06	[-0.03, 0.17]	.186		
TOTAL PA X SEX	-0.03	[-0.12, 0.08]	.705	R^2 = .046	ΔR^2 = .005

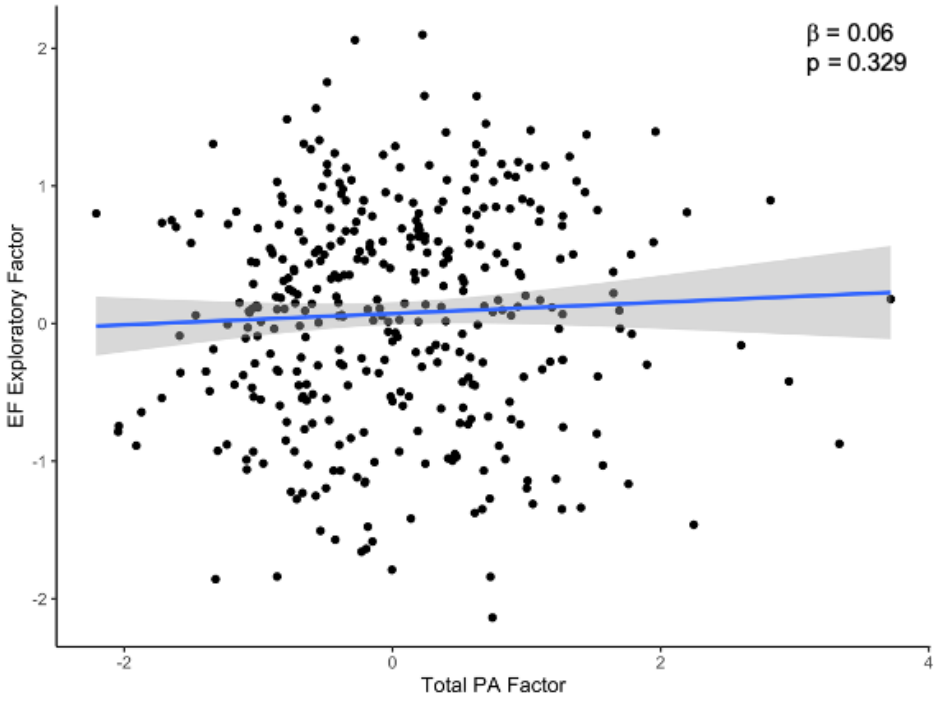


Figure 10 The Main Effect of the Total PA Factor on the EF Exploratory Factor

Grey shading represents 95% confidence interval.

3.4.2.2 Cognitive Components

The same regression model described above was applied to the individual cognitive components confirmed with PCA to better understand potential relationships between the Total PA factor and EF subdomains.

3.4.2.2.1 Working Memory

Inconsistent with Hypotheses 1a, 2a, and 2b, there were no significant relationships between the Total PA factor or any interaction terms and working memory after controlling for all relevant covariates (all $\beta \leq |0.126|$, all *p*-values ≥ 0.104), despite a significant model, $F(10, 392) =$

5.601, $R^2 = 0.125$, model $p < 0.001$. Removing 19 highly influential data points did not change the model significance, $F(10, 373) = 8.635$, $R^2 = 0.188$, model $p < 0.001$. The updated model showed a marginal main effect of the Total PA factor ($\beta = 0.121$, $p = 0.093$) and a marginal interaction between Total PA factor x Sex ($\beta = -0.159$, $p = 0.081$). In line with Hypothesis 1a, greater total PA engagement was trending toward an association with better working memory, though only for males (see Table 10, Figures 11A, 13A). However, these associations were marginally significant and demonstrated small effect sizes, indicating that overall PA engagement was not associated with working memory. Additionally, age did not moderate these relationships, in contrast with Hypothesis 2a (see Figure 12A).

3.4.2.2.2 Inhibitory Control

In contrast with Hypotheses 1a, 2a, and 2b, after controlling for all relevant covariates, there was no significant relationship between the overall model and inhibitory control, $F(10, 369) = 2.261$, $R^2 = 0.017$, model $p = 0.794$. There were no significant main or interaction effects of the Total PA factor (all $\beta \leq 0.061$, all p-values ≥ 0.122). Removing 18 highly influential data points did not change the overall model fit, $F(10, 351) = 0.870$, $R^2 = 0.024$, model $p = 0.562$, nor did it change the lack of significant main or interaction effects of PA, suggesting total PA engagement was not associated with inhibitory control (see Table 10, Figures 11B, 12B, 13B).

3.4.2.2.3 Abstraction

Inconsistent with Hypotheses 1a, 2a, and 2b, that greater PA engagement would be associated with better EF, there were no significant main effects of the Total PA factor or interactions with the Total PA factor on abstraction component scores (all $\beta \leq |0.081|$, all *p*-values ≥ 0.356), despite a significant overall model, $F(10, 408) = 14.928$, $R^2 = 0.268$, model $p < 0.001$. Removing 23 highly influential data points did not change these results, with a model fit of $F(10, 385) = 14.571$, $R^2 = 0.275$, model $p < 0.001$ and all PA $\beta \leq |0.123|$, all PA *p*-values ≥ 0.147. This suggests that total PA engagement was not associated with abstraction (see Table 10, Figures 11C, 12C, 13C).

3.4.2.2.4 Processing Speed

After controlling for all relevant covariates, there was no significant relationship between the overall model and processing speed, $F(10, 371) = 0.925$, $R^2 = 0.024$, model $p = 0.510$, nor were there any significant associations with the Total PA factor or PA interactions (all $\beta \leq |0.079|$, all *p*-values ≥ 0.155). Removing 24 highly influential data points did not change these results, with a nonsignificant overall model, $F(10, 347) = 1.191$, $R^2 = 0.033$, model $p = 0.296$. This indicates that total PA engagement was not associated with processing speed (see Table 10, Figures 11D, 12D, 13D).

Table 10 Standardized Regression Coefficients (β) for the Main and Interaction Effects of Total PA Factor Variables on Each of the Cognitive Factors

∫ indicates p < 0.10; * indicates p < 0.05; ** indicates p < 0.01 – prior to correcting for multiple comparisons with FDR. *Note:* EXPLOR., exploratory; EF, executive functioning; ABSTRACT., abstraction; PROCESS., Processing; PA, physical activity; ME, main effect; METS, metabolic equivalents; MEAS., measured; AEE, active energy expenditure; MINS, minutes.

		EXPLOR. EF	WORKING MEMORY	INHIBITORY CONTROL	ABSTRACT.	PROCESS. SPEED
TOTAL PA FACTOR	*ME*	0.06	0.12∫	-0.03	-0.02	-0.05
	x Age	0.06	0.05	0.00	-0.01	0.07
	x Sex	-0.03	-0.16∫	0.06	0.09	-0.00
METS	*ME*	.01	-.10	.09	-.07	-.06
	x Age	-.02	.14**	.00	.00	-.09∫
	x Sex	-.09	.04	-.02	.01	.13
MEAS. AEE	*ME*	-.09	-.05	-.10	-.14	-.06
	x Age	.05	.07	.02	-.15	-.03
	x Sex	.04	.09	.16	-.01	.22*
BOUTS RATIO	*ME*	-.05	-.02	-.18*	.20**	-.18*
	x Age	-.04	.02	.00	.00	-.03
	x Sex	-.03	.13	.09	.01	.12
TOTAL PA MINS	*ME*	.03	.09	.07	.04	-.11
	x Age	.01	.11*	.00	-.03	-.04
	x Sex	-.11	-.10	-.22*	-.05	.03

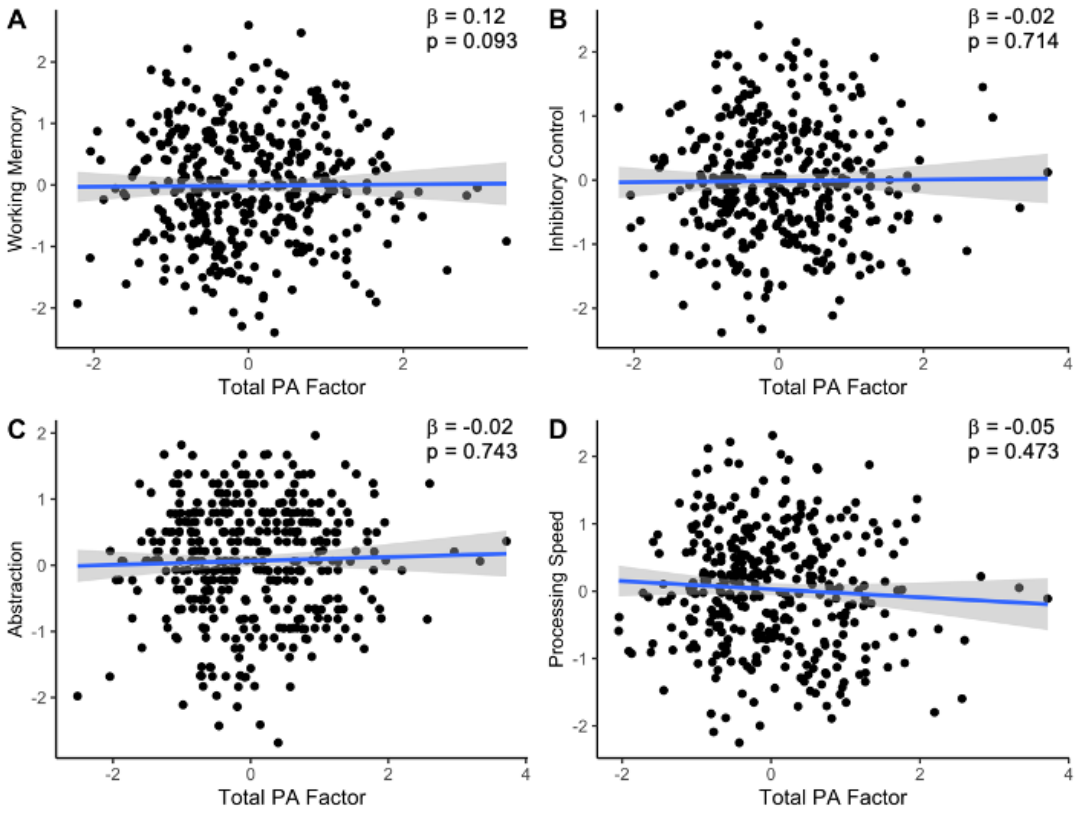


Figure 11 The Total PA Factor Main Effects on Each of the Cognitive Component Scores

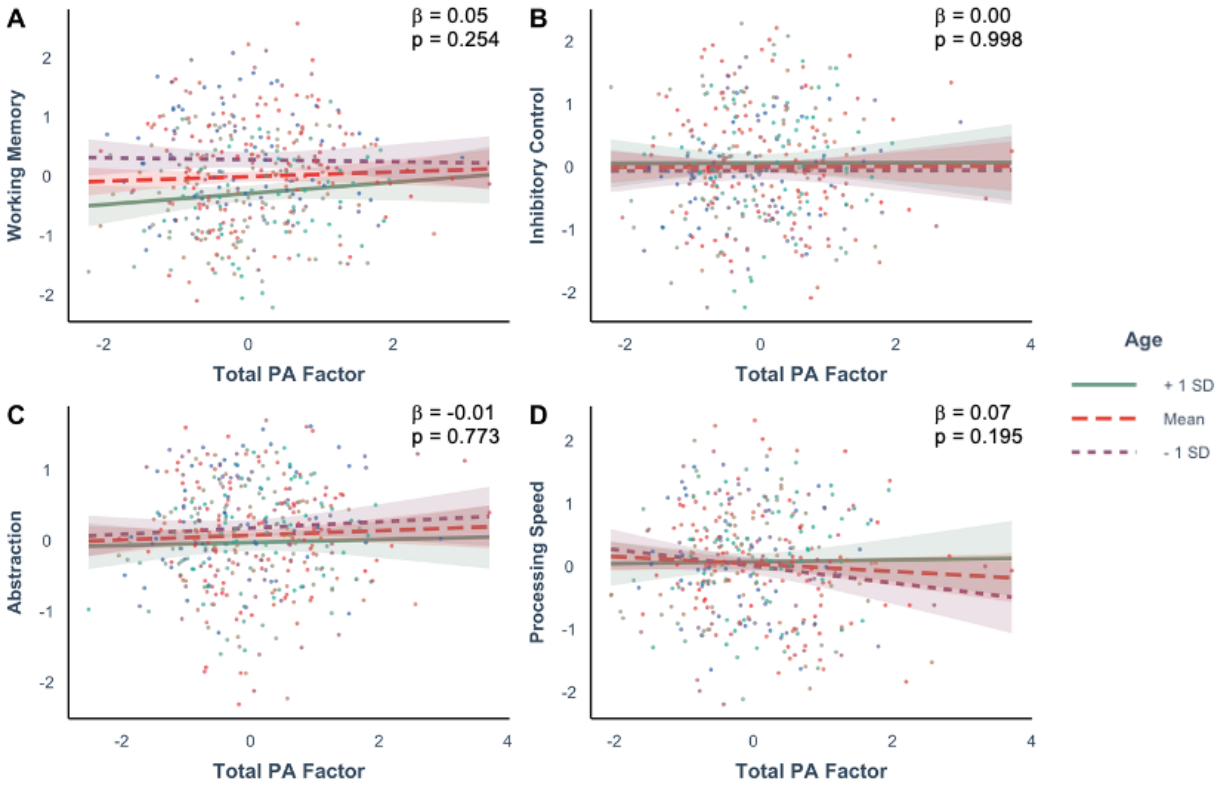


Figure 12 The Total PA Factor x Age Interactions on Each of the Cognitive Component Scores

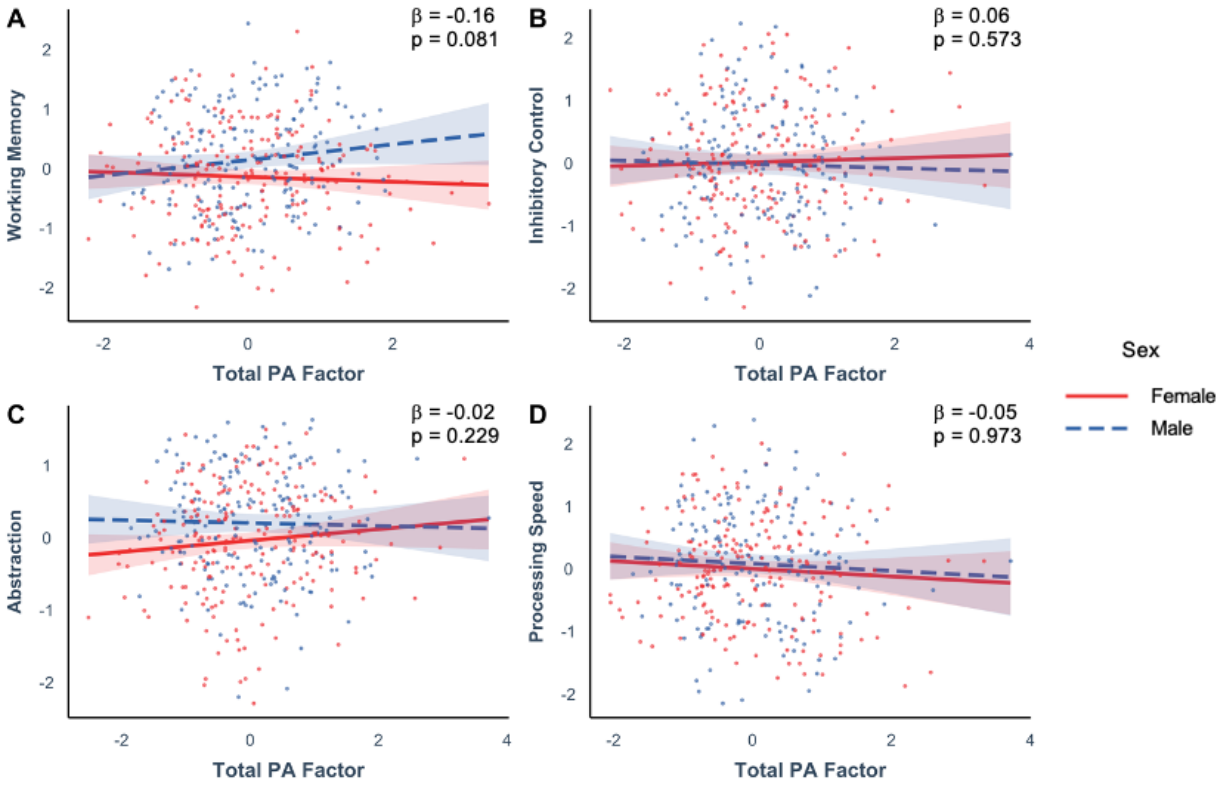


Figure 13 The Total PA Factor x Sex Interactions on Each of the Cognitive Component Scores

3.4.3 Covariates

Some associations were found between covariates (i.e., age, sex, education, smoking status) and the EF exploratory factor and between the covariates and the cognitive component scores. These associations are described in detail in the Appendix.

3.4.4 Comparison with Individual Physical Activity Parameters

Hypotheses 1b and 1c of the current study were that the derived PA latent factors would have stronger associations with EF than any individual parameter (1b) and that individual PA parameters would have different, but related, associations with EF (1c). To test these hypotheses,

Fisher's r to z transformations compared the partial correlations of PA factor scores, the PA factor x Age interactions, and the PA factor x Sex interactions with the partial correlations of each individual PA parameter and its interactions with Age or Sex on EF. Since only one significant relationship between PA and an EF subdomain was observed when using either of the PA factor scores, all partial correlations between PA variables and EF/EF subdomain factor scores were compared. Examining all associations increased the likelihood of Type 1 error, which was mitigated by correcting for multiple comparisons using FDR. Examining all associations also eliminated the possibility that significant relationships between individual parameters and EF were washed out by using only the PA factor scores. The main results of these comparisons are described below; details of the individual relationships were shown in Tables 8 and 10.

Any relationships with cognitive functioning that were stronger with the MVPA or Total PA factor would be consistent with Hypothesis 1b, which was that an overall PA index would be more closely related to EF than any individual PA parameter. Notably, there were no significant differences in the strength of the associations between PA factors and PA parameters on the EF exploratory factor, the working memory component, or the processing speed component.

3.4.4.1 MVPA Factor

First, all relationships between the MVPA factor and any EF/EF subdomain factor were compared with the same associations between individual PA parameters and those cognitive factors. These comparisons revealed several significant differences, though only for inhibitory control and abstraction. The MVPA factor had a significantly stronger main effect on the inhibitory control component than average daily METs (Fisher's $z = 2.54$, $p = 0.011$). Here, greater MVPA factor scores were associated with poorer inhibitory control ($\beta =$ -0.22, $p = 0.005$), while the association with average METs was nonsignificant. These relationships indicate that the overall

PA index score was more closely related to inhibitory control than average METs alone, and that greater overall MVPA engagement was associated with poorer inhibitory control task scores. While this finding was consistent with Hypothesis 1b that the MVPA factor would be more closely related to EF than any individual PA parameter, it contrasted with Hypothesis 1a that greater PA engagement would be associated with better EF.

In contrast with Hypothesis 1b, the MVPA factor demonstrated a significantly weaker main effect on abstraction than measured AEE (Fisher's $z = -2.55$, $p = 0.011$). MVPA factor scores were not associated with abstraction, while greater measured AEE was associated with poorer abstraction ($\beta = -0.348$, $p = 0.012$). This suggests that more energy expended was related to poorer abstraction, which was also inconsistent with Hypothesis 1a. Both of these significantly different associations between the MVPA factor and average METs or measured AEE withstood correction for multiple comparisons. The pattern of these relationships suggest that greater PA engagement is associated with poorer inhibitory control and abstraction, which contradicts the hypotheses and previously published evidence that greater PA engagement is associated with better EF.

The MVPA factor did not reliably differ from any other individual PA parameters in the strength of the associations with any other cognitive scores (i.e., the exploratory EF factor, working memory, or processing speed; all p-values ≥ 0.060). Average METs and MVPA minutes both demonstrated significant interactions with age on working memory (see Table 8), though these effects were not significantly different from the interaction between the MVPA factor score and age. Despite the two significantly different main effects on inhibitory control and abstraction, the overall results indicate that a PA index may not be necessary to create when determining the relationship between PA engagement and cognitive functioning. The inconsistent pattern between the MVPA factor scores' relationships with inhibitory control and abstraction relative to average

METs and measured AEE also suggest that some parameters and certain cognitive domains are more sensitive than others, despite most relationships not being significantly different from one another.

3.4.4.2 Total PA Factor

Next, all relationships between the Total PA factor and any EF/EF subdomain factor score were compared with the same associations between individual PA parameters and those same cognitive factor scores. As with the analyses described above, any relationships with cognitive functioning that were stronger with the Total PA factor would be consistent with Hypothesis 1b, which stated that an overall PA index would be more closely related to EF than any individual PA parameter.

Comparison of the associations with the Total PA factor versus the individual PA parameters revealed only one significant difference. In contrast with Hypothesis 1b, the individual Bouts Ratio variable had a significantly stronger main effect on the abstraction component score than the Total PA factor (Fisher's $z = 2.19$, $p = 0.029$). Here, higher Bouts Ratios were associated with better abstraction ($\beta = 0.211$, $p = 0.007$), while the Total PA factor was not associated with abstraction. Although the nonsignificant relationship between the Total PA factor and abstraction was not predicted, the positive association with Bouts Ratio was consistent with Hypothesis 1a. The individual main effect of Bouts Ratio on abstraction withstood correction for multiple comparisons, but the difference between the main effect of Bouts Ratio and that of the Total PA factor on abstraction did not. This suggests that the stronger relationship between Bouts Ratio and abstraction may be spurious, as it would be unlikely that spending more time engaging in each bout of MVPA would be more important than the cumulative contribution of being active.

The Total PA factor did not reliably differ from any other individual PA parameters in the strength of the associations with any other cognitive scores (i.e., the exploratory EF factor, working memory, inhibitory control, or processing speed; all *p*-values $\geq$ 0.200). There was a significant interaction between average METs and age on working memory that withstood correction for multiple comparisons (see Table 10) but did not significantly differ from the nonsignificant interaction between the Total PA factor and age. This again indicates that a PA index may not be necessary to use when determining the relationship between PA engagement and cognitive functioning. Further, these nonsignificant relationships indicate that total PA engagement, as measured by the factor score or individual PA parameters, was not associated with EF in this midlife sample.

3.4.4.3 Individual Physical Activity Parameters

Finally, to address Hypothesis 1c (that individual PA parameters would differ in their associations with EF and EF subdomains), the partial correlations between a given PA parameter and a cognitive factor score were compared with the partial correlations between all other PA parameters and that same cognitive factor score, then corrected for multiple comparisons using FDR. Since the volume of activity was defined in two distinct ways (i.e., MVPA minutes versus total PA minutes), regression models with individual PA parameters as the variable of interest were analyzed after controlling for MVPA minutes and again after controlling for total PA minutes, in addition to controlling for the remaining individual PA parameters (i.e., METs, measured AEE, Bouts Ratio). Comparison of the associations between EF and individual PA parameters revealed several significant differences, though only for the abstraction component score. Only significant associations that withstood correction for multiple comparisons using FDR

are discussed, though all relationships between individual PA parameters and EF/EF subdomains can be found in Tables 8 and 10.

3.4.4.3.1 Working Memory

As previously described, average METs (after controlling for MVPA minutes or total PA minutes) and MVPA minutes demonstrated significant interactions with age on working memory scores. However, these interactions did not differ from any other (nonsignificant) interactions between individual PA parameters and age. No other PA parameters showed significant main effects or interaction effects on working memory, regardless of which parameter was used as the variable of interest. None of these associations were statistically different from any other, indicating that no individual PA parameter was related to working memory or was different in its relationship with working memory than any other PA parameter.

3.4.4.3.2 Inhibitory Control

No individual PA parameters were significantly different from one another and survived correction for multiple comparisons on inhibitory control. This indicates that individual PA parameters were not related to inhibitory control component scores, nor was any one parameter more closely related to this EF subdomain than any other parameter.

3.4.4.3.3 Abstraction

After controlling for MVPA minutes, the individual Bouts Ratio variable demonstrated a significantly different main effect on the abstraction component than average daily METs (Fisher's $z = 3.51$, $p < 0.001$) or measured AEE (Fisher's $z = 4.23$, $p < 0.001$). After controlling for total PA minutes, Bouts Ratio similarly showed a significantly different main effect on abstraction only compared with measured AEE (Fisher's $z = 3.29$, $p = 0.001$) (see Tables 8, 10). In all models, higher Bouts Ratios were associated with better abstraction scores (all $\beta \geq 0.199$, all p-values ≤ 0.007), which was consistent with Hypothesis 1a that greater PA engagement is related to better EF. However, this contrasted with the hypothesis that the intensity of activity would be more strongly related to EF than the pattern of activity (Hypothesis 1c). Higher Bouts Ratios being associated with better abstraction component scores indicates that spending more time in each MVPA bout may be better for abstract reasoning skills than increasing the intensity of activity. That is, once an individual has achieved at least moderate intensity PA, they may achieve greater benefits to abstraction by spending more time in each bout of activity than if they were to work harder (i.e., beyond a moderate intensity level).

Additionally, greater measured AEE demonstrated a stronger main effect association with abstraction than MVPA minutes (Fisher's $z = 3.26$, $p = 0.001$), which was only trending in its association. Unexpectedly, greater measured AEE was associated with poorer abstraction after controlling for MVPA minutes ($\beta = -0.348$, $p = 0.012$), which was inconsistent with the hypothesis that greater PA engagement would be associated with better EF (see Table 8). It was, however, consistent with the explanation described above that there was no added benefit to abstraction by expending more energy, possibly through higher intensity activity. Despite only trending in

significance, more accumulated MVPA minutes were associated with better abstraction component scores ($\beta = 0.274$, $p = 0.062$), which contrasted with the negative relationship between measured AEE and abstraction. All of these significant differences between associations withstood correction for multiple comparisons. Taken together, these findings indicate that more time spent engaging in bouts of moderate intensity activity was related to better abstraction, while increasing PA intensity was not beneficial.

3.4.4.3.4 Processing Speed

No individual PA parameters demonstrated significant main or interaction effects on processing speed, regardless of which parameter was used as the variable of interest. None of these associations were statistically different from any other, indicating that no individual PA parameter was related to processing speed or was different in its relationship with processing speed than any other PA parameter.

Details about supplementary analyses conducted can be found in the Appendix.

4.0 Discussion

This study examined the relationships between PA and EF in a well-characterized, healthy midlife sample – an age group infrequently studied in the context of PA and cognitive functioning. There were several gaps in the literature that the study aimed to address. First, few studies investigated the combined effect of multiple PA parameters on EF through the use of a latent PA factor. This study utilized objectively measured PA and neuropsychological tests to create factor scores of PA and EF, which reduced measurement error and leveraged the shared variance of the individual variables to better understand the hypothesized relationships between PA engagement and cognitive functioning at the domain level. Capturing the constructs of PA and EF (and EF subdomains) through factor scores permitted exploratory analyses to probe these possible relationships more extensively than in previously published literature, particularly in a midlife sample. Second, there was limited understanding of how PA intensity and pattern of activity were uniquely related to EF. This study determined that distinct PA parameters did not substantially differ in their associations with EF relative to the composite PA factors. Finally, the potentially moderating effects of age and sex on the relationships between PA and EF during midlife were previously unknown. This study found limited evidence to suggest that age or sex were relevant to any association between PA and EF in midlife.

4.1 Physical Activity Factors

The first goal of this study was to develop a PA index to capture multiple features of PA within one score. Two factors were derived using the absolute MET thresholds for activity intensity: one that included the volume of MVPA minutes and one that included the total volume of all active minutes. These two factors were derived to compare the potential contribution of MVPA against total activity on EF. All included variables loaded onto the respective factors, although to varying degrees. Measured AEE and Bouts Ratio loaded similarly onto the MVPA and Total PA factors, but average daily METs and the volume of accumulated PA minutes demonstrated different patterns in their factor loadings. The average METs loading onto the Total PA factor was stronger than onto the MVPA factor, indicating that the intensity of activity contributed more to the Total PA factor – perhaps because the total accumulation of PA minutes was the weakest variable loading onto the Total PA factor. In contrast, MVPA minutes was the strongest variable loading on the MVPA factor. Together with the stronger METs loading on the Total PA factor, this suggests that measurements of higher intensity activity formed a more unidimensional construct of PA in this sample. Notably, only the MVPA factor achieved good internal reliability, suggesting that the MVPA factor represented a unidimensional PA construct while the Total PA factor did not.

On a statistical level, the MVPA factor was a more representative latent factor of PA engagement than the Total PA factor. The MVPA factor explained more of the shared variance between variables, it demonstrated stronger factor loadings for most of the included PA metrics, it achieved a higher eigenvalue, and it achieved higher internal reliability when compared with the Total PA factor. The only difference between these factors was the inclusion of MVPA versus total PA minutes and, critically, the only significant associations with any cognitive factors were

with the MVPA factor. Taken together, these indicate that MVPA was more strongly associated with EF than any, or total, PA. In fact, a recent meta-analysis demonstrated that moderate intensity exercise in healthy older adults yielded significant improvements in EF when comparing intensities (i.e., light, moderate, high) of aerobic interventions (Sanders, Hortobágyi, la Bastide-van Gemert, van der Zee, & van Heuvelen, 2019). This suggests that there is something uniquely beneficial about achieving moderate intensity during exercise with regard to EF, as high intensity activity did not yield the same improvements. The present results suggest that midlife adults should aim to achieve moderate intensity PA, which was associated with better abstraction, since higher AEE (i.e., greater energy expenditure indicating more vigorous activity) did not demonstrate added benefits. Most adults achieve little high or vigorous intensity PA in everyday life (Berkemeyer et al., 2016; Troiano et al., 2008), which was also true of the current study sample. PA prescriptions that focus on activities to achieve a moderate intensity, such as taking a brisk walk, may be the most effective and attainable in preserving EF abilities during midlife.

Despite the MVPA factor likely being a better representation of overall PA engagement, the Total PA factor was important to examine in this study due to recent evidence showing the contributions of light PA to positive health outcomes. In the past decade, light PA has been linked to lower cardiometabolic risk, including lower BMI, diastolic BP, and insulin resistance, in addition to lower rates of chronic disease (Chastin et al., 2019; Loprinzi, 2015; Loprinzi et al., 2013; Riou et al., 2014). However, there is little evidence that light PA enhances, or is even related to, cognitive functioning. While most evidence suggests that any activity is better for cognitive functioning than sedentary behavior, testing the effects of light PA is difficult because light PA should not substantially engage the aerobic system. A recent meta-analysis of PA interventions found that increasing light PA improved working memory task performance, though with several

caveats (Rathore & Lom, 2017). First, only one of 15 interventions utilized a chronic, light PA intervention. Second, the authors transformed the data to create three intensity groups (i.e., light, moderate, and high), which they noted may have skewed their results because it led to the categorization of five light PA interventions, including non-aerobic activities such as yoga or Tai Chi. Finally, the light PA interventions included only participants aged at least 55 years. With the sample for the current study including adults aged between 30-55 years, it is possible that the results of this meta-analysis do not extend to younger adults. Even in samples of older adults, light PA is often unrelated to cognitive functioning. All objectively measured PA with accelerometry was not associated with EF in a cross-sectional study of 136 postmenopausal breast cancer survivors (Marinac et al., 2015), nor was it associated with changes in EF over approximately three years in 6,452 older adults in an epidemiological cohort study (W. Zhu et al., 2017). Together, the evidence is limited that light PA adds to the relative contribution of MVPA in the context of EF. Instead, it is possible that combining light PA with MVPA dilutes the benefits of MVPA on cognitive functioning. The current study corroborated these findings in a younger sample, suggesting that habitual, objectively monitored total PA engagement was not associated with EF in midlife.

4.2 Executive Functioning Factors

4.2.1 Exploratory Factor

To capture EF, reduce measurement error, and leverage shared variance, an exploratory factor analysis determined whether the neuropsychological measures in this study represented one

underlying construct or several subdomains of EF. Only one latent factor was derived from the six neuropsychological measures used to quantify EF. This solitary factor corroborated the theory that there is a general EF process underlying the more specific executive processes thought to be represented by each task or task condition (i.e., working memory, inhibitory control, abstraction) (Friedman & Miyake, 2017; Miyake et al., 2000). Each of the included EF measures were closely related and shared sufficient variance to represent the latent EF factor, which was consistent with past research (Baddeley & Della Sala, 1996; Miyake et al., 2000). Further, several iterations of this exploratory factor analysis (described in the Appendix) did not reveal different patterns of variable loadings. Instead, the inclusion of additional subtests often resulted in latent factors that emerged from entire neuropsychological measures, indicating that all conditions of one task loaded together (e.g., Stroop Color, Word, CW, and Interference onto one Stroop task factor). The internal reliability for this exploratory factor was adequate and did not demonstrate any significant associations with the PA factors, indicating that overall EF was not related to PA in this midlife sample. While the presence of just one EF factor did not contradict this study's hypotheses, it precluded further investigation into exploratory subdomains of EF and their potential relationships with PA.

The sole emergent exploratory factor might also represent the limitations of the neuropsychological tasks that were available to measure EF. While clinically useful, some conventional neuropsychological measures may lack the sensitivity needed to detect subtle differences in cognitive abilities as a function of PA. For example, the Digit Span subtest of the WAIS utilizes two conditions that each are scored between a finite range of 0-16 (Wechsler, 1997a). All other Wechsler subtests included in this study were also somewhat constrained by their ranges of attainable scores. With four of six measures utilizing a confined range of scores, it is

possible that there was insufficient variability in these EF variables to detect subtle relationships with PA. Additional description of this possible explanation for the current results will be discussed in the section titled *Neuropsychological Considerations*.

These limitations of conventional neuropsychological measures have led to the development of cognitive tasks and packages that are more sensitive to subtle differences between participants, such as the NIH Toolbox (Zelazo et al., 2013) or the Virginia Cognitive Aging Project test battery. The subtests of these batteries rely more heavily on processing and psychomotor speed, which have considerably more variability than simply considering whether a response was correct or incorrect. Only two of the EF measures in this study had scores dependent on time with considerable variability in achievable times. For example, one participant may have taken 63.42 seconds to complete TMT-B, while another took 62.57 seconds, and another took 43.10 seconds. With time-dependent scoring, subtle differences can be detected more easily than scoring solely based on correct responses. Additional EF measures being time-dependent might have been increased variability of factor scores that may have been more accurate representations of participants' abilities. These newer experimental measures should be applied more broadly to determine their clinical applicability and extend possible associations with modifiable protective and risk factors.

4.2.2 Confirmatory Components

Another goal of the current study was to understand whether PA had different associations with EF subdomains, which would suggest that certain cognitive processes may be uniquely sensitive to this healthy lifestyle behavior. Since the exploratory factor analysis resulted in only one latent EF factor, confirmatory PCA were used to test theoretical distinctions with the EF

subdomains of working memory, inhibitory control, and abstraction. Given the dependency of many of these cognitive processes on processing speed, processing speed was also included as a component of interest. These secondary analyses investigated whether subdomains of EF were differently related to PA engagement, since little work has explored these relationships in the context of cognitive factors.

The components were derived from theory and previously published work using the same sample (Marsland et al., 2015), then tested with data-driven approaches to determine their internal reliability. The working memory, inhibitory control, and processing speed components achieved acceptable to good internal reliability, indicating that these components likely represented their respective cognitive processes. This was expected, as these subtests have been widely used to capture each respective cognitive component. In contrast, the abstraction component achieved poor internal reliability, indicating that the Matrix Reasoning and Similarities subtests were unlikely to represent a unidimensional construct when combined. Although both subtests rely on abstract reasoning skills, they are not often grouped together when considering latent factors of the WASI (Ryan et al., 2003; Sharratt, Boduszek, & Retzler, 2020). Therefore, is possible that abstraction as a cognitive construct was not particularly sensitive, as it is difficult to test. Matrix Reasoning and Similarities additionally rely on other cognitive processes more than some of the other EF tests used in this study. In addition to abstraction, Matrix Reasoning required visuospatial processing and mental flexibility; Similarities also required auditory-verbal processing and vocabulary knowledge for each of the presented words. Therefore, it is possible that these two subtests were actually measuring disparate cognitive processes more than they measured a shared, underlying process.

4.3 Aim 1: Does Physical Activity Modulate Executive Functioning?

4.3.1 Hypothesis 1a

4.3.1.1 Exploratory Executive Functioning Factor

The first aim of this study was to determine whether PA was associated with EF in a healthy midlife sample. Hypothesis 1a stated that greater PA engagement, as measured by a latent factor score, would be associated with higher EF factor scores. Overall, there were no statistically significant associations between the exploratory EF factor and either PA factor. Although there was a trending negative association between higher MVPA factor scores and poorer EF, it contrasted with the hypotheses and the published literature, where most work has shown positive relationships between greater PA engagement and better EF (Cox et al., 2016; de Greeff et al., 2018; Groot et al., 2016; Kramer & Colcombe, 2018). Together, these results suggest that activity levels captured by a PA factor were unrelated to EF in a midlife sample.

This aim tested the presence of an underlying general EF process, but there are specific subdomains of EF that may not be equivalently sensitive to the effects of PA. Certain subdomains, such as inhibitory control, have been shown to be more sensitive to health and decline earlier in life than others (Diamond, 2013). Considering the possible differences between subdomains in their associations with EF, these relationships were probed further using EF subdomain component scores.

4.3.1.2 Cognitive Components

4.3.1.2.1 Inhibitory Control

In contrast with the hypothesis that greater PA would be associated with better EF, higher MVPA factor scores were associated with poorer inhibitory control after accounting for relevant demographic and health covariates and possible interaction effects. This finding also contradicted some of the published evidence to date. In children and older adults, increased PA is often associated with better inhibitory control (Alvarez-Bueno et al., 2017; Guiney & Machado, 2012); however, the evidence is mixed for younger and midlife adults. Meta-analytic findings suggest that the overall benefit of PA on inhibitory control is smaller in young adult and midlife samples relative to children or older adult samples (Alvarez-Bueno et al., 2017; Cox et al., 2016; Kelly et al., 2014). The current results corroborated a small effect size in the relationship between PA and inhibitory control, although the effect itself contradicted any benefit of PA engagement. Possible reasons for this unexpected effect are discussed in the section titled *Possible Mechanistic Explanations*. Additionally, the Total PA factor was not associated with inhibitory control in this sample, which suggests that only higher intensity activity is important for inhibitory control, rather than all activity.

4.3.1.2.2 Working Memory, Abstraction, and Processing Speed

In contrast to the hypothesis that greater PA engagement would be associated with better EF, there were no significant main effects of either PA factor on working memory, abstraction, or

processing speed component scores. The inconsistent relationships between PA and these EF subdomains suggests some specificity in the cognitive processes in their associations with PA. Additional explanation of these inconsistencies is described in the sections titled *Possible Mechanistic Explanations* and *Neuropsychological Considerations*.

4.3.2 Hypothesis 1b: Comparison of Physical Activity Factors Versus Individual Parameters

4.3.2.1 Exploratory Executive Functioning Factor

This study aimed to investigate whether a PA index could better explain some of the variance in EF abilities when compared with individual PA parameters. In contrast to the hypothesis that a latent factor of PA would be related to EF, neither PA factor nor any of the individual PA parameters demonstrated significantly different associations with the exploratory EF factor.

4.3.2.2 Cognitive Components

4.3.2.2.1 Inhibitory Control

Comparisons were made between associations between EF subdomains and latent scores of PA versus individual parameters of PA to determine whether a PA index could better explain the variance in EF abilities. The main effect between inhibitory control and the MVPA factor was significantly stronger than with average METs, which was not related to inhibitory control.

Although the effect was opposite of what was hypothesized in Hypothesis 1a, using a PA factor was a stronger predictor of inhibitory control than average intensity alone.

4.3.2.2.2 Abstraction

In contrast with Hypothesis 1b that a PA factor score would be more closely related to EF than any individual parameter, measured AEE demonstrated a stronger main effect association on abstraction than the MVPA factor. Greater measured AEE was associated with poorer abstraction, which also contrasted with Hypothesis 1a. Measured AEE may have been more closely related to this EF subdomain due to its increased specificity relative to a PA factor score. Since AEE was calculated based on age, gender, and weight, it may have been more sensitive to subtle differences between participants than the other parameters. As it was a direct calculation of energy expenditure while engaging in at least moderate intensity activity, this metric likely had more variability than any of the other PA parameters evaluated. It demonstrated a much wider range of values than any other PA variable, likely due to its measurement scale (i.e., kilocalories) rather than a finite scale, such as minutes per day.

4.3.2.2.3 Working Memory and Processing Speed

In contrast with Hypothesis 1b, which stated that the PA factor scores would be more strongly associated with EF than any individual parameter, there were no significant differences in any relationships between the MVPA or Total PA factor and working memory or processing

speed. Further, no individual PA parameters demonstrated significant main effects on either of these EF subdomains.

In summary, some individual parameters differed in their associations with the inhibitory control and abstraction components compared with either PA factor, although not in consistent patterns. Specifically, the MVPA factor was more closely related to inhibitory control relative to average daily METs but measured AEE was more closely related to abstraction relative to the MVPA factor. This suggests that it may not be necessary to create a PA index to evaluate relationships with EF and EF subdomains, as the MVPA factor was not consistently associated more strongly with any EF factor compared to any individual PA parameters. It also may not matter which PA parameter is used to estimate PA engagement, as no one parameter had reliably different associations with EF than the PA factors. Notably, the bulk of significant or marginally significant associations were between EF and the MVPA factor, and any significant relationships with individual PA parameters were those that depended on MVPA engagement (i.e., measured AEE, Bouts Ratio). This provides additional evidence that moderate intensity PA is uniquely related to EF, at least in midlife, and ensuring that individuals achieve this intensity of activity may be more important than the exact measurement used. Thus, objectively measuring PA in the most feasible capacity for a given study may be sufficient for testing associations with EF.

4.3.3 Hypothesis 1c: Comparison of Individual Physical Activity Parameters

4.3.3.1 Exploratory Executive Functioning Factor

In contrast with the hypothesis that individual PA parameters would differ in their associations with the exploratory EF factor, no individual parameters were significantly related to

the factor, nor were they different from one another. These results were consistent with the nonsignificant relationships between the exploratory EF factor and the PA factor scores.

4.3.3.2 Cognitive Components

4.3.3.2.1 Abstraction

In line with Hypothesis 1c, several individual PA parameters demonstrated significantly different main effects on the abstraction component score from other parameters that withstood correction for multiple comparisons. Specifically, measured AEE and Bouts Ratio showed significantly different and contradictory effects. As described above, measured AEE may have been more sensitive to subtle differences than the other parameters due to the additional demographic factors considered in its calculation. The associations with Bouts Ratio may simply reflect that spending more time in each MVPA bout was more closely related to abstraction than the total accumulation of PA or average intensity of PA. The critical feature these two parameters share was that they were only measured once a participant achieved at least moderate intensity activity. However, the same pattern of association was not observed with the MVPA minutes parameter. That nonsignificant relationship may indicate that the total volume of MVPA does not matter, but the length of time spent in each MVPA bout does. Longer MVPA bouts likely reflect more intentional exercise, suggesting that short spurts of activity may be insufficient to affect abstraction. Significant associations may not have been observed with average daily METs because that variable accounts for sedentary time, which might have captured too broad of a set of behaviors to have specific associations with EF.

The contradictory patterns in the relationships between measured AEE and Bouts Ratio with abstraction suggest that spending a longer period of time engaging in each bout of activity may be more beneficial than the amount of energy expended. Since both the measured AEE and Bouts Ratio parameters only evaluate energy and/or time while engaging in MVPA, the current results indicate that longer, moderate intensity activity may be more beneficial for abstraction than shorter, higher intensity bouts of activity.

Evidence suggests that spending more continuous time in moderate intensity activity is associated with better cardiometabolic outcomes (LaMonte et al., 2017; Liou et al., 2016) and that there may be little added benefit of engaging in PA at higher intensities than moderate (Curtis et al., 2017; Humphreys et al., 2014; D. H. Lee et al., 2019). The current results show potential that similar effects may be at play in the context of abstract reasoning abilities. In spite of the nonsignificant relationship between the MVPA factor and abstraction component scores, the significant associations with individual parameters dependent on MVPA show that both PA intensity and duration have important contributions to this EF subdomain. This study was the first to demonstrate that increased time spent in MVPA bouts at an PA intensity closer to moderate was associated with better abstraction. It suggests that longer periods of moderate intensity activity may be best for abstract reasoning abilities, which can inform PA as a prescription for maintaining cognitive functioning.

4.3.3.2.2 Working Memory, Inhibitory Control, and Processing Speed

No other individual PA parameters demonstrated significantly different main effects on any other EF subdomain than the other parameters that withstood correction for multiple

comparisons. Together, the differences in the relationships between individual parameters and EF suggest a small degree of specificity. That is, more time spent in moderate intensity activity may be beneficial to abstract reasoning, but no other distinct ways of measuring PA are more useful than any other with regard to working memory, inhibitory control, processing speed, or overall EF.

4.4 Aim 2: Moderating Effects of Age and Sex

Aim 2 examined whether age or sex moderated the relationship between PA and EF during midlife. It was hypothesized that older age would be associated with less PA engagement and poorer EF task performance (Hypothesis 2a). It was also hypothesized that males engaging in the least PA would have lower EF scores than females and that females engaging in the most PA would have the highest EF scores (Hypothesis 2b).

4.4.1 Hypothesis 2a: Age as a Moderator

In contrast with Hypothesis 2a, age did not interact with PA factor scores on overall EF, inhibitory control, abstraction, or processing speed. Instead, age only interacted with the MVPA factor score on working memory performance. In line with previous evidence, greater PA engagement was associated with better working memory component scores only for the oldest participants in the sample (i.e., 51-55 years old). However, this PA x age interaction was only trending in significance after correcting for multiple comparisons. Notably, it was the only significant relationship in this sample that was consistent with the hypotheses and literature,

although the effect was small and did not withstand correction for multiple comparisons. The Total PA factor also showed a PA x age interaction on working memory, although the effect was smaller than with the MVPA factor and also did not withstand statistical correction for multiple comparisons. Some of the individual PA parameters (i.e., METs, MVPA minutes) showed similar interactions with age on working memory, but none were significantly different from the interaction with the MVPA factor. This indicates that the magnitude of the association between working memory and PA did not vary based on the parameter used to quantify PA.

The pattern of the PA x age interaction on working memory highlights the importance of activity during the aging process, given that the effect of the MVPA factor was only significant for the oldest participants in this sample. Despite being only marginally significant after statistical correction, this suggests that achieving at least moderate intensity activity is more important for working memory task performance than the cumulative effect of all PA, including light intensity activity. The current results suggest that there might be an inflection point in late middle age when working memory begins to decline, and the importance of habitual PA becomes more apparent. This may be a time in life when the brain begins to undergo greater losses in volume and function and PA may be able to mitigate some of these age-related losses (Guiney & Machado, 2012; Hillman et al., 2008; Kramer & Erickson, 2007), which could allow older adults to reap greater benefits of PA than younger adults. Various factors can accelerate or mitigate age-related declines in brain health and cognitive functioning, including genetic factors or lifestyle factors (Erickson, Hillman, & Kramer, 2015; Leckie, Weinstein, Hodzic, & Erickson, 2012). Thus, as brain health declines, there may be more opportunity to attenuate changes by increasing engagement in beneficial lifestyle behaviors, such as PA. There is evidence that younger adults do not show the same cognitive or brain benefits from engaging in PA compared to older adults (Guiney &

Machado, 2012). This might suggest that there are limitations to which groups or age ranges might benefit from PA. Possible mechanisms explaining this effect are described below under the section titled *Possible Mechanistic Explanations*.

The MVPA factor x age interaction on working memory was only evident for participants engaging in the lowest amount of PA. Participants engaging in the most PA had similar working memory component scores, regardless of age, suggesting that greater PA engagement later in life might be able to mitigate some of the age-related declines in working memory. This was consistent with a recent meta-analysis that demonstrated a small but significant positive effect of eight PA interventions to improve working memory abilities (Rathore & Lom, 2017). Further, the meta-analysis revealed a significant moderation by age, such that working memory performance improved to a greater extent as participants' age increased. The results of the current study are in line with those findings, which suggest that engaging in higher levels of PA may slow age-related decline in working memory performance. Since maintaining working memory abilities during aging has important implications for preserving independence (Diamond, 2013), this MVPA factor x age interaction indicates that a modifiable lifestyle behavior has the potential to prevent or delay some cognitive impairments, thereby sustaining quality of life as long as possible.

4.4.2 Hypothesis 2b: Sex as a Moderator

In contrast with Hypothesis 2b, sex did not moderate any effect of the PA factor scores on overall EF, working memory, inhibitory control, abstraction, or processing speed after correcting for multiple comparisons. Although prior evidence suggests that sex may moderate the benefits of PA on cognitive functioning (Barha, Hsiung, et al., 2017; Liu-Ambrose et al., 2018), this cross-

sectional study of midlife adults did not reveal sex differences in the associations between PA and EF.

4.5 Possible Mechanistic Explanations

4.5.1 Physiological Benefits of Physical Activity on Cognitive Functioning

4.5.1.1 Central Mechanisms

The benefits of PA may influence cognitive functioning through central and peripheral mechanisms. At present, PA is a leading non-pharmacologic treatment to maintain, or improve, brain health across the lifespan. There are direct physiological effects of PA engagement on the brain, which have downstream benefits on cognitive functioning. One such mechanism is through neurotrophic factor release, where greater PA engagement is associated with greater central and peripheral levels of BDNF (Cotman et al., 2007; Dishman et al., 2006; Ratey & Loehr, 2011; Yang, Lin, Chuang, Bohr, & Mattson, 2014). Mouse models show that four weeks of aerobic PA training can increase central BDNF expression (Almeida et al., 2015), which has downstream neurological benefits. In humans, greater PA engagement is associated with heightened levels of circulating BDNF (Ratey & Loehr, 2011) and increasing PA through RCTs increases circulating BDNF (Jimenez-Maldonado, Renteria, Garcia-Suarez, Moncada-Jimenez, & Freire-Royes, 2018). Heightened neurotrophic factor expression, including BDNF, promotes neurogenesis that improves brain integrity, which can increase capacity for LTP (Cotman & Engesser-Cesar, 2002; Ma, 2008) and benefit cognitive functioning.

Greater PA engagement is also directly related to angiogenesis and greater cerebral blood flow (Chieffi et al., 2017). Engaging in longer bouts of MVPA is associated with increased CRF (Warburton et al., 2006), and higher CRF is associated with more efficient resting CBF (Brown et al., 2010; Nishijima, Torres-Aleman, & Soya, 2016). Since better cerebrovascular functioning is associated with better cognitive functioning (Lucas et al., 2012), it is possible that greater PA engagement is associated with cognition via cerebrovascular health. A randomized crossover trial demonstrated that breaking up sedentary time with a longer (i.e., 30 minutes) bout of moderate intensity activity acutely improved middle cerebral artery functioning, while remaining sedentary or taking several three-minute, light PA breaks did not (Wheeler et al., 2019). Better cerebrovascular perfusion further reduces the risk of future cerebrovascular disease (Tarumi & Zhang, 2018), limiting the potential burden of cognitive impairment later in life.

Greater PA engagement is also associated with increased brain volume, specifically in frontal and temporal regions critical for EF (Arnardottir et al., 2016; Dougherty et al., 2016; Erickson, Leckie, & Weinstein, 2014; Radak et al., 2010). For example, in mid- and late-life adults aged between 50-78 years, higher self-reported PA engagement was associated with larger regional gray matter spanning most of the PFC, anterior and posterior cingulate cortices, occipitotemporal area, and cerebellum (Floel et al., 2010). Longitudinal studies suggest that greater PA engagement earlier in life is associated with greater total and regional brain volume at least three years later, particularly in areas critical for EF and memory (Arnardottir et al., 2016; Erickson et al., 2010; Hautasaari et al., 2017; Tan et al., 2017). RCTs in older adults and children provide causal evidence that increasing aerobic PA can increase the volume or mitigate the age-related deterioration of specific brain regions including the previously described areas of the PFC and hippocampus (Donnelly et al., 2016; Gomez-Pinilla & Hillman, 2013). These regions are particularly sensitive

to cerebrovascular and neurotrophic changes (Cotman et al., 2007; Dishman et al., 2006), which are influenced by engagement in PA. Thus, PA may promote healthy brain aging through increasing gray matter volume or at least mitigating gray matter atrophy (Adlard & Cotman, 2004; Wang & Holsinger, 2018). By reducing atrophy, PA may also reduce the risk of future cognitive impairment, particularly for the cognitive domains linked to the aforementioned brain regions (i.e., EF, attention, memory). Still, some studies fail to show associations between PA engagement and total or regional gray matter volume (Ho et al., 2011; Niemann, Godde, & Voelcker-Rehage, 2016), indicating that other factors may moderate or mediate these relationships.

4.5.1.2 Peripheral Mechanisms

PA may influence cognitive functioning by acting through peripheral effects that, in turn, influence the brain. Current understanding about these indirect effects is limited and it is likely that multiple central and peripheral mechanisms work in tandem to produce the neural and cognitive benefits of PA. Engaging in PA reduces BP, insulin sensitivity, and systemic inflammation, all of which are related to better brain health (Kubota et al., 2017; Sattelmair et al., 2011; Zhang et al., 2017). Additional discussion of these peripheral mechanisms is described below.

4.5.1.2.1 Blood Pressure

BP is one modifiable risk factor that may explain the relationship between PA and cognitive functioning. Numerous meta-analyses indicate that PA RCTs can reduce BP across individuals who are normotensive, pre-hypertensive, or hypertensive (Cornelissen & Smart, 2013;

Costa et al., 2018; X. Liu et al., 2017; Murtagh et al., 2015; Sosner et al., 2017). BP acutely increases during PA engagement (Kim & Ha, 2016), followed by post-exercise hypotension that is directly related to the intensity and duration of PA (Romero, Minson, & Halliwill, 2017; Sabbahi, Arena, Elokda, & Phillips, 2016). Post-exercise hypotension is strongly correlated with chronic reductions in BP following habitual PA (S. Liu, Goodman, Nolan, Lacombe, & Thomas, 2012) due to changes in vascular structure and function, including reduction of excess, deleterious enzymes and improving arterial compliance (Adams et al., 2005; Sabbahi et al., 2016). If left untreated, elevated systolic BP can reduce cerebral perfusion through acceleration of the progression of cerebral atherosclerosis through vessel remodeling (Baumbach & Heistad, 1989; Laurent & Boutouyrie, 2015; Meissner, 2016). This then reduces the availability of nutrients, glucose, and oxygen that are needed for the brain to support structural integrity and cognitive functioning.

In support of this, numerous reviews and meta-analyses have revealed that higher BP is associated with poorer EF, attention, and global cognition, while memory, language, and visuospatial processing remain largely intact (Birns & Kalra, 2009; Iadecola & Gottesman, 2019; Iadecola et al., 2016). Observational longitudinal studies also suggest that higher midlife BP is associated with poorer later-life cognitive functioning (Gorelick et al., 2012; Hughes & Sink, 2016). By contrast, reviews and meta-analyses have indicated that pharmacological RCTs reducing BP demonstrate nonsignificant, or very small, improvements to EF, processing speed, memory, and global cognition (Birns, Morris, Donaldson, & Kalra, 2006; Iadecola & Gottesman, 2019; McGuinness, Todd, Passmore, & Bullock, 2009; Zanchetti et al., 2014). Although PA RCTs have not yet investigated whether reducing BP is causally linked with improving cognitive functioning, BP remains a plausible mechanism by which PA might promote cognition.

4.5.1.2.2 Insulin Sensitivity

Greater PA engagement is associated with better insulin sensitivity, which is a marker for metabolic health (Conn et al., 2014). PA interventions demonstrate improvements in insulin sensitivity (Conn et al., 2014; Roberts, Little, & Thyfault, 2013; Troiano et al., 2008), with some studies showing a dose-response effect of exercise with higher intensity and greater energy expenditure resulting in greater benefits (Bird & Hawley, 2016; Helmrich, Ragland, Leung, & Paffenbarger, 1991). Poor insulin sensitivity and subsequent hyperglycemia are associated with slowed processing speed and impaired EF, learning, and memory (Bruehl, Sweat, Hassenstab, Polyakov, & Convit, 2010; Cholerton, Baker, & Craft, 2013; McCrimmon, Ryan, & Frier, 2012), suggesting some cognitive domain specificity to these effects. Longer duration and greater severity of metabolic dysfunction are directly related to poorer cognitive abilities (Kloppenborg, van den Berg, Kappelle, & Biessels, 2008), which may be due to poorer white matter integrity, heightened white matter lesion load, and/or lower prefrontal gray matter volume in adults with insulin resistance relative to healthy adults (Kloppenborg et al., 2008; McCrimmon et al., 2012). Each of these markers of poor brain health have direct effects on worsening cognitive dysfunction. Increasing PA engagement can improve insulin sensitivity, which has downstream cellular and molecular effects on brain health (Cotman et al., 2007) and potentially restore cognitive abilities. Further, insulin sensitivity is related to inflammatory markers that may permeate the blood-brain-barrier (BBB) (Gleeson et al., 2011; Nguyen, Killcross, & Jenkins, 2014), providing another route through which PA might influence cognitive functioning.

4.5.1.2.3 Inflammation

Engaging in PA can help to regulate inflammation both in the brain and in the periphery (Cotman et al., 2007), which has downstream benefits on cognitive functioning (Ratey & Loehr, 2011). Habitual PA engagement is associated with lower levels of peripheral pro-inflammatory cytokines (i.e., CRP, interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α)) (Stranahan, Martin, & Maudsley, 2012; Tegeler et al., 2016). Circulating inflammatory markers have direct effects on the brain by permeating the BBB, with greater inflammation being associated with reduced brain volume and cortical thickness in regions of the prefrontal cortex, hippocampal formation, and cingulate cortex in middle-aged and older adults (Arfanakis et al., 2013; Braskie et al., 2014; Marsland, Gianaros, Abramowitch, Manuck, & Hariri, 2008). Systemic inflammation (i.e., higher levels of circulating pro-inflammatory cytokines) is associated with poorer EF (Tegeler et al., 2016), processing speed (Trollor et al., 2012), and visuospatial abilities (Arfanakis et al., 2013) in older adults. Together, these findings indicate that systemic inflammation may have domain-specific effects on cognitive deficits. Previously published work using the AHAB-II sample indicated that total and cortical gray matter volumes mediated the relationship between inflammatory markers and EF (Marsland et al., 2015), suggesting that this pathway is a promising target for PA to benefit cognitive functioning. Given that PA engagement has been linked with improvements in EF and processing speed (Cox et al., 2016; Etnier, Drollette, & Slutsky, 2019), it is possible that greater PA engagement could benefit these cognitive domains by reducing inflammation.

4.5.2 Age Considerations

The previously described physiological mechanisms that link PA engagement with cognitive functioning may not be as effective in young, healthy samples, which could explain the overall nonsignificant relationship between PA and EF in the current study. Studies examining the mechanistic underpinnings of the relationship between PA and cognitive functioning demonstrate significantly stronger associations in unhealthy populations, such as those with hypertension, diabetes, MCI, or dementia. It is possible that cognitive associations with PA are more robust and/or detectable when the brain is particularly sensitive – either due to age or disease. Most evidence to date on the relationship between PA and cognitive functioning has focused on children or older adults. These populations are in developmentally sensitive periods, with children undergoing neurological growth and older adults experiencing age-related atrophy. While some work has demonstrated that healthy lifestyle factors are linked with better cognition in young and middle-aged adults, the bulk of the work in this area focuses on CRF, rather than habitual PA engagement (Belsky et al., 2015; Raichlen, Klimentidis, Bharadwaj, & Alexander, 2019; Tarumi et al., 2013). This suggests that there may not be detectable associations between habitual PA and cognitive functioning during young adulthood and midlife. Perhaps there is an increased need for neuroplasticity related to age or disease pathology that allows the benefits of PA to become apparent in cognition. Thus, in a younger, healthy sample, strong associations between PA engagement and EF do not exist. Instead, there may be a critical age range in which cognitive decline begins and PA engagement becomes more important and effective.

Another possibility is that healthy midlife adults are too close to their cognitive 'peak' for PA engagement to modify their EF abilities. While some cognitive abilities begin to decline as early as the fourth decade of life, such as memory (Salthouse, 1996; Verhaeghen & Salthouse,

1997), other abilities do not show the same deterioration until much later. EF is one such domain that, although also sensitive to cardiometabolic health, does not show significant decline until later in life (Diamond, 2013; Jurado & Rosselli, 2007). A basic assumption of cognitive research is that each individual has an inherent maximum ability level that cannot be exceeded regardless of modifications to lifestyle. If this were not true, engaging in healthy lifestyle behaviors, such as PA, would permit infinite improvements to brain health and cognitive functioning – a concept for which there is no evidence and is logically implausible. If there is a true ceiling for cognitive abilities (that may differ by domain) and healthy midlife adults are still near enough to their peak in cognitive functioning, PA engagement may not show any significant relationship with task performance, as was shown in the current study.

4.5.3 Physical Activity Considerations

The range of PA engagement in the current sample may have influenced the current results. Specifically, these participants engaged in limited PA compared to most studies examining habitual activity. For example, the midlife participants in this sample engaged in 21 minutes of MVPA per day using age-specific MET thresholds, which is consistent with MVPA engagement in older adult samples (ranging from 17-22 minutes per day) (Dougherty et al., 2016; Makizako et al., 2015) and at the lower end of the range reported for midlife adult samples (20-90 minutes per day) (Luzak et al., 2017; Spartano et al., 2019; Strath et al., 2008). Participants' truncated range of PA engagement and relatively low variability in activity may have skewed the relationship between habitual activity and EF, thereby resulting in unanticipated negative and/or nonsignificant associations.

No studies to date have created a PA index from objectively monitored activity to quantify multiple components of PA simultaneously, which may be because a composite variable could wash out the influences of individual PA parameters. Although the purpose of using factor analyses to combine PA components was to reduce measurement error and account for shared variance, it is possible that different features of PA make distinct contributions to cognitive functioning. The current results do not provide substantial evidence to support the creation of a PA index through factor analyses, rather than using any individual PA parameter. With the exceptions of the MVPA factor score being more strongly associated with inhibitory control than average METs and measured AEE being more strongly associated with abstraction than either PA factor, there were no significant differences in associations between EF and PA factors versus individual PA variables. This suggests that individual metrics of PA that are easier to measure, such as total volume of MVPA minutes, may be sufficient to test associations with cognitive functioning in midlife.

4.5.4 Neuropsychological Considerations

4.5.4.1 Executive Functioning Subdomain Specificity Relative to Physical Activity

Working memory was one of two EF subdomains that showed a significant association with PA and the only one with an association in the expected pattern. This was consistent with the evidence that some cognitive processes may be more sensitive to PA than others. Indeed, prior studies have found that working memory may be more sensitive to PA than other areas of cognition, including verbal fluency or learning (Kelly et al., 2014), or EF subdomains such as decision making (Bartsch et al., 2016). The interaction between the MVPA factor score and age suggests that there is a greater distinction in working memory abilities beginning in late midlife.

This may be a time at which some of the previously described neurological changes associated with aging, especially in regions supporting working memory, could become increasingly sensitive to the effects of PA. It is also possible that there is a greater range of working memory abilities that are exacerbated in the aging process. That is, working memory may be one of the earlier executive processes to decline with normal aging (Diamond, 2013), which allows the effects of PA engagement to be more detectable into midlife. Since working memory tasks rely on attentional control, encoding, and processing speed, a higher cognitive load during these tasks may also be more sensitive to PA engagement. However, the interaction between MVPA and age on working memory was not sufficiently robust to withstand correction for multiple comparisons, and so all interpretations of this association should be made with caution.

Inhibitory control was the other EF subdomain to demonstrate a significant relationship with PA engagement, such that greater PA engagement was associated with poorer inhibitory control. These findings contrasted with the hypotheses and previously published evidence suggesting that greater PA engagement was related to better inhibitory control (de Greeff et al., 2018; Hsu et al., 2018; Peven et al., 2018). There is inherently a tradeoff between speed and accuracy, particularly on difficult cognitive tasks that require a greater attentional control. The neuropsychological measures included in the inhibitory control component all required participants to be both accurate and fast to achieve higher scores. This speed-accuracy tradeoff is exacerbated in aging, as evidence demonstrates that older adults respond slower in order to increase accuracy on cognitive tasks (Forstmann et al., 2011; Salthouse, 2012). It is not clear whether this same pattern persists in midlife, although the nonsignificant PA x age interaction suggests that age was not an important feature in this relationship. Instead, it is possible that the participants in this sample who engaged in the greatest amount of PA were more concerned about

accuracy than speed on these tasks, resulting in lower scores relative to individuals who engaged in less activity.

Although the PA x sex interaction on inhibitory control did not withstand correction for multiple comparisons, the main effect of PA was driven by the males in this sample. Across the lifespan, males demonstrate poorer performance on inhibitory control tasks, such as stop-signal tasks, relative to females (Li, Huang, Constable, & Sinha, 2006; Mansouri, Fehring, Gaillard, Jaberzadeh, & Parkington, 2016). These behavioral differences are reflected in functional neurological differences, with males exhibiting greater brain activation in diffuse regions associated with task performance (e.g., prefrontal cortex, cingulate cortex, thalamus) (Li et al., 2006; J. Liu, Zubieta, & Heitzeg, 2012). It is possible that hormonal or functional sex differences yield greater neurological sensitivity to PA in males, which manifested behaviorally as the current findings. It may also be that the males in this sample engaging in the most PA were aware of a speed-accuracy tradeoff that, in combination with poorer inhibitory control relative to females, resulted in poorer performance because they slowed down to answer correctly. Nonetheless, this explanation seems unlikely because there was no main effect of sex on inhibitory control component scores.

4.5.4.2 Neuropsychological Measures

There are several considerations regarding the neuropsychological measures used in this study that may have influenced the current results. Six of the twelve measures used were subtests that had a finite range of possible scores, which may have limited the observed relationships between PA and EF. With limitations on participants' achievable scores, their variability was inherently more restricted than the variability for tests that relied on time. For example, the Digit Span and Spatial Span WAIS-III subtests have possible scores that range from 0-16 for each of

their conditions (Wechsler, 1997a). The scores in the average range for each condition vary by age but are typically raw scores between 8-12. If most participants score within the average range, the number of possible scores falls from 17 down to five. A truncated range of scores may be concerning, as fewer observed values restricts the relationship that can be observed with another variable, such as PA. In the current study, the working memory and abstraction components were created entirely from Wechsler subtests that had finite ranges of achievable scores. It may be possible that the observed associations were not a true reflection of the relationships between PA and working memory or abstraction, but rather limitations of the data. However, it seems unlikely the truncated score range played a role in the current data because the marginally significant MVPA x age interaction on working memory was in line with prior evidence that older adults benefit more from PA than younger adults. It is possible that a reduced range of scores influenced any potential relationships between PA engagement and abstraction, although the Matrix Reasoning and Similarities subtests had a wider range of scores than any of the subtests that made up the working memory component. So, if a reduced score range likely did not affect the relationship between PA and working memory, a wider score range probably did not affect the relationship between PA and abstraction. Further, the association between PA and inhibitory control contrasted with hypotheses and prior evidence. Since all tasks included in the inhibitory control component were scored based on time and had considerable variability, it is unlikely that a truncated range of neuropsychological scores skewed the current results.

It is also possible that some of the neuropsychological measures used in the current study were not sensitive to subtle changes on a sub-clinical level (i.e., for healthy, cognitively normal, midlife adults). If PA was associated with subtle changes in cognitive functioning, the tests used to measure EF may not have captured those changes. Specifically, subtests that did not rely on

time (i.e., in the working memory and abstraction components: Matrix Reasoning, Similarities, Digit Span, Spatial Span) were scored on whether participants were correct or incorrect. If there were differences in other cognitive processes based on PA engagement, such as psychomotor speed, these changes would not have been detected from some of the measures used. Future work incorporating timed working memory or abstraction tasks, such as computerized N-Back or Matrix Reasoning tasks, might better capture subtle changes related to PA engagement that could not be quantified here. Notably, however, sub-clinical changes to EF likely were not present in the current sample, given that the more sensitive inhibitory control and processing speed components did not demonstrate relationships with PA that were consistent with the hypotheses.

4.6 Limitations

Despite a well-characterized, large sample of midlife adults with multiple assessments of EF and objectively measured PA, the current study was not without its limitations. First, participants were instructed to remove the SenseWear device when they went to sleep. Although participants were instructed to wear the SenseWear monitor during all awake time, it cannot be known if they forgot to put the armband on immediately after awakening or bathing, or if they engaged in any activity after taking them off. As the armband was not designed to be worn in water, any aquatic activity could not be captured with the device. Thus, it is possible that the collected data did not capture the full range of participant activity.

Second, it is possible that participants were less active while they wore the SenseWear devices than was typical for their daily lives because they simultaneously wore ABP monitors, which were relatively cumbersome. While the ABP monitors would systematically reduce PA

across the sample, the variability in PA engagement would be truncated relative to what would be considered 'habitual' activity. The current study did not test for a difference in the relationship between PA engagement on ABP monitoring versus non-monitoring days with EF because this would have drastically reduced the available PA data for each participant and increased the number of statistical comparisons. Participants were required to have at least three days with sufficient data to be included in statistical analyses. Splitting their data into monitoring versus non-monitoring days may have left some participants with only one or two days of data in each category, which would limit the generalizability of the current results.

Third, the algorithms used by SenseWear to calculate MET levels and measured AEE were proprietary and not accessible for the current study. Without knowing how demographic factors were weighted in those measurements, it is possible that including age and sex as covariates was overcontrolling for those characteristics. Further, without a clear understanding of how MET levels factored into measured AEE, hypotheses about which PA parameters would be more closely related to EF than others may not have been sufficiently informed. It is possible that some of the parameters were too similar to capture different dimensions of PA, as was the case in attempting to extract factors from the age-specific intensity thresholds.

Fourth, only absolute MET thresholds were used to define PA intensity despite the existence of age-specific thresholds that aim to avoid over- or under-estimating PA engagement (ACSM, 2017). The current study attempted to utilize these thresholds to create PA factors and examine their associations with EF but was unable to derive those PA factors successfully. Therefore, it is possible that PA engagement was over-estimated in this sample, as the absolute MET threshold for moderate intensity activity is lower than the age-specific thresholds. When individual PA parameters created using age-specific thresholds were regressed onto EF, no

significant relationships emerged. Despite an inability to extract age-specific PA factors, the nonsignificant relationships between age-derived parameters and EF suggest that this representation of PA would not have changed the current results.

Fifth, given that this was a healthy midlife sample, participants' EF scores were well within the average range and may not have had sufficient variability to detect differences relative to PA. Prior research on healthy, midlife adults showed sufficient variability to test associations with PA engagement, although much of this work focused on individual neuropsychological measures, rather than latent cognitive factors. As previously described, the finite range of scores for all Wechsler subtests restricted their variability, which would have affected the factor scores. A limited range of observed values further limited the confidence that could be placed in the observed relationships between PA and EF. It is possible that a wider range of scores would have transformed these associations to be more closely in line with prior literature or to confirm nonsignificant relationships between PA and EF in midlife.

Sixth, participants in the AHAB-II study completed their neuropsychological assessments over the course of several days, which may have affected their performance. While cognitive abilities are thought to be stable in the short-term, neuropsychological testing on separate days introduced potential confounds including fatigue from many study visits, possible fluctuations in attentiveness dependent upon the sessions' time of day, or personal factors that could not be controlled, such as interpersonal conflicts or stress from work. However, the high number of study visits permitted the characterization of the study sample and allowed the hypotheses to be tested with a rich, comprehensive dataset.

Finally, due to the cross-sectional nature of the study, no causal inferences regarding the relationships between PA and EF could be made. It is possible that the expected associations, or

nonsignificant relationships, found in this study were due to any of the previously described possible physiological mechanisms, although this study did not test those relationships directly. Therefore, it is possible that other biological markers mediate the relationship between PA and EF, and so reduce or eliminate any potential direct effects.

4.7 Contributions

4.7.1 Strengths of the Study

First, as previously stated, this study included a well-characterized, large sample of healthy midlife adults. Participants underwent multiple assessment visits to measure cardiometabolic health in multiple ways, which were used as covariates in all reported analyses. The thorough characterization of these participants will allow for potential future research to extend from the current study to evaluate possible mediators of the PA-EF relationships.

Second, EF was measured in several ways that permitted the use of factor analyses to derive an exploratory latent factor and several confirmatory components of EF subdomains. While factor analyses are commonly used to reduce measurement error of neuropsychological testing in the broader cognitive literature, they are less frequently used in the context of a relationship with PA. Rather, many studies that include objectively measured PA do not include multiple cognitive assessments and therefore are only able to apply their results to the specific task or cognitive process evaluated by that task.

Third, this is the first study to utilize exploratory factor analysis to create a PA index from objectively measured data. While most subjective PA questionnaires compile their data into one

index (e.g., International Physical Activity Questionnaire (Craig et al., 2003), Paffenbarger Physical Activity Index (Paffenbarger, Wing, & Hyde, 1978)), most objectively measured PA studies utilize only one metric of PA, such as total MVPA minutes or MET-minutes per day. By combining several objectively measured PA metrics into one index, the frequency, intensity, and time of activity were comprehensively captured in one factor score. Although the associations between those individual PA parameters and EF were also examined, the factor scores reduced measurement error from those individual parameters and accounted for the variance shared between them.

4.7.2 Broader Implications

This study examined associations between PA and EF during midlife to better inform the prescription of PA as a preventative measure against poor cognitive aging. Overall, the results did not suggest that PA was related to overall EF in a healthy midlife sample. The results did not provide evidence to indicate that creating PA factor scores were better or worse at predicting EF than any individual parameter. Since most PA research to date has focused only on PA parameters individually, it remains unclear whether the volume, intensity, or pattern of activity is more important for cognitive functioning during midlife.

The current study suggested that longer time spent engaging in each bout of moderate intensity activity was related to better abstract reasoning skills in midlife. This finding is particularly beneficial to individuals who may have limitations that prevent them from participating in vigorous PA, as achieving only moderate intensity was associated with better abstraction. It also suggests that prescribing moderate PA in longer bouts may be preventative against later life cognitive decline, although that hypothesis was not tested here.

A notable outcome of this study was that only MVPA – and not total PA – was associated with EF during midlife. This suggests that there may be something unique about MVPA in its relationship with EF, particularly when compared with all PA (including light intensity). Studies of older adults have suggested that greater overall PA engagement, not just MVPA, is associated with better long-term outcomes, including reduced rates of MCI and dementia (Hamer & Chida, 2009). Further, light PA has been shown to preserve brain volume, particularly in the hippocampus and prefrontal cortex, in healthy older adults (Tamura et al., 2015; Varma, Chuang, Harris, Tan, & Carlson, 2015). Thus, it is possible that the full range of activity intensity is not related to cognitive functioning in midlife but shows promise for improving and/or maintaining cognitive function later in life.

4.8 Future Directions

This study demonstrated that moderate intensity PA is related to some aspects of EF in midlife but not to the same degree as has been shown in previous studies with samples of children or older adults. It is possible that the age-related declines in cognitive abilities were not yet detectable in this sample of 30-55-year-old adults. A key consideration is that the age-related neurodegeneration likely begins years prior to the ability to detect cognitive decline (Jack Jr et al., 2010). Future work attempting to probe the effects of PA in midlife should target the brain, potentially in the context of gray matter volume in select regions or white matter microstructural integrity that connects those gray matter areas. It is possible that midlife is a point at which brain-related changes are beginning to take shape, which places the brain as a potential outcome or mediator of the relationship between PA and EF.

Although this study did not include an assessment of CRF, prior literature demonstrated that CRF is a particularly sensitive measure that has been related to EF and other cognitive processes (Belsky et al., 2015; Brown et al., 2010; N. Zhu et al., 2014). Higher CRF has been related to greater gray matter volume across the lifespan (Hayes, Hayes, Cadden, & Verfaellie, 2013; Ruotsalainen et al., 2019; Tian, Studenski, Resnick, Davatzikos, & Ferrucci, 2016), which may mediate the relationship between CRF and EF (Weinstein et al., 2012). Several studies have demonstrated differences in the associations between PA or CRF with cognition and brain volume and/or integrity (Burzynska et al., 2014; Engeroff et al., 2018; Oliveira et al., 2017; Raichlen et al., 2019), suggesting that PA and CRF are distinct, yet related, constructs that should both be tested in the context of cognitive functioning.

As this study tested only the direct effects of PA on EF, it is possible that there are untested mediators that could better explain these relationships (Stillman, Cohen, Lehman, & Erickson, 2016). First, as alluded to above, brain health may be an important mediator, since neurological changes precede cognitive changes. Although this was a cross-sectional study, it is possible that greater gray matter volume in certain brain regions is both related to PA and EF and is a statistical mediator. This can be tested with the AHAB-II sample and may be a promising avenue to understand some of these unanticipated findings. Second, neurotrophic factors, such as BDNF, may also be promising mediators of the PA-EF relationships, as circulating levels of these factors are related to PA engagement and may affect cognitive functioning (Leckie et al., 2014; Nishijima et al., 2016; Tari et al., 2019). Future work should investigate whether circulating neurotrophic factors mediate these relationships in midlife, as much of this work has only examined their role in late life. Third, although the current study controlled for Metabolic Syndrome criteria and 10-year risk of a CHD event, it is possible that there were more specific cardiometabolic markers that

mediate the relationship between PA engagement and EF. Specifically, insulin resistance (Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Tarumi et al., 2013), BP (Cherbuin et al., 2015; Gianaros, Greer, Ryan, & Jennings, 2006; Hughes & Sink, 2016), and inflammatory markers (Braskie et al., 2014; Marsland et al., 2015) have all been linked with PA engagement, cognitive functioning, brain health, or a combination. Given these relationships, it is possible that these cardiometabolic markers serve as statistical or causal mediators in the PA-EF relationship. Testing these mediators could be done cross-sectionally within the AHAB-II sample or with RCTs designed to evaluate whether physiological changes due to exercise engagement are related to changes in cognition or the brain.

Finally, the funded follow-up of the AHAB-II sample could allow future work to test whether there is a relationship between midlife PA and later life EF. As this follow-up is in the process of collecting the same EF measures as in the baseline assessments, factor structures could be re-evaluated and/or confirmed in a later life sample. Since most of the research relating PA to cognitive functioning has focused on older adults, an AHAB-II follow-up provides a unique opportunity to investigate whether changes in EF are related to midlife behaviors. This would extend the literature to determine whether there is an inflection point in age when cognitive functioning is more closely related to healthy lifestyle characteristics, such as PA.

4.9 Conclusions

This study largely suggests that objectively monitored PA engagement was not related to EF during midlife in a healthy population. It provides evidence that MVPA was more closely related to EF than total PA, suggesting that moderate intensity activity may be a better target for

detecting PA-related differences in cognitive functioning. The study also provides preliminary evidence that there may be a benefit to engaging in longer periods of moderate intensity activity with regard to abstract reasoning abilities but did not indicate that any other parameters of PA were more important than any others for overall EF, working memory, inhibitory control, or processing speed. In fact, the findings here suggest that engaging in more PA during midlife may have been detrimental to inhibitory control abilities, although this unexpected result may be due to other considerations for this sample, including a small range of PA engagement. The small effect sizes overall indicate that healthy midlife adults may not yet be experiencing the age-related losses to brain structure and function that would allow the benefits of PA engagement to be more apparent. The study demonstrated no differences in associations with EF between PA indices and individual PA parameters, suggesting that measuring activity by the most accessible method may be sufficient to understand potential relationships with cognitive functioning.

Appendix A Participants

44 participants had incomplete cognitive data but were included in several of the regression analyses examining the relationships between PA and EF. Details about group differences between those with and without complete cognitive data can be found in Appendix Table 1.

Appendix Table 1 Comparison of Demographic, Health, and Physical Activity Characteristics Between Participants With and Without Complete Cognitive Data

Values reported as mean (standard deviation) or n (percentage). *Note:* SIGN., significance; %, percentage; SMOK. STAT., smoking status; BMI, body mass index; KG, kilograms; M, meters; METAB. SYND., Metabolic Syndrome; CHD, Coronary Heart Disease.

	COMPLETE (N = 412)	INCOMPLETE (N = 44)	SIGN.
AGE	43.15 (7.17)	41.89 (7.92)	.272
SEX (% FEMALE)	218 (52.91%)	22 (50%)	.752
RACE (% WHITE)	340 (82.52%)	37 (84.09%)	.619
EDUCATION (YEARS)	15.90 (1.51)	16.13 (1.15)	.408
SMOK. STAT. (% NEVER SMOKER)	261 (63.34%)	34 (72.72%)	.095
BMI (KG/M^2)	26.85 (5.10)	25.70 (4.81)	.153
METAB. SYND. CRITERIA	1.27 (1.22)	1.09 (0.98)	.341
10-YEAR CHD RISK	1.99 (3.56)	1.49 (1.86)	.363
MVPA FACTOR SCORE	-0.02 (0.97)	0.15 (1.17)	.297
TOTAL PA FACTOR SCORE	-0.01 (0.93)	0.12 (1.14)	.369

22 participants reported a history of concussion, though none reported cognitive sequelae. To determine whether concussion history should be included as a covariate in all regression

models, participants with and without history of concussion were compared on demographic, health, PA, and cognitive characteristics. These details can be found in Appendix Table 2.

Appendix Table 2 Comparison of Demographic, Health, and Physical Activity Characteristics Between Participants With and Without History of Concussion

Values reported as mean (standard deviation) or n (percentage). *Note:* HX, history; SIGN., significance; %, percentage; SMOK. STAT., smoking status; BMI, body mass index; KG, kilograms; M, meters; METAB. SYND., Metabolic Syndrome; CHD, Coronary Heart Disease; PA, physical activity; EF, executive functioning; EXPLOR., exploratory; WM, working memory; ABSTR., abstraction; PS, processing speed.

	CONCUSSION HX (N = 22)	HEALTHY (N = 434)	SIGN.
AGE	45.73 (6.30)	42.89 (7.27)	.073
SEX (% FEMALE)	10 (45.45%)	230 (52.99%)	.318
RACE (% WHITE)	10 (81.81%)	359 (82.77%)	.184
EDUCATION (YEARS)	15.38 (1.69)	15.95 (1.47)	.089
SMOK. STAT. (% NEVER SMOKER)	11 (50%)	282 (64.98%)	.093
BMI (KG/M^2)	28.76 (4.55)	26.64 (5.09)	.056
METAB. SYND. CRITERIA	1.59 (1.10)	1.24 (1.20)	.179
10-YEAR CHD RISK	3.09 (4.17)	1.88 (3.39)	.108
MVPA FACTOR SCORE	-0.19 (1.22)	0.01 (0.98)	.354
TOTAL PA FACTOR SCORE	-0.09 (1.15)	0.004 (0.94)	.656
EF EXPLOR. FACTOR	-0.11 (1.07)	0.001 (0.88)	.586
WM COMPONENT	-0.13 (0.95)	0.007 (1.00)	.536
EF COMPONENT	0.12 (1.63)	-0.003 (0.96)	.600
ABSTR. COMPONENT	-0.27 (1.08)	0.01 (1.00)	.193
PS COMPONENT	0.29 (1.34)	-0.01 (0.98)	.181

Appendix B Executive Functioning Factor Analyses

Appendix B.1 Exploratory Factor Analyses

Prior to entry into separate confirmatory principle component analyses for each EF subdomain, all neuropsychological measures were entered into factor analyses to determine whether the inclusion of additional subtests would be beneficial to identifying distinct EF processes. First, all variables were entered into an exploratory factor analysis using pairwise deletion and reliance on an eigenvalue of at least 1.0. A latent factor was considered to be derived from any test scores with factor loadings of at least 0.4. The Scree plot was examined to identify the inflection point for relevant factors. An Oblimin rotation was used to allow for inter-factor correlation, given that all neuropsychological measures were associated with at least one other measure.

Three factors were derived from all the neuropsychological measures: 1) a working memory/visuospatial factor, 2) a Stroop task attention factor, and 3) a Stroop task inhibition factor. The working memory/visuospatial factor explained 39.70% of the variance, achieved an eigenvalue of 4.764, and included WAIS-III Digit Span Forward and Backward, WMS-II Spatial Span Forward and Backward, and WASI Matrix Reasoning subtests with variable loadings between 0.44-0.84. The Stroop task attention factor explained 13.52% of the variance, achieved an eigenvalue of 1.623, and included the Stroop task Color and Word conditions with factor loadings between 0.72-0.80. The Stroop task inhibition factor explained 8.48% of the variance, achieved an eigenvalue of 1.018, and included the Stroop task Color-Word condition and

Interference score with factor loadings between 0.80-0.85. TMT-A and TMTB-A did not load onto any derived factor. See Appendix Table 3 for details.

Using a Varimax rotation did not change the three derived factors' explained variance or eigenvalues. However, the working memory/visuospatial factor also included the WASI Similarities subtest and all variable loadings fell between 0.40-0.77. The Stroop task attention factor was also derived from the Stroop CW score with variable loadings between 0.46-0.81. The Stroop task inhibition factor remained unchanged, although the variable loadings fell between 0.80-0.83 (see Appendix Table 3).

Since this exploratory factor analysis did not separate the included neuropsychological measures into EF subdomains as was anticipated based on theoretical shared cognitive processes, all measures were entered into deterministic principle component analyses.

Appendix Table 3 Cognitive Factor Characteristics Derived From Exploratory Factor Analyses

Note: **NEUROPSYCH, neuropsychological; EIGEN, eigenvalue; VAR. EXPL., variance explained; VISUOSPAT., visuospatial; TMTB-A, Trail Making Test Part B–Part A; TMT-A, Trail Making Test–Part A.**

FACTOR (ROTATION METHOD)	N	NEUROPSYCH MEASURES	FACTOR LOADING	EIGEN.	% VAR. EXPL.	CRONBACH'S α
WORKING MEMORY/ VISUOSPAT. (OBLIMIN)	426	Matrix Reasoning Digit Span Forward Digit Span Backward Spatial Span Forward Spatial Span Backward	.645 .444 .591 .636 .833	4.764	39.703	.775
STROOP ATTENTION (OBLIMIN)	417	Stroop Color Stroop Word	.777 .726	1.623	13.521	.815
STROOP INHIBITION (OBLIMIN)	416	Stroop Color-Word Stroop Interference	.802 .842	1.018	8.484	.968
WORKING MEMORY/ VISUOSPAT. (VARIMAX)	426	Matrix Reasoning Similarities Digit Span Forward Digit Span Backward Spatial Span Forward Spatial Span Backward	.635 .404 .458 .595 .591 .768	4.764	39.703	.777
STROOP ATTENTION (VARIMAX)	416	Stroop Color Stroop Word Stroop Color-Word	.810 .749 .464	1.623	13.521	.832
STROOP INHIBITION (VARIMAX)	416	Stroop Color-Word Stroop Interference	.806 .827	1.018	8.484	.968

Appendix B.2 Principle Component Analyses

Next, all neuropsychological variables were entered into a principle component analysis using pairwise deletion and reliance on an eigenvalue of at least 1.0. Again, a latent factor was considered to be derived from any test scores with factor loadings of at least 0.4. The Scree plot was examined to identify the inflection point for relevant factors. An Oblimin rotation was used

to allow for inter-factor correlation, given that all neuropsychological measures were associated with at least one other measure.

Three factors were derived from all the neuropsychological measures: 1) a general EF factor, 2) a Stroop task factor, and 3) a visual attention factor. The general EF factor explained 39.70% of the variance, achieved an eigenvalue of 4.674, and included WAIS-III Digit Span Forward and Backward subtests, WMS-II Spatial Span Backward subtest, WASI Matrix Reasoning subtest, and TMT B-A with variable loadings between 0.48-0.68. The Stroop task factor explained 13.52% of the variance, achieved an eigenvalue of 1.623, and included all three conditions of the Stroop task and the Interference score with factor loadings between 0.69-0.86. The visual attention factor explained 8.48% of the variance, achieved an eigenvalue of 1.018, and included the WMS-II Spatial Span Forward and Backward subtests and TMT-A with factor loadings between 0.63-0.81. See Appendix Table 4 for details.

Using a Varimax rotation did not change the three derived factors' explained variance or eigenvalues. However, the general EF factor also included the Stroop CW and Interference scores, and all variable loadings fell between 0.44-0.64. The Stroop task factor was derived from all four Stroop variables with loadings between 0.73-0.84. The visual attention factor also included the WASI Matrix Reasoning subtest with all variable loadings between 0.41-0.79 (see Appendix Table 4).

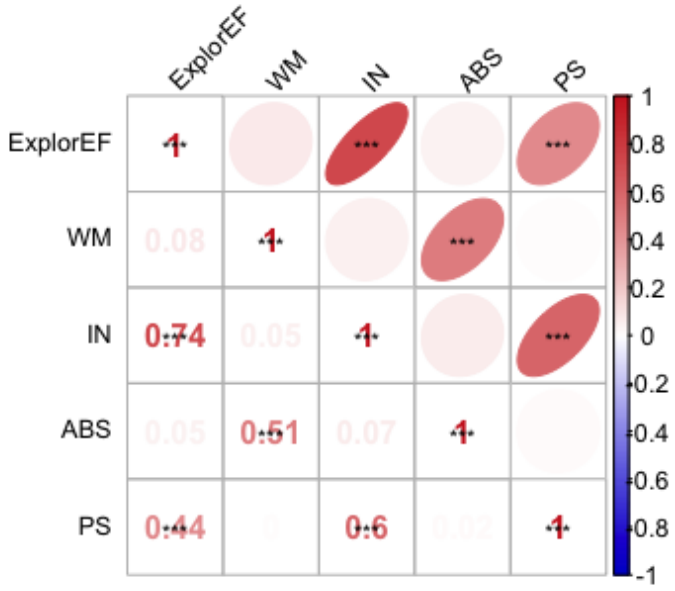
Appendix Table 4 Cognitive Factor Characteristics Derived From Principle Component Analyses

Note: **NEUROPSYCH, neuropsychological; EIGEN, eigenvalue; VAR. EXPL., variance explained; TMTB-A, Trail Making Test Part B–Part A; TMT-A, Trail Making Test–Part A.**

FACTOR (ROTATION METHOD)	N	NEUROPSYCH MEASURES	FACTOR LOADING	EIGEN.	% VAR. EXPL.	CRONBACH'S α
GENERAL EXECUTIVE FUNCTIONING (OBLIMIN)	423	Matrix Reasoning Similarities Digit Span Forward Digit Span Backward Spatial Span Backward TMTB-A	.618 .671 .548 .621 .484 .609	4.674	39.703	.763
STROOP (OBLIMIN)	416	Stroop Color Stroop Word Stroop Color-Word Stroop Interference	.845 .858 .741 .692	1.623	13.521	.877
VISUAL ATTENTION (OBLIMIN)	424	TMT-A Spatial Span Forward Spatial Span Backward	.808 .634 .578	1.018	8.484	.650
GENERAL EXECUTIVE FUNCTIONING (VARIMAX)	412	Matrix Reasoning Similarities Digit Span Forward Digit Span Backward Spatial Span Backward TMTB-A Stroop Color-Word Stroop Interference	.626 .640 .563 .642 .522 .604 .446 .460	4.674	39.703	.830
STROOP (VARIMAX)	416	Stroop Color Stroop Word Stroop Color-Word Stroop Interference	.839 .838 .783 .735	1.623	13.521	.877
VISUAL ATTENTION (VARIMAX)		TMT-A Spatial Span Forward Spatial Span Backward Matrix Reasoning	.782 .671 .643 .417	1.018	8.484	.718

Appendix B.3 Between-Factor Correlations

Pearson product-moment correlations evaluated whether the factor scores described in the main text were correlated with one another. Correlation values between the factors ranged from 0.002 – 0.738 and *p*-values for these correlations ranged from <0.001 – 0.691, indicating that some factors were closely related while others were not. A plot of the correlations between cognitive factors described in the main text can be found in Appendix Figure 1.



Appendix Figure 1 Correlation Plot of All EF and EF Subdomain Factor Scores

*** indicates *p* < .05; ** indicates *p* < .01; *** indicates *p* < .001. *Note:* ExplorEF, exploratory EF factor; WM, working memory component; IN, inhibitory control component; ABS, abstraction component; PS, processing speed component.**

Appendix C Covariate Contributions to the Relationships between Physical Activity and Executive Functioning

All reported results below were significantly related to EF or an EF subdomain after removal of highly influential data points revealed in Cook's Distance sensitivity analyses. All significant associations reported below withstood correction for multiple comparisons. Details about these associations can be found in Appendix Tables 5 (MVPA) and 6 (Total PA).

Appendix C.1 MVPA Factor

Appendix C.1.1 Exploratory Executive Functioning Factor

Of all covariates included in the regression model, only smoking status was significantly related to EF ($\beta = -0.12$, $p = .041$). In line with prior evidence, having never smoked was associated with better EF factor scores (see Table 7 of the main text).

Appendix C.1.2 Cognitive Components

In order to further probe the potential relationships between PA and EF subdomains, the same regression model described above was applied to the individual cognitive components confirmed with PCA and corrected for multiple comparisons using FDR.

Younger age, being male, and higher education were all associated with better working memory component scores (all $\beta \geq |0.170|$, all p-values ≤ 0.003). Being younger and having higher education being associated with better cognitive functioning were consistent with prior evidence, although it was not predicted that sex would independently be related to EF.

There were no significant associations between any covariates and the inhibitory control component scores (all p-values > 0.170).

Consistent with prior evidence, being younger and having higher education were associated with better Abstraction scores (all $\beta \geq |0.160|$, all p-values ≤ 0.003).

The model examining the relationship between MVPA factor and Processing Speed revealed an age x sex interaction ($\beta = -0.160$, $p = .006$). In this sample, being male was associated with faster processing speed only in participants younger than 31 or older than 46 (Johnson-Neyman age interval [31.02, 46.90]) (see Appendix Figure 2-A).

Appendix Table 5 Standardized Regression Coefficients (β) for Selected Covariates on Each of the Cognitive Factors Using the MVPA Factor and Variables

∫ indicates p < 0.10; * indicates p < 0.05; ** indicates p < 0.01 – prior to correction for multiple comparisons with FDR. *Note:* EXPLOR., exploratory; ABSTRACT., abstraction; PROCESS., processing; MVPA, moderate-to-vigorous physical activity; MEAS., measured; MINS, minutes.

		EXPLOR. EF	WORKING MEMORY	INHIBITORY CONTROL	ABSTRACT.	PROCESS. SPEED
MVPA FACTOR	*Age*	0.12	-0.27**	0.10	-0.07	0.17*
	Sex	0.03	-0.31**	-0.05	-0.21*	-0.11
	Age x Sex	-0.07	-0.02	-0.12	-0.11	-0.29**
	Education	0.05	0.18**	0.00	0.36**	-0.01
METS	*Age*	0.12	-0.19*	0.11	-0.06	0.17
	Sex	0.03	-0.31**	-0.01	-0.33**	-0.07
	Age x Sex	-0.10	-0.11**	-0.16	-0.12	-0.29**
	Education	0.04	0.15**	0.01	0.33**	0.01
MEAS. AEE	*Age*	0.08	-0.28**	0.09	-0.08	0.16∫
	Sex	0.01	-0.30*	-0.03	-0.30**	-0.14
	Age x Sex	-0.02	-0.01	-0.10	-0.09	-0.31**
	Education	0.06	0.15**	0.01	0.33**	0.00
BOUTS RATIO	*Age*	0.11	-0.23**	0.13	-0.06	0.18*
	Sex	0.00	-0.27*	0.00	0.31**	-0.08
	Age x Sex	-0.7	-0.07	0.17	-0.12	-0.30**
	Education	0.06	0.15**	0.01	0.32**	-0.01
MVPA MINS	*Age*	0.10	-0.27**	0.13	-0.08	0.14
	Sex	0.01	-0.28*	-0.01	-0.30**	-0.15
	Age x Sex	-0.05	0.12**	-0.16	-0.11	-0.27*
	Education	0.05	0.16**	0.01	0.32**	0.01

Appendix C.2 Total PA Factor

All previously described regression models were conducted again using Total PA factor, which included all PA minutes. This model examined understand whether engagement in *any* activity, regardless of the intensity, was differentially related to EF.

Appendix C.2.1 Exploratory Executive Functioning Factor

There were no significant associations between covariates and the exploratory EF factor score (all *p*-values $\geq$ 0.078) (see Table 9 of the main text).

Appendix C.2.2 Cognitive Components

Younger age, being male, and having higher education were all associated with better Working Memory ($\beta \geq |0.150|$, all *p*-values $\leq$ 0.006). Consistent with the model using the MVPA factor score, being younger and having higher education being associated with better cognitive functioning were consistent with prior evidence, although it was not predicted that sex would be independently related to EF.

There were no significant associations between any covariates and inhibitory control component scores that withstood correction for multiple comparisons (all uncorrected *p*-values $\geq$ 0.045, all corrected *p*-values $\geq$ 0.180).

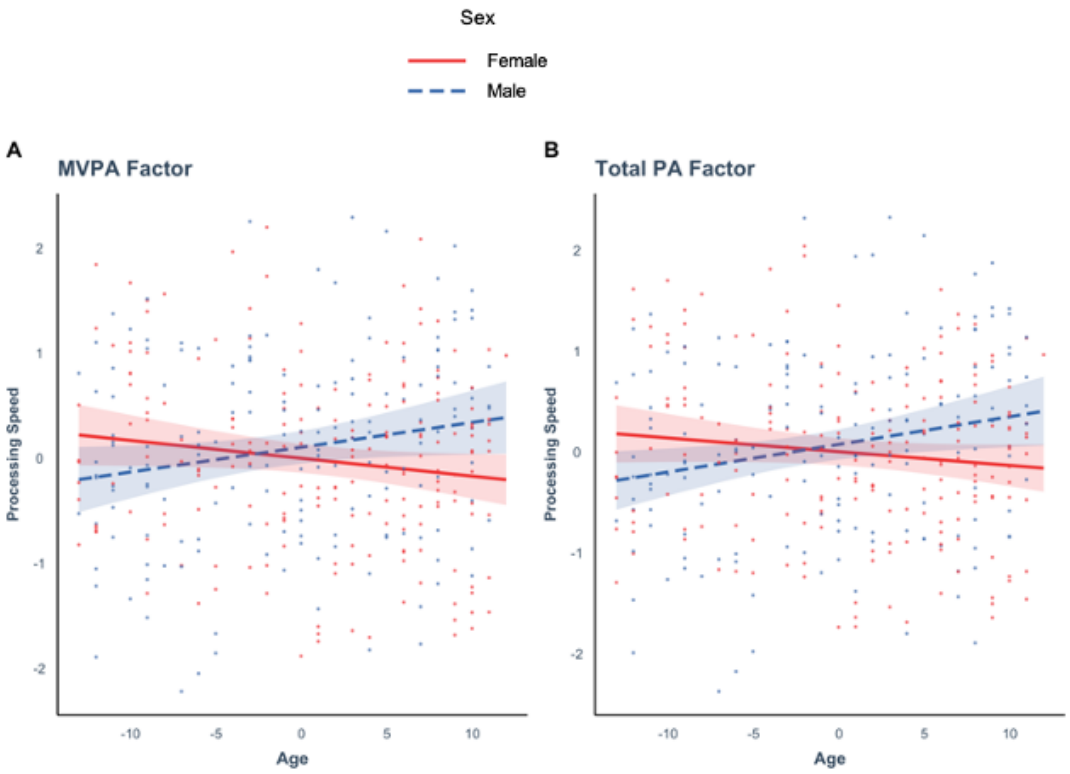
Again, being male and having higher education were both associated with better Abstraction scores ($\beta \geq |0.140|$, all *p*-values $\leq$ 0.010).

There was a significant age x sex interaction on processing speed component scores (β = -0.170, p = .004). Here, being male was associated with faster processing speed only in participants younger than 34 or older than 47 (Johnson-Neyman age interval [33.91, 47.96]) (see Appendix Figure 2-B).

Appendix Table 6 Standardized Regression Coefficients (β) for Selected Covariates on Each of the Cognitive Factors Using the Total PA Factor and Variables

[∫] indicates p < 0.10; * indicates p < 0.05; ** indicates p < 0.01 – prior to correction for multiple comparisons with FDR. *Note:* EXPLOR., exploratory; ABSTRACT., abstraction; PROCESS., processing; PA, physical activity; MEAS., measured; MINS, minutes.

		EXPLOR. EF	WORKING MEMORY	INHIBITORY CONTROL	ABSTRACT.	PROCESS. SPEED
TOTAL PA FACTOR	*Age*	0.14[∫]	-0.23**	0.17*	-0.04	0.20*
	Sex	0.05	-0.29**	0.04	-0.24**	-0.08
	Age x Sex	-0.10	-0.09	-0.21*	-0.12	-0.29**
	Education	0.04	0.19**	0.01	0.37**	0.02
METS	*Age*	0.12	-0.21**	0.12	-0.04	0.19*
	Sex	0.04	-0.31**	-0.02	-0.27**	-0.06
	Age x Sex	-0.10	-0.10	0.00	-0.15	-0.32**
	Education	0.03	0.17**	0.01	0.32**	-0.01
MEAS. AEE	*Age*	0.08	-0.30**	0.09	-0.04	0.18*
	Sex	0.01	-0.27*	0.02	-0.14**	-0.12
	Age x Sex	-0.03	0.01	-0.15	-0.15[∫]	-0.35**
	Education	0.04	0.16**	0.03	0.32**	0.00
BOUTS RATIO	*Age*	0.11	-0.27**	0.15[∫]	-0.05	0.16[∫]
	Sex	0.01	-0.24*	0.00	-0.24*	-0.06
	Age x Sex	-0.09	-0.05	-0.19[∫]	-0.16[∫]	-0.30**
	Education	0.06	0.17**	0.01	0.31**	-0.01
TOTAL PA MINS	*Age*	0.14[∫]	-0.20*	0.11	-0.03	0.19*
	Sex	0.00	-0.29**	-0.01	-0.27**	-0.13
	Age x Sex	-0.11	-0.12	-0.19[∫]	-0.18*	-0.35**
	Education	0.05	0.17**	0.03	0.32**	0.01



Appendix Figure 2 The Age x Sex Interaction on Processing Speed Component Scores

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