

The Role of Physical Activity in Preventing Cognitive Decline in Individuals
with Hypertension and Diabetes

by

Raquel Graham
B.A. (Hons.), University of British Columbia, 2012

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of

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Supervisory Committee

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Dr. Scott Hofer, Department of Psychology
Supervisor

Dr. Ryan Rhodes, Department of Exercise Science, Physical and Health Education
Outside Member

Abstract

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Supervisor

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Outside Member

While some cognitive decline is part of the normal aging process, certain changes have been linked to physical health or lifestyle-related diseases and may be preventable. Hypertension and type 2 diabetes are two conditions that have been associated with a heightened risk of accelerated cognitive decline. In terms of protective factors, physical activity can positively impact a broad range of cognitive processes including memory, attention, and executive function and may also protect against or delay cognitive decline and dementia. The present study examined the extent to which physical activity moderates the impacts of hypertension and diabetes (and their interactions) on different cognitive functions. Data are from the Memory and Aging Project (MAP), a longitudinal study of older adults ($N = 1400$, mean age = 79). A series of multilevel models evaluated baseline differences and linear and quadratic change on four cognitive measures: mental status, perceptual speed, and immediate and delayed episodic memory. Higher levels of self-reported physical activity were associated with better perceptual speed at baseline, and significantly less linear decline across all four measures. Physical activity was not significantly associated with curvilinear change. Individuals with diabetes had significantly worse immediate episodic memory performance at baseline, but diabetes was largely unrelated to rate of change and initial performance on the other measures. Hypertension was associated with better initial mental status (linear and quadratic models) and delayed episodic memory (quadratic model). Contrary to expectations, most interactions between physical activity and the two health

conditions were non-significant. However, physical activity appeared to moderate the relationship between comorbid diabetes and hypertension on immediate episodic memory, such that individuals with the two conditions who were more physically active experienced a reduced rate of linear and curvilinear decline compared to inactive individuals with diabetes and hypertension. The findings from this study suggest that physical activity may reduce the impact of comorbid conditions on certain cognitive functions, and that immediate episodic memory may be particularly susceptible.

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Introduction

It is estimated that 747,000 Canadians are currently living with cognitive impairment or dementia, and with the aging baby boomer generation this number is expected to double to 1.4 million by the year 2031 (Alzheimer Society of Canada, 2012). Similar trends are expected worldwide and most healthcare systems are not financially equipped to deal with the associated costs (Kamegaya, Araki, Kigure, & Yamaguchi, 2014). Some changes in cognition are part of the normal aging process (Hofer & Sliwinski, 2001); however, certain changes have been linked to physical health or lifestyle-related diseases and may be preventable. As such, a growing number of studies are focusing on identifying modifiable risk factors that may prevent or delay the onset of dementia and cognitive decline. Brookmeyer, Johnson, Ziegler-Graham, and Arrighi (2007) estimated that there would be 9.2 million fewer cases of dementia worldwide in the year 2050 if current interventions could delay the onset and progression of the disease by only one year.

Physical activity has been shown to positively impact a broad range of cognitive processes related to normal aging including memory, attention, and executive functioning (Colcombe & Kramer, 2003), and may also protect against or delay cognitive decline and dementia (Barnes & Lautenschlager, 2013; Williams, Plassman, Burke, Holsinger, & Benjamin, 2010). In contrast, a number of preventable chronic health conditions are known to increase the risk of cognitive decline and dementia. For instance, mid-life high blood pressure (hypertension) has been associated with declines in cognition (Gottesman et al., 2014), and individuals with type 2 diabetes are at risk of accelerated cognitive decline compared to individuals without diabetes (Spauwen, Kohler, Verhey, Stehouwer, & van Boxtel, 2013). Despite growing evidence associating these chronic health conditions with cognitive decline, and literature implicating

physical activity as a protective factor, surprisingly little research has examined how physical activity might specifically reduce the risk of cognitive decline among these populations. This project aims to evaluate the extent to which higher levels of physical activity may attenuate cognitive decline in individuals with hypertension and/or type 2 diabetes. Longitudinal data from the Rush Memory and Aging Project (MAP) will be used to address the research question.

Overview of Age-Related Cognitive Decline.

Some changes in cognitive abilities are expected with age. In particular, processing speed, some aspects of memory, and executive function are commonly affected by the normal aging process (Harada, Natelson Love, & Triebel, 2013; Kraft, 2012). However, cognitive decline is not inevitable and there is substantial variability in the prevalence and rate of decline among older adults. Indeed, many older adults remain quite high functioning well beyond 80 years of age despite changes in brain structure and function (Harada et al., 2013).

While chronological age is commonly used to describe trajectories of cognitive decline, biological health factors have been causally linked to cognitive decline, and may be better predictors than age alone (DeCarlo, Tuokko, Williams, Dixon, & MacDonald, 2014). For instance, inflammation, cholesterol levels, hypertension, diabetes, cardiovascular disease, smoking, alcohol, and oxidative stress have all been associated with a heightened risk of cognitive decline (DeCarlo et al., 2014; Hassing et al., 2004; Szoeki et al., 2016; Yaffe et al., 2009). Conversely, participating in physical, social, and cognitive activities has been linked to a reduced risk of cognitive decline (Bielak, Gerstorf, Anstey, & Luszcz, 2014; Brown et al., 2012; Robitaille et al., 2014). Although there is a large body of literature associating these risk and protective factors with cognitive outcomes, many studies are cross-sectional, which limits our understanding of how these associations unfold over time. Moreover, it is common for

researchers to focus solely on one variable, without considering how multiple variables may interact to alter an individual's cognitive health. A better understanding of the underlying mechanisms and potential interactions between these factors is needed to inform health recommendations and to design effective interventions in order to prevent or delay age-related cognitive decline.

Diabetes and Cognition

There is growing evidence to suggest that type 2 diabetes is associated with a heightened risk of cognitive decline and dementia (Cholerton, Baker, & Craft, 2013). Population-based studies have revealed relatively consistent patterns between diabetes and cognitive function among older adults (Gregg et al., 2000; Nooyens et al., 2010; Spauwen et al., 2013; Yaffe et al., 2004). For example, Vilvis and colleagues (2004) found that compared to individuals without diabetes, those with diabetes were up to twice as likely to experience declines in global cognitive functioning over a five-year period. In a retrospective study, diabetes was associated with an earlier onset of dementia, and reduced survival time among individuals with comorbid diabetes and dementia (Zilkens et al., 2013).

Findings from cross-sectional and longitudinal studies suggest that certain domains of cognition are more susceptible to diabetes than others. In a cross-sectional analysis, Arvanitakis, Wilson, Li, Aggarwal, and Bennett (2006) found that diabetes was associated with worse performance on tests of semantic memory and perceptual speed, but not with global cognition, visuospatial ability, episodic memory, or working memory. After including confounding health variables in the model, only perceptual speed remained significant. In a separate longitudinal cohort, Arvanitakis, Wilson, Bienas, Evans, and Bennett (2004) found associations between diabetes and lower levels baseline performance on tests of semantic memory, working memory,

episodic memory, visuospatial ability, and general cognition, but not perceptual speed. However, over the course of nine years, individuals with diabetes experience significantly greater declines in perceptual speed. Nooyens and colleagues (2010) followed 2,613 men and women over five years, with cognitive outcomes (memory, cognitive flexibility, processing speed) measured at baseline and five years later. Compared to individuals without diabetes, those with type 2 diabetes experienced 2.6 times greater decline in global cognitive function, and individuals aged 60 and older with prevalent diabetes also had a 3.6 times greater decline in cognitive flexibility compared to people without diabetes. In the Maastricht Aging Study, prevalent type 2 diabetes was associated with greater decline in processing speed and executive function over 12 years, but incident diabetes was only associated with accelerated decline in processing speed (Spauwen et al., 2013).

A number of potential mechanisms have been put forth to explain the association between diabetes and cognitive impairment (Luchsinger, 2012). Cerebrovascular mechanisms are perhaps the most compelling link, given that diabetes is known to cause cerebrovascular disease. In particular, it is well-established that diabetes is an independent risk factor for stroke (Schmidt, 1992). Independent of cerebrovascular disease, insulin can have a direct impact on cognitive functioning (Luchsinger, 2012). Insulin is capable of crossing the blood-brain barrier, and it has been proposed that abnormal levels of insulin in the brain can lead to increased amyloid depositions and tau proteins, which are implicated in Alzheimer's Disease (AD). High levels of peripheral insulin initially correspond to high levels of insulin in the brain and cerebrospinal fluid. However, prolonged peripheral hyperinsulinemia can cause insulin receptors on the blood-brain-barrier to downregulate, thereby reducing the amount of insulin in the brain (Cholerton et al., 2013). Further evidence for this mechanism stems from the fact that there are

insulin receptors in the brain, which are particularly dense in structures that are impacted early in AD, such as the entorhinal cortex, the hippocampus (Frolich et al., 1998), and the olfactory bulb (Cholerton et al., 2013). As such, it seems that individuals with diabetes eventually experience a loss of optimal insulin levels in the brain, which can lead to changes in overall brain function.

Taken together, these findings suggest that individuals with diabetes are likely to experience greater rates of cognitive decline and have a heightened risk for dementia. This is particularly concerning, given that approximately 27% of adults over the age of 65 have diabetes in the United States (CDC, 2011), and prevalence rates are expected to continue to increase.

Hypertension and Cognition

Hypertension has also been identified as a risk factor for cognitive decline, Alzheimer's disease, and other dementias (Reitz, Tang, Manly, Mayeux, & Luchsinger, 2007). Reitz and colleagues (2007) followed a sample of 918 adults over the age of 65 for over 4 years. Baseline hypertension was associated with a greater risk of mild cognitive impairment (MCI).

Hypertension was specifically associated with declines in executive function, but not with changes in other cognitive domains such as language or memory. Executive function appears to be particularly susceptible to decline in relation to elevated blood pressure (Hachinski et al., 2006), but there is evidence to suggest that other cognitive processes such as verbal and non-verbal memory are also at risk (Reed et al., 2007). In a recent longitudinal study, Szoeki and colleagues (2016) examined the association between several health factors and verbal memory performance over the course of 20 years. They found that hypertension had the third strongest effect on later life verbal memory, next to physical activity and high density lipoprotein cholesterol.

Not all studies have found an association between hypertension and cognition (Di Carlo et al., 2000; Hebert et al., 2004; Van Boxtel et al., 1997). One possible reason for the inconsistent results could be that hypertension appears to have an age-dependent relationship with cognitive decline. Specifically, mid-life hypertension has been most strongly associated with subsequent risk of cognitive decline, whereas hypertension in late-life (typically over the age of 65) often shows no relationship with cognition, and has even been observed to have a protective effect in some studies (Qiu, Winblad, & Fratiglioni, 2005). For example, Gottesman and colleagues (2014) followed 13,476 individuals over a 20-year period and found that mid-life hypertension was related to a heightened risk of cognitive decline over the course of the study. However, no relationship between late-life hypertension and cognition was observed (Gottesman et al., 2014). Thorvaldson and colleagues (2012) designed a study to tease apart the between-person and within-person associations between blood pressure and cognition. In a sample of older adults (aged 70+) who were followed for 30 years, between-person associations were non-linear. An inverted U shape was observed, such that both low and high blood pressure were associated with worse cognitive performance on verbal, spatial, and perceptual speed tests. On the other hand, within-person associations were linear and positive, such that declines in blood pressure were significantly associated with declines in performance in perceptual speed. Verbal and spatial abilities were not significantly related to within-person effects over time. These discrepancies across different periods in the lifespan and methodologies illuminate the importance of conducting longitudinal research in order to capture the ways in which these relationships change within and between individuals over time.

The mechanisms underlying the link between hypertension and cognition are complex and are not entirely understood. It is likely that hypertension impacts cognitive functioning

through multiple pathways (Snyder et al., 2015). Like diabetes, hypertension is causally related to the development of cardiovascular and cerebrovascular diseases (Launer, 2013). One study found that the relationship between hypertension and risk of mild cognitive impairment was reduced after adjusting for stroke and related vascular risk factors (Reitz et al., 2007). A second pathway may be through brain atrophy directly related to elevated blood pressure (Launer, 2013). Specifically, abnormal blood flow can lead to lesions in both the white and grey matter in the brain, ultimately contributing to white matter hyperintensities and microinfarcts (Gasecki, Kwarciany, Nyka, & Narkiewicz, 2013). Some research has shown that individuals with hypertension are more likely to have smaller hippocampal volume (Korf, White, Scheltens, & Launer, 2004) and total brain volume (den Heijer et al., 2003) than individuals whose blood pressure is within the normal range.

Comorbidity

Given that hypertension and diabetes are both related to lifestyle factors, it is not surprising that these conditions often co-occur. It is estimated that one third of adults have hypertension, and about half of these individuals are also insulin resistant (CDC, 2011). The impact that these comorbidities have on cognition has been investigated longitudinally and there is evidence to suggest that comorbid diabetes and hypertension lead to a greater risk of cognitive decline than each condition individually (Hassing et al., 2004). However, this study used only one measure of mental status, the Mini Mental State Examination (MMSE). More recently, Kelly and colleagues (2016) conducted a coordinated analysis of three longitudinal studies to investigate the independent and interactive impacts of diabetes and hypertension on verbal memory. The associations between the impacts of hypertension and diabetes varied across the studies and different verbal memory measures. Diabetes was associated with worse baseline

performance in one of the three studies (the English Longitudinal Study on Aging), while hypertension was related to accelerated decline in one study (OCTO-Twin), but attenuated decline in another (the Rush Memory and Aging Project). In terms of interactions between the conditions, participants in the Memory and Aging Project also exhibited less decline over time if they had comorbid diabetes and hypertension. Although few associations were observed between hypertension, diabetes, and cognition, this study only looked at verbal memory and examined linear trajectories. More research is needed to evaluate how other domains of cognition may be impacted by comorbid conditions, including considerations of a curvilinear trajectory.

Physical Activity and Cognition

A substantial body of literature has demonstrated that physical activity is associated with better cognitive performance and a reduced risk of accelerated decline over time (Carvalho, Rea, Parimon, & Cusack, 2014; Rockwood & Middleton, 2007). Observational research has shown that older adults who live more active lifestyles have a reduced risk of cognitive impairment and dementia (Gregory, Parker, & Thompson, 2012). For example, Bixby and colleagues (2007) were interested in determining whether physical activity was associated with better executive function in older adults. A sample of 120 healthy men and women between the ages of 65 and 92 completed a series of measures including health history, self-reported level of physical activity, and tests of executive function. The Yale Physical Activity Survey (YPAS) was used to obtain frequency, duration, and intensity of various physical activity domains such as household chores, recreation, and structured exercise (Dipietro, Caspersen, Ostfeld, & Nadel, 1993). The findings revealed that even after controlling for age, education and IQ, YPAS scores were significantly correlated with executive function but not with other domains of cognition. Additional cross-sectional studies have arrived at similar conclusions. Anel and colleagues (2008) found that

individuals who reported no regular physical activity were also more likely to have a diagnosis of dementia compared to individuals who reported regularly engaging in light exercise activities. Similarly, a study conducted by Winker and colleagues (2010) found that among adults over the age of 60, those who were marathon runners and cyclists performed better than inactive individuals on the Five Point Test, a measure of non-verbal fluency.

Several studies have examined the relationship between physical activity and cognitive function using longitudinal designs. By monitoring the same people repeatedly, longitudinal studies aim to provide a better understanding of the ways in which individuals change over time. Sliwinski and Buschke (1999) argue that in order to test theories of cognitive aging, it is essential to measure individual change over time. For example, Ravaglia and colleagues (2008) conducted a 4-year prospective study on 749 individuals aged 65 and older. Physical activity was assessed at baseline using the Paffenbarger Physical Activity Questionnaire (Paffenbarger, Wing, & Hyde, 1978). Specifically, participants reported how much they typically walked each day, how many flights of stairs they climbed each day, and frequency and duration of participation in other recreational or sporting activities over the past year. Participants were then classified into categories based on whether or not they met the recommended requirements of 30 minutes of moderate-intensity physical activity at least four days per week, or a total of 120 minutes per week. Follow-up data were collected approximately four years after baseline and at this point, 54 participants had been diagnosed with Alzheimer's disease and 27 had been diagnosed with vascular dementia. Baseline physical activity was associated with a reduced risk of developing vascular dementia, but not Alzheimer's disease. The authors of the study suggest these findings may have occurred because physical activity improves blood flow to the brain, thereby reducing the risk of dementia associated with vasculature, but not necessarily affecting the complex

development of Alzheimer's pathology. In another study, Gow, Mortensen, and Avlund (2012) followed a cohort of community-dwelling adults every ten years from age 50 to age 80, and found an association between physical activity at age 60 or 70 and reduced risk of cognitive decline at age 80. This finding remained even after controlling for baseline cognitive ability, social class, sex, and education.

A recent coordinated analysis examined the relationship between physical activity and change in cognition in four separate longitudinal studies (Lindwall et al., 2012). Within each study, the authors evaluated four cognitive domains: reasoning, memory, fluency, and semantic knowledge. Higher levels of baseline physical activity were associated with better performance on fluency and reasoning tests. Importantly, this study also examined how *change* in physical activity relates to *change* in cognitive function. Change in physical activity was related to change in reasoning in all four studies, and change in fluency in two of the studies. These findings suggest that physical activity is more strongly associated with fluid cognition than with more crystallized forms of cognition. More research is needed to better understand how various forms of cognition are differentially affected by physical activity, and to identify what other factors may moderate these relationships.

Intervention studies have demonstrated that physical activity can improve cognitive functioning (Baker, Frank, Foster-Schubert, Green, Wilkinson, McTiernan, Cholerton, et al., 2010; Cassilhas et al., 2007). Colcombe and Kramer (2003) conducted a seminal meta-analysis on the effects of fitness training on cognitive function in older adults. From the 18 intervention studies that were reviewed, the authors found that fitness training was associated with an average increase in performance of .5 standard deviations across cognitive measures, training methods, and individual characteristics. Processes related to executive function exhibited the largest

improvements, with visuospatial tasks also showing impactful benefits. Since this meta-analysis, many more intervention studies have found similar results. Suzuki and colleagues (2012) evaluated a 12-month exercise intervention in older adults with mild cognitive impairment (MCI). In this study, 50 participants were randomly assigned to a 12-month exercise intervention or a control group. Those in the exercise intervention engaged in supervised 90-minute exercise sessions twice weekly. Each session incorporated aerobic exercise, strength training, and stretching. In contrast, participants in the control group attended three educational health promotion classes. At baseline, all 50 participants completed the mini-mental state examination (MMSE) which measures general cognitive function, the Stroop test, as well as measures of logical memory, verbal fluency, and processing speed. At the 12-month follow-up, individuals in the intervention group demonstrated significant improvement in immediate memory recall, verbal fluency, and MMSE scores compared to those in the educational control group. In fact, those in the control group actually exhibited declines in MMSE scores over the 12 months. However, there were no significant differences between the groups on delayed memory recall and processing speed. The authors concluded that physical activity is beneficial for at least some aspects of cognitive performance in older adults with MCI. This may indicate that not all facets of cognition are amenable to exercise interventions or that perhaps certain areas of cognition simply take longer to demonstrate change.

Physical activity likely prevents cognitive decline through multiple mechanisms. Research with animals has revealed that engagement in regular aerobic exercise results in improved synaptogenesis, neurogenesis, angiogenesis, and promotes the brain's immune response and synaptic plasticity (Berchtold & Cotman, 2013). With regards to dementia pathology, physical activity in animals has also been associated with reductions in amyloid

deposition and increases in cerebral blood flow (Lautenschlager, Cox, & Cyarto, 2012). Human neuroimaging studies have associated physical activity with increases in hippocampus and grey matter volume, as well as increased hippocampal blood flow (Erickson et al., 2011).

Additionally, participation in physical activity in older adulthood may involve social contact and cognitive stimulation, two other factors that are associated with attenuated cognitive decline (Robitaille et al., 2014).

Associations between hypertension, diabetes, and physical activity

In 2010, Baker and colleagues conducted the first study to evaluate the impact of a physical activity intervention on cognition among individuals with type 2 diabetes or pre-diabetes (Baker, Frank, Foster-Schubert, Green, Wilkinson, McTiernan, Cholerton, et al., 2010). Participants were randomly assigned to a 6-month aerobic exercise program or a stretching control group. After six months, individuals in the aerobic exercise condition showed improvements in executive function, including working memory, cognitive flexibility, selective and divided attention, as well as improved insulin sensitivity. In a 2013 review, this study was the only available example of research evaluating the impact of physical activity among individuals with a heightened metabolic risk for Alzheimer's disease (Smith, Nielson, Woodard, Seidenberg, & Rao, 2013). Indeed, more research is needed to understand whether, or to what extent, older adults with diabetes may cognitively benefit from physical activity, and if similar trends can be observed among individuals with hypertension.

A recent cross-sectional study by Loprinzi (2016) was the first to examine how physical activity may moderate the relationship between multiple chronic conditions and cognitive functioning in older adults. In this paper, multimorbidity was defined as having at least two of the following conditions: arthritis, coronary artery disease, stroke, congestive heart failure, heart

attack, emphysema, chronic bronchitis, hypertension, diabetes, cancer, and obesity. Loprinzi (2016) found that multimorbidity was associated with worse performance on the Digit Symbol Substitution Test, a measure of processing speed. However, this association was not observed in participants who engaged in higher levels of physical activity. This study illuminates the importance of evaluating how risk factors and protective factors may interact to influence cognition. The finding that physical activity can moderate the relationship between multimorbidity and cognitive function is very intriguing, but replication studies are needed. Lorprinzi evaluated cognitive function using only one cognitive test, a measure of processing speed, but it is not clear whether these findings can be extrapolated to other cognitive systems. Furthermore, prospective, longitudinal studies are needed to examine whether physical activity can moderate the impacts that chronic health conditions have on trajectories of cognition across time.

Limitations of Past Research

Despite the well-established link between these health conditions and risk of cognitive decline, and physical activity as a protective factor for cognitive decline, little research has examined how physical activity might protect against, or delay the onset of, cognitive decline or dementia among individuals with hypertension and/or diabetes.

Another limitation of past research in this area is that many studies have been cross-sectional, analyzing individuals at only one point in time. As such, less is known about how these risk and protective factors unfold within individuals across the lifespan. Intervention studies have provided evidence that physical activity is causally related to improved cognition (Baker, Frank, Foster-Schubert, Green, Wilkinson, McTiernan, Plymate, et al., 2010; Lautenschlager et al., 2008; Liu-Ambrose, Nagamatsu, Voss, Khan, & Handy, 2012). However,

intervention studies typically have small sample sizes with an observation period comprised of a relatively short length of time. Analyses conducted on large samples of individuals using repeated assessments into old age are needed to better understand how these factors interact within individuals over time. Previous studies in this area often limit cognitive outcomes to one domain of cognition (Barnes et al., 2003; Hassing et al., 2004). This is problematic given that studies that use multiple domains of cognition often find that risk and protective factors relate to certain cognitive domains, but not others (Fontbonne, Berr, Ducimetière, & Alperovitch, 2001; Lindwall et al., 2012).

Although physical activity is a well-established recommendation for maintaining overall physical and mental health, a staggering proportion of the population is relatively inactive. If physical activity emerges as a protective factor for these populations, the findings may inform care and treatment guidelines for older adults at risk of or living with hypertension and/or diabetes as complement to drug therapy. Importantly, this line of research is needed to improve health researchers' understanding of the lifestyle and risk factors that moderate the association between chronic health conditions and cognitive decline and dementia. Physical activity as recommended or prescribed by a physician poses minimal costs to the healthcare system, yet has the potential to reduce the increasing costs associated with dementia.

The Current Study

The current study has two primary objectives. The first objective is to evaluate the association of baseline physical activity with initial performance and rate of change in three domains of cognition: mental status, episodic memory, and perceptual speed. The second objective is to evaluate the extent to which physical activity may protect against cognitive decline specifically in individuals with diabetes and/or hypertension. In other words, *does*

physical activity interact with diabetes and hypertension to mitigate the effects these conditions can have on cognitive decline? It is hypothesized that physical activity will be associated with better baseline performance and a *reduced* rate of decline on all four cognitive measures. Further, we hypothesize that diabetes and hypertension will be associated with worse baseline performance and *greater* rates of decline over time on all four cognitive measures, but that physical activity will moderate these associations. This project will extend work by Kelly and colleagues (2016) by including physical activity as a potential moderator of the impacts of hypertension and diabetes (and their interactions) on different cognitive functions. To answer these research questions, a series of multilevel models will be applied to a longitudinal sample of older adults with up to 17 assessment occasions. Compared to other statistical techniques, multilevel models are robust against data that are missing at random, and therefore provide greater power for detecting effects (Quene & van den Bergh, 2004). In order to determine the most appropriate trajectory for these complex interactions, both linear and quadratic models will be evaluated.

Method

Participants

Participants were from the Rush Memory and Aging Project, an ongoing longitudinal study that aims to identify factors associated with the maintenance of cognitive health (Bennett et al., 2012). Eligible participants were individuals aged 50 and older, who were free of dementia and willing to agree to annual testing and organ donation (N = 1,485). Participants were recruited from retirement communities, local churches, and subsidized housing units in Northeastern Illinois (Bennett et al., 2005). Rolling admission began in 1997, and participants were assessed annually for a maximum of 17 years. Individuals with a dementia diagnosis at baseline were excluded from the present study, resulting in a sample of 1,400 participants. This study utilized all waves of data collection, although only 15 participants had data for the 17th wave.

Procedure

Participants were assessed by a team of trained nurses, neuropsychological test technicians, phlebotomists, and research assistants (Bennett et al., 2005). Testing sessions were conducted in participants' homes, which reduced participant burden and therefore facilitated higher retention rates. Each testing session included cognitive and motor function assessments, complete neurological examination, and a medical history taking.

Measures

Demographic Information

Demographic information was collected during the baseline assessment and included age, sex, and years of education.

Hypertension

Hypertension was measured with a mercury sphygmomanometer during three trials (two sitting and one standing) and recorded as systolic over diastolic. Self-report measures were also obtained by asking participants were also asked if they have ever been told by a doctor, nurse, or therapist that they had high blood pressure. This question was coded as *Yes*, *Suspect*, or *No*. A cumulative hypertension variable was created based on whether participants have ever reported a hypertension diagnosis. For the present analyses, a between-person variable was used to differentiate between individuals who had ever had hypertension from those who have not.

Diabetes

Diabetes status was assessed by asking participants if they had ever been told by a doctor, nurse, or therapist that they have diabetes, or sugar in the urine, or high blood sugar. Participants were also asked if they had ever been told to take insulin injections for high blood sugar or if they had ever been told to take medication by mouth for high blood sugar. Diabetic status was coded as *Yes*, *Suspect or possible*, or *No*. Similar to hypertension, a dichotomous variable was created based on cumulative self-report of diabetes diagnosis, differentiating individuals who reported a diagnosis in the past and those who have never been diagnosed with diabetes.

Physical Activity

Physical activity was measured using questions adapted from the 1985 National Health Interview Survey (McPhillips, Pellettera, Barret-Connor, Wingard, & Criqui, 1989). Participants were asked whether they had engaged in any of the following activities over the past two weeks: *walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding-including stationary bikes, and swimming or water exercises*. For each activity, participants were asked to report the number of occasions and average minutes per session over the past two

weeks. Finally, minutes engaged in each activity were summed and expressed as the total number of hours of activity per week. For this study, participants' average level of physical activity across all available occasions was used as a between-person predictor. Existing longitudinal studies commonly use baseline physical activity in their models (e.g., Andel et al., 2008; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001), but conceptualizing physical activity as an average level across multiple occasions provides a more reliable estimate of activity level over time.

Cognitive Measures

Mental Status

Mental status was assessed using the Mini Mental State Examination (MMSE; Folstein et al., 1975). The MMSE is a 30-item measure that is widely used to evaluate mental status and as a screening measure of dementia severity. Specifically, participants are verbally asked questions about orientation to time and place, recall ability, short-term memory, and arithmetic ability. Total scores on the MMSE range from 0 to 30, with scores of 24 or higher representing normal cognition, 19-23 indicating mild cognitive impairment, 10-18 indicating moderate cognitive impairment and 9 or less indicating severe cognitive impairment.

Perceptual Speed

The oral version of the Symbol-Digit Modalities Test (SDMT; Smith, 1982) was used to measure perceptual speed. In this test, participants are shown a series of symbols each corresponding to a number between 1 and 9. They are asked to call out the numbers that match the symbols in a sequential order. Scores represent the total number of correctly identified symbols during the 90 second trial, ranging from 0 to 110. This measure of perceptual speed has

demonstrated excellent short-term stability, and is sensitive to aging and Alzheimer's disease (Smith, 1982).

Episodic Memory

Episodic memory was assessed using the East Boston Memory Test (Albert et al., 1991). In this test, a three sentence story is read out loud to participants, and they are asked to recall as many components as possible immediately after listening, and again after a 3-minute distractor-filled delay. For each recall test, possible scores range from 0 to 12, with each point corresponding to a correctly recalled component. Scores on both the immediate and delayed recall tasks are included as separate outcome measures in the present study.

Covariates

Two potentially confounding variables, lifetime alcohol intake and stroke, were included as between-person covariates in the final model. Lifetime daily alcohol intake was measured at baseline and represents the amount of alcoholic beverages consumed per day during the period in which participants drank the most in their lifetime. Possible values range from 0 to 6, with 6 representing 6 or more drinks per day during this period. Diagnosis of stroke was determined by a clinician based on a review of self-report questions, neurological exam (when available), and interview with the participant. A dichotomous variable was created to distinguish individuals who had ever had a stroke and those who had never had a stroke.

Statistical Analysis

For each cognitive outcome, a series of multilevel growth curve models were fit to evaluate baseline differences and change as a function of time. The initial model (M1) included basic demographic predictors, with each subsequent model adding additional predictors and interactions (M2-M6). First, all models were estimated to determine initial performance and rate of change using linear slopes only. Next, identical models were estimated with the addition of quadratic terms. All models were conducted using Mplus version 7.4 (Muthen & Muthen, 2015). These models describe change as a function of years in study, are robust to data missing at random, and provide optimal power to detect the presence of effects relative to other methods for repeated measures data (Quene & van den Bergh, 2004). The six growth models were:

- M1: Level 1: $y_{ti} = \beta 0_i + \beta 1_i \text{Time}_i + \epsilon_{ti}$
 Level 2: $\beta 0_i = \gamma 0.0 + \gamma 0.1 \text{AGE}_i + \gamma 0.2 \text{SEX}_i + \gamma 0.3 \text{EDU}_i$
 $\beta 1_i = \gamma 1.0 + \gamma 1.1 \text{AGE}_i + \gamma 1.2 \text{SEX}_i + \gamma 1.3 \text{EDU}_i$
- M2: Level 1: $y_{ti} = \beta 0_i + \beta 1_i \text{Time}_i + \epsilon_{ti}$
 Level 2: $\beta 0_i = \gamma 0.0 + \gamma 0.1 \text{AGE}_i + \gamma 0.2 \text{SEX}_i + \gamma 0.3 \text{EDU}_i + \gamma 0.4 \text{DM}_i + \gamma 0.5 \text{HT}_i + \gamma 0.6 \text{DM} * \text{HT}_i$
 $\beta 1_i = \gamma 1.0 + \gamma 0.1 \text{AGE}_i + \gamma 1.2 \text{SEX}_i + \gamma 1.3 \text{EDU}_i + \gamma 1.4 \text{DM}_i + \gamma 1.5 \text{HT}_i + \gamma 1.6 \text{DM} * \text{HT}_i$
- M3: Level 1: $y_{ti} = \beta 0_i + \beta 1_i \text{Time}_i + \epsilon_{ti}$
 Level 2: $\beta 0_i = \gamma 0.0 + \gamma 0.1 \text{AGE}_i + \gamma 0.2 \text{SEX}_i + \gamma 0.3 \text{EDU}_i + \gamma 0.4 \text{PA}_i$
 $\beta 1_i = \gamma 1.0 + \gamma 1.1 \text{AGE}_i + \gamma 1.2 \text{SEX}_i + \gamma 1.3 \text{EDU}_i + \gamma 1.4 \text{PA}_i$
- M4: Level 1: $y_{ti} = \beta 0_i + \beta 1_i \text{Time}_i + \epsilon_{ti}$
 Level 2: $\beta 0_i = \gamma 0.0 + \gamma 0.1 \text{AGE}_i + \gamma 0.2 \text{SEX}_i + \gamma 0.3 \text{EDU}_i + \gamma 0.4 \text{DM}_i + \gamma 0.5 \text{HT}_i + \gamma 0.6 \text{DM} * \text{HT}_i + \gamma 0.7 \text{PA}_i$
 $+ \gamma 0.8 \text{DM} * \text{PA}_i + \gamma 0.9 \text{PA} * \text{HT}_i + \gamma 0.10 \text{PA} * \text{DM} * \text{HT}_i$
 $\beta 1_i = \gamma 1.0 + \gamma 1.1 \text{AGE}_i + \gamma 1.2 \text{SEX}_i + \gamma 1.3 \text{EDU}_i + \gamma 1.4 \text{DM}_i + \gamma 1.5 \text{HT}_i + \gamma 1.6 \text{DM} * \text{HT}_i + \gamma 1.7 \text{PA}_i$
 $+ \gamma 1.8 \text{DM} * \text{PA}_i + \gamma 1.9 \text{PA} * \text{HT}_i + \gamma 1.10 \text{PA} * \text{DM} * \text{HT}_i$
- M5: Level 1: $y_{ti} = \beta 0_i + \beta 1_i \text{Time}_i + \epsilon_{ti}$
 Level 2: $\beta 0_i = \gamma 0.0 + \gamma 0.1 \text{AGE}_i + \gamma 0.2 \text{SEX}_i + \gamma 0.3 \text{EDU}_i + \gamma 0.4 \text{DM}_i + \gamma 0.5 \text{HT}_i + \gamma 0.6 \text{DM} * \text{HT}_i + \gamma 0.7 \text{PA}_i$
 $+ \gamma 0.8 \text{DM} * \text{PA}_i + \gamma 0.9 \text{PA} * \text{HT}_i + \gamma 0.10 \text{PA} * \text{DM} * \text{HT}_i + \gamma 0.11 \text{AGE} * \text{DM}_i + \gamma 0.12 \text{AGE} * \text{HT}_i$
 $+ \gamma 0.13 \text{AGE} * \text{PA}_i + \gamma 0.14 \text{SEX} * \text{DM}_i + \gamma 0.15 \text{SEX} * \text{HT}_i + \gamma 0.16 \text{SEX} * \text{PA}_i$

$$\begin{aligned} \beta_{1i} = & \gamma_{1.0} + \gamma_{1.1}AGE_i + \gamma_{1.2}SEX_i + \gamma_{1.3}EDU_i + \gamma_{1.4}DM_i + \gamma_{1.5}HT_i + \gamma_{1.6}DM*HT_i + \gamma_{1.7}PA_i \\ & + \gamma_{1.8}DM*PA_i + \gamma_{1.9}PA*HT_i + \gamma_{1.10}PA*DM*HT_i + \gamma_{1.11}AGE*DM_i + \gamma_{1.12}AGE*HT_i \\ & + \gamma_{1.13}AGE*PA_i + \gamma_{1.14}SEX*DM_i + \gamma_{1.15}SEX*HT_i + \gamma_{1.16}SEX*PA_i \end{aligned}$$

M6: Level 1: $y_{ti} = \beta_{0i} + \beta_{1i}Time_i + \varepsilon_{ti}$
 Level 2: $\beta_{0i} = \gamma_{0.0} + \gamma_{0.1}AGE_i + \gamma_{0.2}SEX_i + \gamma_{0.3}EDU_i + \gamma_{0.4}DM_i + \gamma_{0.5}HT_i + \gamma_{0.6}DM*HT_i + \gamma_{0.7}PA_i$
 $+ \gamma_{0.8}DM*PA_i + \gamma_{0.9}PA*HT_i + \gamma_{0.10}PA*DM*HT_i + \gamma_{0.11}ALC_i + \gamma_{0.12}STRK_i$
 $\beta_{1i} = \gamma_{1.0} + \gamma_{1.1}AGE_i + \gamma_{1.2}SEX_i + \gamma_{1.3}EDU_i + \gamma_{1.4}DM_i + \gamma_{1.5}HT_i + \gamma_{1.6}DM*HT_i + \gamma_{1.7}PA_i$
 $+ \gamma_{1.8}DM*PA_i + \gamma_{1.9}PA*HT_i + \gamma_{1.10}PA*DM*HT_i + \gamma_{1.11}ALC_i + \gamma_{1.12}STRK_i$

Where y_{ti} is individual i 's performance on the cognitive measure at time t , β_{0i} is the intercept for person i , β_{1i} is the slope for person i , and ε_{ti} is the residual variance for person i at time t . In the between-person model, $\gamma_{0.0}$ represents the main effect of the intercept and $\gamma_{1.0}$ represents the main effect of the slope. Specific fixed effects on the random intercept correspond with $\gamma_{0.1}$ through $\gamma_{0.12}$, while fixed effects on the random slope correspond with $\gamma_{1.1}$ through $\gamma_{1.12}$. In the quadratic models, the equation was identical, except an additional term for time was added, $Time^2$, as shown in this modified model M6 incorporating the quadratic effect:

M6_quadratic: Level 1: $y_{ti} = \beta_{0i} + \beta_{1i}Time_i + \beta_{2i}Time_i^2 + \varepsilon_{ti}$
 Level 2: $\beta_{0i} = \gamma_{0.0} + \gamma_{0.1}AGE_i + \gamma_{0.2}SEX_i + \gamma_{0.3}EDU_i + \gamma_{0.4}DM_i + \gamma_{0.5}HT_i + \gamma_{0.6}DM*HT_i + \gamma_{0.7}PA_i$
 $+ \gamma_{0.8}DM*PA_i + \gamma_{0.9}PA*HT_i + \gamma_{0.10}PA*DM*HT_i + \gamma_{0.11}ALC_i + \gamma_{0.12}STRK_i$
 $\beta_{1i} = \gamma_{1.0} + \gamma_{1.1}AGE_i + \gamma_{1.2}SEX_i + \gamma_{1.3}EDU_i + \gamma_{1.4}DM_i + \gamma_{1.5}HT_i + \gamma_{1.6}DM*HT_i + \gamma_{1.7}PA_i$
 $+ \gamma_{1.8}DM*PA_i + \gamma_{1.9}PA*HT_i + \gamma_{1.10}PA*DM*HT_i + \gamma_{1.11}ALC_i + \gamma_{1.12}STRK_i$
 $\beta_{2i} = \gamma_{2.0} + \gamma_{2.1}AGE_i + \gamma_{2.2}SEX_i + \gamma_{2.3}EDU_i + \gamma_{2.4}DM_i + \gamma_{2.5}HT_i + \gamma_{2.6}DM*HT_i + \gamma_{2.7}PA_i$
 $+ \gamma_{2.8}DM*PA_i + \gamma_{2.9}PA*HT_i + \gamma_{2.10}PA*DM*HT_i + \gamma_{2.11}ALC_i + \gamma_{2.12}STRK_i$

In order to improve interpretation of the results, age was centered at the baseline mean and education was centered at 12 years. The reference category for sex was female. The intercepts and slopes represent expected baseline performance and annual rate of change for a 79-year-old female with 12 years of education who does not have diabetes or hypertension, and is not physically active

Results

Participant Characteristics

Descriptive characteristics are presented in Table 1. Although participants were assessed annually, data are reported in two year intervals in order to illustrate trends across the study period. Some participants had up to 17 years of assessments ($n=15$), but fewer than 100 participants had more than 12 years of follow-up. Attrition rates were primarily due to death, and 4,081 participants had available mortality data. Age of death ranged from 65.9 to 103.4 and on average, participants died at age 90.5. Across the sample average time spent engaging in physical activity declined over time, whereas rates of diabetes and hypertension increased. At baseline, hypertension was more prevalent (52.8%) than diabetes (12.7%), and this trend remained as rates of both conditions increased over time. Average performance on the four cognitive measures also declined over time. The observed individual trajectories from a random sample of 100 participants is presented in Figure 1. For each measure, the bold line represents the average of the between and within-person effects.

Table 1. Participant Characteristics Across Years of Study

Measure	Baseline (n=1400) M (SD)	Year 2 (n=1161) M (SD)	Year 4 (n=878) M (SD)	Year 6 (n=618) M (SD)	Year 8 (n=429) M (SD)	Year 10 (n=282) M (SD)	Year 12 (n=140) M (SD)
Age	79.7 (7.5)	81.8 (7.2)	83.1 (7.1)	84.9 (6.7)	86.1 (6.6)	87.7 (6.5)	89.3 (5.6)
Sex (% female)	74.1	74.8	75.3	75.9	76.9	77.7	77.9
Education	14.6 (3.2)	14.7 (3.1)	14.7 (3.0)	14.6 (3.1)	14.8 (2.9)	14.8 (3.0)	15.0 (3.)
Diabetes (% diagnosed)	12.7	14.4	17.7	19.4	19.6	18.8	18.6
Hypertension (% diagnosed)	52.8	56.2	60	65.6	65.5	68.4	66.4
Diabetes + Hypertension (%)	9.2	11	13.3	15.3	16.2	16	13.6
Physical Activity (hrs/week)	3.3 (3.7)	3.0 (3.8)	2.8 (3.3)	2.8 (3.4)	2.7 (3.3)	2.8 (3.2)	2.5 (2.8)
Dementia (% diagnosed)	0	10.2	12.6	15.7	20	17.7	22.9
Mental Status	27.8 (2.2)	26.9 (4.2)	26.4 (4.8)	25.5 (6.2)	25.1 (6.5)	24.7 (6.7)	24.1 (7.9)
Perceptual Speed	37.4 (10.8)	35.8 (12.6)	35.7 (13.3)	33.6 (14.2)	33.6 (14.1)	34.9 (13.8)	32.5 (15.5)
Episodic Memory - Immediate	9.5 (1.8)	9.1 (2.3)	8.8 (2.5)	8.6 (2.8)	8.6 (2.8)	8.7 (2.8)	8.2 (3.4)
Episodic Memory - Delayed	8.9 (2.2)	8.4 (3.0)	8.2 (3.3)	8.0 (3.5)	7.8 (3.6)	8.0 (3.6)	7.6 (3.9)

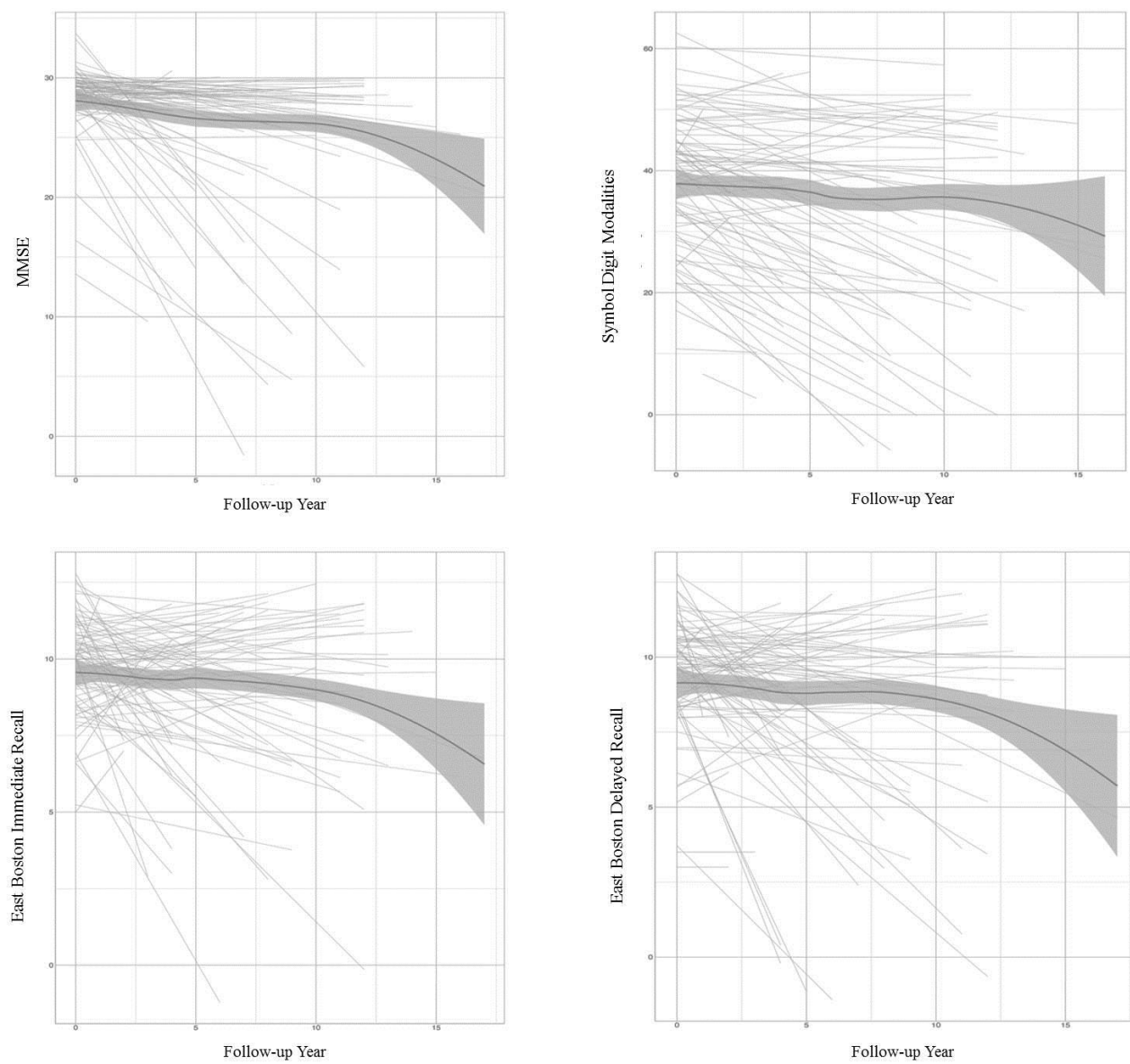


Figure 1. Random Selections of Observed Trajectories on Four Cognitive Outcomes (N = 100)

Multilevel Growth Curve Models

A total of 12 models, six with linear change and six with both linear and quadratic terms, were fit to each of the four outcome measures. Age and sex interactions were not significantly associated with the primary predictors, and as such model 5 was eliminated from the tabled results from the multilevel models, presented in Tables 2 - 9. Across all four cognitive outcomes, older individuals had significantly lower scores at baseline and declined at a quicker rate ($p < .001$). This finding was observed in both the linear only models and the linear plus quadratic models. Males had significantly lower scores than females on all four cognitive outcomes at baseline ($p < .05$), but did not significantly differ from females in their rate of decline. More education was significantly associated with better baseline performance on all four tests ($p < .01$), but was not related to change in cognitive performance over time. The slope and intercept variances were significant ($p < .001$) for all models, suggesting additional variability across individuals that was not captured by the predictor variables selected for this study.

Hypertension

Linear change

In the models that included a linear slope only, hypertension was not associated with intercepts or slopes on the Symbol Digit Modalities Test or the Immediate or Delayed Recall on the East Boston Memory Test. These results are illustrated in Tables 3-5. However in these models, hypertension was significantly associated with better initial performance ($b = .55, p < .05$) and a reduced rate of decline ($b = .31, p < .01$) on the MMSE (see Table 2).

Curvilinear change

Similar patterns were observed in the fully adjusted model with linear and quadratic slopes. Individuals with hypertension had higher initial scores on the MMSE ($b = .48, p < .05$) and significantly less linear decline ($b = .37, p < .05$) but did not have significantly different curvilinear decline (see Table 6). As illustrated in Table 9, hypertension was also associated with better baseline performance on the East Boston Delayed Recall ($b = .54, p < .01$), but did not show a relationship with rate of change on this test. Although hypertension was not significantly associated with initial performance or rate of decline on the Symbol Digit Modalities Test or the East Boston Immediate recall, the effect was in the same direction, such that individuals with hypertension performed better on these tests initially and had slightly less decline over time (Tables 7 and 8).

Diabetes

Linear change

As illustrated in Tables 2, 3, and 5, diabetes was not significantly associated with initial performance or rate of change on the MMSE, Symbol Digit Modalities Test, or the Delayed East Boston Memory Test. However, diabetes was significantly associated with worse initial performance on the Immediate East Boston Memory Test ($b = -.78, p < .05$), but with significantly less steep declines over time ($b = .32, p < .01$).

Curvilinear change

In the quadratic models, diabetes was not significantly associated with baseline performance or steeper declines on any of the cognitive measures.

Physical Activity

Linear change

Higher levels of physical activity were associated with significantly less linear decline on all four cognitive tests ($p < .01$). Additionally, in the models that included a linear slope only, individuals with higher mean levels of physical activity initially performed better on the Symbol Digit Modalities Test ($b = .31, p < .05$) than those who were less physically active. Differences in physical activity were not significantly related to initial performance on the MMSE or either East Boston Memory Test. These results are illustrated in Tables 2-5.

Curvilinear change

In the models that included a quadratic term, physical activity remained significantly associated with a reduced risk of linear decline on the Symbol Digit Modalities test only ($b = .10, p < .01$; Table 7). More engagement in physical activity was associated with significantly better baseline performance on the MMSE in the quadratic models, but not with accelerated rate of change (Table 6).

Interactions among predictors

Linear change

A significant interaction was observed between comorbid diabetes and hypertension on the Immediate East Boston Memory Test, such that comorbid conditions were associated with better initial performance ($b = .93, p < .05$), but an accelerated rate of decline ($b = -.35, p < .01$).

Interactions between physical activity and hypertension and diabetes were observed on slope estimates for the immediate East Boston Memory Test when linear slopes were tested (Table 4).

Specifically, a significant interaction was observed between physical activity and diabetes ($b = -$

.07, $p < .05$), such that individuals with diabetes who were more physically active, declined at a steeper rate than their physically inactive peers. Higher levels of physical activity were associated with better initial performance on this measure for individuals with diabetes, but the association was only approaching statistical significance, ($b = .17, p = .08$). Analyses also revealed a significant 3-way interaction between physical activity, diabetes, and hypertension on immediate episodic memory ($b = .07, p < .05$). In this case, individuals with comorbid diabetes and hypertension who were more active declined at a slower rate than individuals with comorbid conditions who were less physically active.

Curvilinear change

The significant interactions between physical activity and diabetes and hypertension were also observed when a curvilinear slope was considered. The interactions between diabetes and hypertension alone were not associated with significant curvilinear change. All of the aforementioned associations from the multilevel model results remained significant after lifetime alcohol use and stroke were added to the model (see Table 8).

Table 2. Parameter Estimates from Linear Growth Models: Mental Status

Model Term	Model 1	Model 2	Model 3	Model 4	Model 6
	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)
Intercept	27.93 (.10)***	27.63 (.16)***	27.85 (.12)***	27.34 (.21)***	27.43 (.21)***
Age	-.05 (.01)***	-.05 (.01)***	-.04 (.01)***	-.04 (.01)***	-.04 (.01)***
Sex	-1.16 (.17)***	-1.16 (.17)***	-1.17 (.17)***	-1.1 (.17)***	-1.1 (.18)***
Education	.18 (.02)***	.18 (.02)***	.18 (.02)***	.18 (.02)***	.17 (.02)***
Age x Sex	-.06 (.02)**	-.06 (.02)**	-.06 (.02)**	-.06 (.02)**	-.06 (.02)*
Hypertension		.39 (.17)*		.65 (.25)**	.55 (.25)*
Diabetes		.32 (.41)		-.19 (.62)	-.39 (.63)
Hypertension x Diabetes		-.22 (.46)		.60 (.69)	.84 (.70)
Physical Activity			.03 (.02)	.08 (.04)*	.07 (.04)
Physical Activity x Diabetes				.19 (.16)	.23 (.16)
Physical Activity x Hypertension				-.07 (.05)	-.05 (.06)
Physical Activity x Hypertension x Diabetes				-.32 (.18)	-.38 (.19)*
Alcohol					.08 (.07)
Stroke					-.17 (.20)
Slope	-.72 (.04)***	-.85 (.06)***	-.85 (.05)***	-1.11 (.09)***	-1.05 (.09)***
Age	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***	-.03 (.00)***
Sex	.02 (.07)	.04 (.07)	-.01 (.07)	.01 (.07)	.00 (.07)
Education	.01 (.01)	.01 (.01)	.01 (.01)	.01 (.01)	.00 (.01)
Age x Sex	.009 (.01)	.01 (.01)	.01 (.01)	.01 (.01)	.01 (.01)
Hypertension		.19 (.07)**		.35 (.10)**	.31 (.10)**
Diabetes		.03 (.17)		.34 (.27)	.27 (.27)
Hypertension x Diabetes		-.09 (.19)		-.35 (.30)	-.28 (.30)
Physical Activity			.05 (.01)***	.08 (.01)***	.07 (.01)***
Physical Activity x Diabetes				-.08 (.07)	-.06 (.07)
Physical Activity x Hypertension				-.03 (.02)	-.03 (.02)
Physical Activity x Hypertension x Diabetes				.07 (.08)	.05 (.08)
Alcohol					.05 (.02)
Stroke					-.19 (.08)*
Variance Components					.
Intercept	5.81 (.34)***	5.77 (.34)***	5.80 (.34)***	5.70 (.33)***	5.59 (.33)***
Slope	.85 (.05)***	.85 (.06)***	.83 (.05)***	.82 (.05)***	.79 (.04)***
Residual	4.60 (.08)***	4.60 (.08)***	4.60 (.08)***	4.60 (.08)***	4.62 (.08)***

Note. *b* = parameter estimate; SE = standard error; **p* < .05, ***p* < .01, ****p* < .001

Table 3. Parameter Estimates from Linear Growth Models: Perceptual Speed

Model Term	Model 1 <i>b</i> (SE)	Model 2 <i>b</i> (SE)	Model 3 <i>b</i> (SE)	Model 4 <i>b</i> (SE)	Model 6 <i>b</i> (SE)
Intercept	35.87 (.37)***	35.62 (.57)***	35.48 (.45)***	34.63 (.76)***	34.98 (.78)***
Age	-.42 (.04)***	-.42 (.04)***	0.41 (.04)***	-.41 (.04)***	-.41 (.04)***
Sex	-2.36 (.63)***	-2.26 (.64)***	-2.42 (.63)***	-2.29 (.64)***	-2.19 (.66)**
Education	1.02 (.08)***	1.02 (.08)***	1.01 (.08)***	1.01 (.08)***	.97 (.08)***
Age x Sex	-.18 (.08)*	-.18 (.08)*	-.18 (.08)*	-.17 (.08)*	-.19 (.08)*
Hypertension (HT)		.61 (.62)		1.39 (.91)	1.49 (.93)
Diabetes (DM)		-.18 (1.5)		1.11 (2.3)	1.52 (2.34)
Hypertension x Diabetes		-.77 (1.7)		-1.44 (2.55)	-1.60 (2.59)
Physical Activity (PA)			.14 (.10)	.30 (.15)*	.31 (.15)*
PA x DM				-.41 (.60)	-.50 (.61)
PA x HT				-.22 (.31)	-.22 (.22)
PA x DM x HT				.16 (.68)	.12 (.70)
Alcohol					.12 (.25)
Stroke					-2.18 (.76)**
Slope	-1.38 (.06)***	-1.41 (.11)***	-1.62 (.08)***	-1.70 (.15)***	-1.63 (.15)***
Age	-.07 (.00)***	-.08 (.00)***	-.07 (.00)***	-.07 (.00)***	-.07 (.00)***
Sex	.09 (.11)	.10 (.11)	.01 (.11)	.02 (.11)	.01 (.11)
Education	.00 (.01)	.00 (.01)	.00 (.01)	.00 (.01)	-.00 (.01)
Age x Sex	.00 (.01)	.00 (.01)	.01 (.01)	.01 (.01)	.01 (.01)
Hypertension (HT)		.04 (.11)		.06 (.17)	.06 (.17)
Diabetes (DM)		-.14 (.27)		.25 (.47)	.19 (.46)
Hypertension x Diabetes		.11 (.30)		-.19 (.51)	-.09 (.50)
Physical Activity (PA)			.09 (.01)***	.095 (.03)**	.08 (.03)**
PA x DM				-.11 (.12)	-.08 (.12)
PA x HT				.01 (.04)	.01 (.04)
PA x DM x HT				.10 (.13)	.06 (.13)
Alcohol					.05 (.04)
Stroke					-.44 (.12)***
Variance Components					
Intercept	90.83 (4.02)***	90.68 (4.01)***	90.71 (4.01)***	90.28 (4.0)***	89.15 (3.9)***
Slope	1.4 (.11)***	1.4 (.11)***	1.34 (.11)***	1.34 (.11)***	1.31 (.10)***
Residual	28.26 (.52)***	28.26 (.52)***	28.26 (.52)***	28.26 (.51)***	28.30 (.52)***

Table 4. Parameter Estimates from Linear Growth Models: Episodic Memory (Immediate)

Model Term	Model 1 <i>b</i> (SE)	Model 2 <i>b</i> (SE)	Model 3 <i>b</i> (SE)	Model 4 <i>b</i> (SE)	Model 6 <i>b</i> (SE)
Intercept	9.39 (.06)***	9.23 (.10)***	9.41 (.07)***	9.22 (.13)***	9.22 (.13)***
Age	-.03 (.00)***	-.03 (.00)***	-.03 (.00)***	-.03 (.00)***	-.02 (.00)***
Sex	-.38 (.10)***	-.35 (.11)**	-.36 (.11)**	-.35 (.11)**	-.40 (.11)***
Education	.08 (.01)***	.09 (.01)***	.08 (.01)***	.09 (.01)***	.08 (.01)***
Age x Sex	-.007 (.01)	-.007 (.01)	-.009 (.01)	-.006 (.01)	-.008 (.01)
Hypertension (HT)		.20 (.10)		.27 (.15)	.21 (.16)
Diabetes (DM)		-.18 (.25)		-.60 (.39)	-.78 (.39)*
Hypertension x Diabetes		.29 (.28)		.69 (.43)	.93 (.44)*
Physical Activity (PA)			-.009 (.01)	.004 (.02)	-.002 (.02)
PA x DM				.14 (.10)	.17 (.10)
PA x HT				-.02 (.03)	-.007 (.03)
PA x DM x HT				-.12 (.11)	-.18 (.11)
Alcohol					.12 (.04)**
Stroke					-.01 (.12)
Slope	-.23 (.01)***	-.26 (.02)***	-.28 (.02)***	-.34 (.03)***	-.33 (.03)***
Age	-.01 (.00)***	-.01 (.00)***	-.01 (.00)***	-.01 (.00)***	-.01 (.00)***
Sex	-.001 (.03)	.000 (.03)	-.01 (.03)	-.01 (.03)	-.006 (.03)
Education	.007 (.00)	.008 (.00)	.006 (.00)	.006 (.00)	.006 (.00)
Age x Sex	.006 (.00)	.006 (.00)	.007 (.00)	.007 (.00)	.007 (.00)
Hypertension (HT)		.04 (.03)		.08 (.04)	.07 (.04)
Diabetes (DM)		.08 (.07)		.31 (.12)*	.32 (.12)**
Hypertension x Diabetes		-.12 (.07)		-.34 (.13)**	-.35 (.13)**
Physical Activity (PA)			.01 (.00)***	.02 (.00)**	.02 (.00)**
PA x DM				-.06 (.03)*	-.07 (.03)*
PA x HT				-.008 (.01)	-.007 (.01)
PA x DM x HT				.07 (.03)*	.07 (.03)*
Alcohol					-.01 (.01)
Stroke					-.02 (.03)
Variance Components					
Intercept	1.91 (.12)***	1.89 (.12)***	1.90 (.12)***	1.88 (.12)***	1.81 (.12)***
Slope	.08 (.00)***	.08 (.00)***	.08 (.00)***	.08 (.00)***	.08 (.00)***
Residual	2.62 (.04)***	2.62 (.04)***	2.62 (.04)***	2.62 (.04)***	2.62 (.04)***

Note. *b* = parameter estimate; SE = standard error; **p* < .05, ***p* < .01, ****p* < .001

Table 5. Parameter Estimates from Linear Growth Models: Episodic Memory (Delayed)

Model Term	Model 1 <i>b</i> (SE)	Model 2 <i>b</i> (SE)	Model 3 <i>b</i> (SE)	Model 4 <i>b</i> (SE)	Model 6 <i>b</i> (SE)
Intercept	8.9 (.08)***	8.64 (.12)***	8.85 (.10)***	8.51 (.16)***	8.53 (.17)***
Age	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***	-.03 (.00)***
Sex	-.51 (.13)***	-.49 (.14)***	-.51 (.14)***	-.49 (.14)***	-.55 (.14)***
Education	.08 (.01)***	.08 (.01)***	.08 (.01)***	.08 (.01)***	.07 (.01)***
Age x Sex	-.01 (.01)	-.01 (.01)	-.01 (.01)	-.01 (.01)	-.02 (.02)
Hypertension (HT)		.35 (.13)*		.46 (.20)*	.39 (.20)
Diabetes (DM)		.14 (.32)		-.07 (.49)	-.20 (.50)
Hypertension x Diabetes		-.12 (.36)		.08 (.55)	.30 (.56)
Physical Activity (PA)			.02 (.02)	.04 (.03)	.03 (.03)
PA x DM				.08 (.13)	.11 (.13)
PA x HT				-.03 (.04)	-.009 (.04)
PA x DM x HT				-.06 (.15)	-.13 (.15)
Alcohol					.15 (.05)**
Stroke					-.17 (.16)
Slope	-.30 (.02)***	-.31 (.03)***	-.36 (.02)***	-.40 (.04)***	-.39 (.04)***
Age	-.01 (.00)***	-.01 (.00)***	-.01 (.00)***	-.01 (.00)***	-.01 (.00)***
Sex	.05 (.03)	.05 (.03)	.03 (.03)	.04 (.03)	.04 (.03)
Education	.01 (.00)*	.01 (.00)*	.008 (.00)	.008 (.00)	.009 (.00)
Age x Sex	.006 (.00)	.006 (.00)	.008 (.00)	.007 (.00)	.007 (.00)
Hypertension (HT)		.02 (.03)		.05 (.05)	.05 (.05)
Diabetes (DM)		-.04 (.08)		.10 (.13)	.11 (.13)
Hypertension x Diabetes		.001 (.08)		-.10 (.15)	-.11 (.15)
Physical Activity (PA)			.02 (.00)***	.02 (.00)**	.02 (.00)**
PA x DM				-.04 (.03)	-.04 (.03)
PA x HT				-.006 (.01)	-.006 (.01)
PA x DM x HT				.02 (.04)	.03 (.04)
Alcohol					-.009 (.01)
Stroke					-.01 (.03)
Variance Components					
Intercept	3.44 (.20)***	3.42 (.19)***	3.43 (.19)***	3.40 (.19)***	3.34 (.19)***
Slope	.10 (.00)***	.10 (.00)***	.10 (.00)***	.10 (.00)***	.10 (.00)***
Residual	3.52 (.06)***	3.52 (.06)***	3.52 (.06)***	3.52 (.06)***	3.51 (.06)***

Note. *b* = parameter estimate; SE = standard error; **p* < .05, ***p* < .01, ****p* < .001

Table 6. Parameter Estimates from Linear and Quadratic Growth Curve Models: Mental Status

Model Term	Model 1	Model 2	Model 3	Model 4	Model 6
	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)
Intercept	27.42 (.08)***	27.25 (.13)***	27.30 (.10)***	26.87 (.17)***	26.96 (.18)***
Age	-.06 (.01)***	-.06 (.01)***	-.06 (.01)***	-.06 (.01)***	-.06 (.01)***
Sex	-.88 (.14)***	-.89 (.14)***	-.91 (.14)***	-.90 (.14)***	-.91 (.15)***
Education	.18 (.02)***	.19 (.02)***	.18 (.02)***	.18 (.02)***	.18 (.02)***
Age x Sex	-.05 (.02)**	-.05 (.02)*	-.05 (.02)*	-.04 (.02)*	-.04 (.02)*
Hypertension (HT)		.20 (.14)		.53 (.21)*	.48 (.21)*
Diabetes (DM)		.23 (.34)		.26 (.53)	.09 (.53)
Hypertension x Diabetes		-.13 (.38)		.15 (.58)	.37 (.59)
Physical Activity (PA)			.04 (.02)	.11 (.03)**	.10 (.03)**
PA x DM				.02 (.13)	.05 (.13)
PA x HT				-.09 (.04)*	-.08 (.05)
PA x DM x HT				-.14 (.15)	-.20 (.16)
Alcohol					.07 (.06)
Stroke					-.35 (.17)*
Linear Slope	-.24 (.08)***	-.49 (.10)***	-.34 (.08)***	-.64 (.14)***	-.57 (.14)***
Age	-.01 (.00)*	-.01 (.00)*	-.01 (.00)*	-.01 (.00)*	-.01 (.00)
Sex	-.23 (.11)	-.19 (.11)	-.24 (.11)*	-.21 (.11)	-.22 (.11)
Education	.001 (.01)	.005 (.01)	-.001 (.01)	.003 (.01)	-.003 (.01)
Age x Sex	-.01 (.01)	-.008 (.01)	-.01 (.01)	-.007 (.01)	-.007 (.01)
Hypertension (HT)		.35 (.11)**		.42 (.17)**	.37 (.16)*
Diabetes (DM)		.08 (.27)		-.21 (.44)	-.30 (.43)
Hypertension x Diabetes		-.13 (.30)		.18 (.48)	.27 (.48)
Physical Activity (PA)			.03 (.01)	.05 (.03)	.04 (.02)
PA x DM				.11 (.12)	.13 (.13)
PA x HT					.18 (.48)
PA x DM x HT					-.11 (.11)
Alcohol					.05 (.04)
Stroke					-.09 (.13)
Quadratic Slope	-.06 (.00)***	-.04 (.01)***	-.06 (.01)***	-.06 (.01)**	-.06 (.01)**
Age	-.004 (.00)***	-.004 (.00)***	-.004 (.00)***	-.004 (.00)***	-.004 (.00)***
Sex	.02 (.01)*	.02 (.01)	.02 (.01)	.02 (.01)	.02 (.01)
Education	.002 (.00)	.002 (.00)	.002 (.00)	.002 (.00)	.002 (.00)
Age x Sex	.003 (.00)	.002 (.00)	.003 (.00)	.003 (.00)	.003 (.00)
Hypertension (HT)		-.02 (.01)		-.009 (.02)	-.005 (.02)
Diabetes (DM)		.001 (.03)		.08 (.06)	.09 (.05)
Hypertension x Diabetes		-.005 (.03)		-.08 (.06)	-.08 (.06)
Physical Activity (PA)			.002 (.00)	.004 (.00)	.004 (.00)
PA x DM				-.02 (.01)	-.02 (.01)
PA x HT				-.002 (.00)	-.003 (.00)
PA x DM x HT				.02 (.01)	.02 (.01)
Alcohol					.000 (.00)
Stroke					-.003 (.01)
Variance Components					
Intercept	3.32 (.26)***	3.30 (.13)***	3.3 (.02)***	3.24 (.26)***	3.17 (.26)***
Linear Slope	1.95 (.14)***	1.93 (.14)***	1.94 (.14)***	1.90 (.14)***	1.82 (.14)***
Quadratic Slope	.01 (.00)***	.01 (.00)***	.01 (.00)***	.01 (.00)***	.01 (.00)***
Residual	3.33 (.06)***	3.33 (.06)***	3.33 (.06)***	3.34 (.06)***	3.35 (.06)***

Table 7. Parameter Estimates from Linear and Quadratic Growth Curve Models: Perceptual Speed

Model Term	Model 1 <i>b</i> (SE)	Model 2 <i>b</i> (SE)	Model 3 <i>b</i> (SE)	Model 4 <i>b</i> (SE)	Model 6 <i>b</i> (SE)
Intercept	35.18 (.36)***	34.93 (.56)***	34.80 (.44)***	34.06 (.74)***	34.38 (.76)***
Age	-.42 (.04)***	-.43 (.04)***	-0.42 (.04)***	-.42 (.04)***	-.41 (.04)***
Sex	-2.04 (.61)**	-1.95 (.62)**	-2.13 (.61)**	-2.01 (.62)**	-1.9 (.64)**
Education	.97 *.08)***	.97 (.08)***	.96 (.08)***	.96 (.08)***	.92 (.08)***
Age x Sex	-.16 (.08)	-.16 (.08)*	-.16 (.08)	-.16 (.08)	-.17 (.08)*
Hypertension (HT)		.59 (.61)		1.12 (.89)	1.21 (.90)
Diabetes (DM)		-.14 (1.4)		1.00 (2.25)	1.40 (2.2)
Hypertension x Diabetes		-.71 (1.6)		-.97 (2.4)	-1.10 (2.5)
Physical Activity (PA)			.14 (.09)	.27 (.15)	.27 (.15)
PA x DM				-.36 (.59)	-.44 (.59)
PA x HT				-.14 (.20)	-.14 (.21)
PA x DM x HT				.02 (.67)	-.02 (.68)
Alcohol					.14 (.25)
Stroke					-2.03 (.74)**
Linear Slope	-.80 (.12)***	-.77 (.18)***	-1.04 (.14)***	-1.17 (.25)***	-1.06 (.25)***
Age	-.06 (.01)***	-.06 (.01)***	-.05 (.01)***	-.05 (.01)***	-.05 (.01)***
Sex	-.15 (.19)	-.13 (.19)	-.20 (.19)	-.17 (.19)	-.14 (.20)
Education	.05 (.02)	.04 (.02)	.04 (.02)	.04 (.02)	.03 (.02)
Age x Sex	-.02 (.02)	-.02 (.02)	-.01 (.02)	-.01 (.02)	-.01 (.02)
Hypertension (HT)		-.002 (.19)		.24 (.29)	.25 (.29)
Diabetes (DM)		-.28 (.47)		.33 (.85)	.32 (.85)
Hypertension x Diabetes		.18 (.52)		-.62 (.92)	-.56 (.92)
Physical Activity (PA)			.09 (.03)**	.12 (.05)*	.11 (.05)*
PA x DM				-.18 (.22)	-.16 (.22)
PA x HT				.06 (.06)	-.04 (.06)
PA x DM x HT				.26 (.25)	.23 (.25)
Alcohol					.02 (.07)
Stroke					-.63 (.22)**
Quadratic Slope	-.06 (.01)***	-.07 (.02)***	-.06 (.01)***	-.06 (.02)*	-.07 (.02)**
Age	-.004 (.00)**	-.004 (.00)**	-.004 (.00)**	-.003 (.00)*	-.003 (.00)*
Sex	.02 (.02)	.02 (.02)	.02 (.02)	.02 (.02)	.01 (.02)
Education	-.005 (.00)	-.005 (.00)	-.006 (.00)	-.005 (.00)	-.005 (.00)
Age x Sex	.004 (.00)	.004 (.00)	.004 (.00)	.004 (.00)	.004 (.00)
Hypertension (HT)		.01 (.01)		-.01 (.03)	-.01 (.03)
Diabetes (DM)		.02 (.04)		-.01 (.10)	-.02 (.10)
Hypertension x Diabetes		-.01 (.05)		.05 (.10)	.06 (.10)
Physical Activity (PA)			.001 (.00)	-.002 (.00)	-.002 (.00)
PA x DM				.01 (.02)	.01 (.02)
PA x HT				.008 (.00)	.007 (.00)
PA x DM x HT				-.02 (.02)	-.02 (.02)
Alcohol					.005 (.00)
Stroke					.02 (.02)
Variance Components					
Intercept	82.05 (3.8)***	81.97 (3.8)***	81.97 (3.8)***	81.64 (3.8)***	80.62 (3.8)***
Linear Slope	2.80 (.35)***	2.79 (.35)***	2.75 (.34)***	2.72 (.34)***	2.64 (.34)***
Quadratic Slope	.01 (.00)***	.01 (.00)***	.01 (.00)***	.01 (.00)***	.01 (.00)***
Residual	26.00 (.50)***	26.00 (.50)***	26.01 (.50)***	25.99 (.50)***	26.04 (.50)***

Table 8. Parameter Estimates from Linear and Quadratic Growth Curve Models: Episodic Memory (Immediate)

Model Term	Model 1 <i>b</i> (SE)	Model 2 <i>b</i> (SE)	Model 3 <i>b</i> (SE)	Model 4 <i>b</i> (SE)	Model 6 <i>b</i> (SE)
Intercept	9.29 (.06)***	9.14 (.10)***	9.31 (.08)***	9.06 (.13)***	9.04 (.13)***
Age	-.03 (.00)***	-.03 (.00)***	-.03 (.00)***	-.03 (.00)***	-.03 (.00)***
Sex	-.22 (.11)*	-.20 (.11)	-.22 (.11)*	-.20 (.11)	-.25 (.11)*
Education	.08 (.01)***	.08 (.01)***	.08 (.01)***	.08 (.01)***	.07 (.01)***
Age x Sex	-.01 (.01)	-.01 (.01)	-.01 (.01)	-.009 (.01)	-.01 (.01)
Hypertension (HT)		.19 (.11)		.34 (.16)*	.29 (.16)
Diabetes (DM)		-.34 (.26)		-.30 (.40)	-.46 (.41)
Hypertension x Diabetes		.50 (.29)		.43 (.45)	.66 (.45)
Physical Activity (PA)			-.007 (.01)	.02 (.02)	.02 (.02)
PA x DM				.006 (.10)	.04 (.10)
PA x HT				-.04 (.03)	-.03 (.03)
PA x DM x HT				.009 (.12)	-.04 (.12)
Alcohol					.13 (.04)**
Stroke					-.005 (.13)
Linear Slope	-.15 (.03)***	-.19 (.05)***	-.20 (.04)***	-.19 (.07)**	-.17 (.07)*
Age	-.006 (.00)	-.007 (.00)	-.006 (.00)	-.006 (.00)	-.006 (.00)
Sex	-.12 (.05)*	-.12 (.05)*	-.13 (.05)*	-.14 (.05)**	-.13 (.05)*
Education	.01 (.00)	.01 (.00)	.01 (.00)	.01 (.00)	.01 (.00)
Age x Sex	.01 (.00)	.01 (.00)	.01 (.00)	.01 (.00)	.01 (.00)
Hypertension (HT)		.05 (.05)		-.006 (.08)	-.01 (.08)
Diabetes (DM)		.23 (.13)		-.08 (.23)	-.07 (.23)
Hypertension x Diabetes		-.30 (.14)*		.01 (.25)	-.005 (.25)
Physical Activity (PA)			.01 (.00)*	.006 (.01)	.004 (.01)
PA x DM				.09 (.06)	.09 (.06)
PA x HT				.01 (.01)	.01 (.01)
PA x DM x HT				-.09 (.07)	-.08 (.07)
Alcohol					-.01 (.02)
Stroke					-.04 (.06)
Quadratic Slope	-.009 (.00)**	-.008 (.00)	-.009 (.00)*	-.01 (.00)*	-.02 (.00)*
Age	-.001 (.00)**	-.001 (.00)*	-.001 (.00)*	-.001 (.00)*	-.001 (.00)*
Sex	.01 (.00)*	.01 (.00)*	.01 (.00)*	.01 (.00)*	.01 (.00)*
Education	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.0012 (.00)
Age x Sex	-.001 (.00)	-.001 (.00)	-.001 (.00)	.000 (.00)	-.001 (.00)
Hypertension (HT)		-.001 (.00)		.01 (.00)	.01 (.00)
Diabetes (DM)		-.01 (.01)		.05 (.02)	.05 (.02)
Hypertension x Diabetes		.02 (.01)		-.05 (.03)	-.04 (.03)
Physical Activity (PA)			.000 (.00)	.002 (.00)	.003 (.00)
PA x DM				-.02 (.00)**	-.02 (.00)**
PA x HT				-.003 (.00)	-.003 (.00)
PA x DM x HT				.02 (.00)*	.02 (.00)*
Alcohol					.001 (.00)
Stroke					.002 (.00)
Variance Components					
Intercept	1.61 (.13)***	1.60 (.13)***	1.60 (.13)***	1.58 (.13)***	1.50 (.13)***
Linear Slope	.16 (.02)***	.15 (.02)***	.16 (.02)***	.15 (.02)***	.15 (.02)***
Quadratic Slope	.001 (.00)***	.001 (.00)***	.001 (.00)***	.001 (.00)***	.001 (.00)***
Residual	2.51 (.04)***	2.51 (.04)***	2.51 (.04)***	2.51 (.04)***	2.50 (.04)***

Table 9. Parameter Estimates from Linear and Quadratic Growth Curve Models: Episodic Memory (Delayed)

Model Term	Model 1 <i>b</i> (SE)	Model 2 <i>b</i> (SE)	Model 3 <i>b</i> (SE)	Model 4 <i>b</i> (SE)	Model 6 <i>b</i> (SE)
Intercept	8.7 (.08)***	8.50 (.12)***	8.75 (.09)***	8.31 (.16)***	8.31 (.16)***
Age	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***	-.04 (.00)***
Sex	-.37 (.13)**	-.35 (.13)**	-.37 (.13)**	-.36 (.13)**	-.44 (.14)**
Education	.07 (.01)***	.07 (.01)***	.07 (.01)***	.07 (.01)***	.06 (.01)**
Age x Sex	-.02 (.01)	-.02 (.01)	-.02 (.01)	-.02 (.01)	-.02 (.01)
Hypertension (HT)		.38 (.13)**		.59 (.19)	.54 (.19)**
Diabetes (DM)		.19 (.32)		.14 (.49)	-.001 (.49)
Hypertension x Diabetes		-.13 (.36)		-.15 (.54)	.08 (.55)
Physical Activity (PA)			.01 (.02)	.05 (.03)	.05 (.03)
PA x DM				.03 (.12)	.07 (.12)
PA x HT				-.06 (.04)	-.04 (.04)
PA x DM x HT				.001 (.14)	-.07 (.14)
Alcohol					.20 (.05)***
Stroke					-.20 (.16)
Linear Slope	-.22 (.03)***	-.19 (.06)***	-.28 (.04)***	-.22 (.08)**	-.19 (.08)**
Age	-.01 (.00)**	-.01 (.00)**	-.01 (.00)**	-.01 (.00)**	-.01 (.00)**
Sex	-.05 (.06)	-.04 (.06)	-.06 (.06)	-.06 (.06)	-.03 (.06)
Education	.01 (.00)*	.01 (.00)*	.01 (.00)*	.01 (.00)	.01 (.00)*
Age x Sex	.01 (.01)	.01 (.01)	.01 (.01)	.01 (.01)	.01 (.01)
Hypertension (HT)		-.009 (.06)		-.08 (.09)	-.09 (.09)
Diabetes (DM)		-.09 (.15)		-.14 (.28)	-.09 (.28)
Hypertension x Diabetes		.02 (.17)		.17 (.30)	.11 (.30)
Physical Activity (PA)			.02 (.01)*	.01 (.01)	.01 (.01)
PA x DM				.01 (.07)	.001 (.07)
PA x HT				.02 (.02)	.02 (.02)
PA x DM x HT				-.04 (.08)	-.02 (.08)
Alcohol					-.05 (.02)*
Stroke					-.007 (.07)
Quadratic Slope	-.008 (.00)*	-.01 (.00)*	-.007 (.00)	-.02 (.00)*	-.02 (.00)*
Age	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.001 (.00)*	-.001 (.00)*
Sex	.01 (.00)	.01 (.00)	.009 (.00)	.01 (.00)	.007 (.00)
Education	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.001 (.00)
Age x Sex	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.001 (.00)	-.001 (.00)
Hypertension (HT)		.004 (.00)		.01 (.01)	.01 (.01)
Diabetes (DM)		.004 (.01)		.02 (.03)	.02 (.03)
Hypertension x Diabetes		-.002 (.01)		-.03 (.03)	-.02 (.03)
Physical Activity (PA)			.000 (.00)	.002 (.00)	.002 (.00)
PA x DM				-.007 (.00)	-.005 (.00)
PA x HT				-.004 (.00)	-.004 (.00)
PA x DM x HT				.009 (.01)	.007 (.01)
Alcohol					.005 (.00)
Stroke					.000 (.00)
Variance Components					
Intercept	2.63 (.19)***	2.60 (.19)***	2.61 (.19)***	2.57 (.19)***	2.50 (.19)***
Linear Slope	.26 (.03)***	.26 (.03)***	.26 (.03)***	.25 (.03)***	.25 (.03)***
Quadratic Slope	.002 (.00)***	.002 (.00)***	.002 (.00)***	.001 (.00)***	.001 (.00)***
Residual	3.36 (.06)***	3.36 (.06)***	3.36 (.06)***	3.37 (.06)***	3.36 (.06)***

Discussion

The goals of this study were to evaluate how physical activity is associated with baseline performance and rate of change on four cognitive measures, and to examine whether physical activity moderates the negative impacts that hypertension and diabetes can have on cognitive decline in older adults. In particular, this study utilized a longitudinal design to examine the associations between these variables and performance on measures of perceptual speed, episodic memory, and mental status. Multilevel growth curve models evaluated initial performance and rate of change using linear and quadratic growth terms. This study yielded mixed results across measures and the type of growth term considered (i.e., linear vs. quadratic slopes).

When considering linear trajectories, higher levels of self-reported physical activity were associated with better perceptual speed performance at baseline, and significantly less cognitive decline across all four measures. These significant main effects suggest that physically active older adults experience less steep declines in multiple cognitive domains across time. However, when a quadratic growth term was used, physical activity was only significantly associated with better mental status at baseline. These discrepant results suggest that the rate of change in cognition is not consistent across time. Therefore, when the curvilinear rate of change was considered, physical activity was not as strongly associated as it was with the more steep linear estimates. It is important to note the robust effect that physical activity had in the final linear models across cognitive measures. Although physical inactivity can contribute to the development of diabetes and hypertension (Diaz & Shimbo, 2013; Gill & Cooper, 2008), there was still a significant relationship between physical activity and cognitive decline when the influence of diabetes and hypertension was held constant. In other words, higher levels of physical activity were associated with less cognitive decline across multiple domains of

cognition, and this remained true after controlling for the variance associated with diabetes and hypertension, as well as lifetime alcohol use and history of stroke. This finding provides support for the hypothesis that physical activity can have cognitive benefits, even in the context of other risk factors.

Contrary to expectations, hypertension and diabetes were not consistently related to worse cognitive performance or greater rates of decline. Hypertension was associated with better initial mental status (linear and quadratic models) and delayed episodic memory (quadratic model). Individuals with hypertension did not experience a steeper rate of cognitive decline compared to individuals without hypertension. Similarly, diabetes was not a consistent risk factor for decline in this sample. While diabetes was not significantly associated with any measures in the quadratic models, there were significant associations between diabetes and performance on immediate episodic memory. Individuals with diabetes had worse initial performance, but did not decline as quickly as those without diabetes. It is likely that this is because their scores were so much lower to begin with, therefore leaving less room for subsequent decline.

In the linear models, comorbid diabetes and hypertension was associated with better baseline performance in immediate episodic memory, but individuals with both conditions declined at a significantly greater rate than individuals who did not have both conditions. Having comorbid diabetes and hypertension was not significantly related to initial scores or quadratic rate of change on any of the curvilinear models.

Physical activity did not significantly interact with diabetes and hypertension in most of the models. This was not entirely surprising, given that hypertension and diabetes had such weak associations with cognitive outcomes when evaluated independently. However, it is important to note that physical activity did reduce the negative impact that comorbid diabetes and

hypertension had on rate of change on immediate episodic memory. Individuals who had both diabetes and hypertension, and who were also inactive declined at a quicker rate than more active individuals with these conditions.

The findings from this study contradict some of the previous work in the literature (Loprinzi, 2016; Shah et al., 2006), but are consistent with some recent findings. For example, Kelly and colleagues (2016) observed significant associations between diabetes and worse verbal memory performance on only one out of three longitudinal studies. In this study hypertension was significantly associated with less steep decline in two out of three studies, demonstrating a trend in the same direction as this study. It is not surprising that we observed better cognitive outcomes in individuals with hypertension given that the average age of participants at baseline was 79. This is in line with previous studies that have found mid-life hypertension to be associated with a greater risk of cognitive decline, but late-life hypertension being associated with a reduced risk of cognitive decline (Gottesman et al., 2014).

We can make extrapolations from these multilevel models to provide a basis to evaluate the clinical significance of these findings. In this study, the slope coefficients represent the expected annual rate of change, and by multiplying these values by ten, an estimate of decade change can be generated. For example, in the linear models, individuals with hypertension and diabetes declined an additional .35 points on the Immediate East Boston Memory Test each year. Over the course of a decade, these individuals would be expected to score 3.5 points less than individuals without the two conditions. This change is quite substantial, given that this test is scored out of a total of only 12 points. Similarly, hypertension was associated with significantly less decline on the MMSE, such that individuals declined .31 points less each year. Over the

course of a decade, their MMSE score would be more than 3 points higher, which could impact the cognitive impairment category they fall in (e.g., mild vs. moderate impairment).

There are a number of limitations to this study that deserve mentioning. One of the major concerns surrounds the way in which physical activity was measured. Physical activity data was based on self-report, which is susceptible to recall bias, particularly in an elderly population in which many individuals have cognitive impairment. Participants report their activity over past two weeks and this is not necessarily indicative of their activity level over the past year.

Additionally, responses would likely have been influenced by the time of year and the weather when the assessment took place. As such, many individuals likely report more or less activity than they engage in throughout the year between assessments. Physical activity was calculated as a total score based on the number of hours participants engaged in specific activities.

Unfortunately, there was no information available on the specific activities reported and we were not able to consider how intensity of activity may play a role. Many previous studies focus specifically on aerobic exercise or resistance exercise (e.g., Baker et al., 2010; Cassilhas et al., 2007), making it challenging to compare our results which represent activity in general. This study used average physical activity across the study duration, but this between-person score may have been impacted by particularly high or low years. Moreover, this method of conceptualizing physical activity does not account for changes in physical activity over time, and it would be worth examining dynamic change in physical activity in follow-up studies. Future studies could also examine the association between sedentary behaviour and trajectories of cognitive decline.

On average, individuals in this study had 14 years of education, and higher levels of education were associated with better cognitive outcomes across all four tests. It is important to

keep in mind that this is a well-educated sample, and the results may not generalize to samples in which participants have less education or come from lower socioeconomic backgrounds. It would be interesting to see if physical activity and chronic health conditions are differentially associated to cognitive decline in samples with less education. Another factor related to generalizability is that participants in this study had to agree to donate their brain and spinal cord at death, and this requirement may have deterred certain individuals.

No information regarding age of onset was available for hypertension and diabetes. This would have been helpful to consider so that we could have evaluated the cumulative effects of long-term conditions. It is likely that the impact of having these conditions for one year would be quite different than an illness that has progressed for over two decades. A final limitation of this study is the rate of attrition across occasions, which was largely due to participant deaths. Follow-up rates did include 90% of individuals who are still alive (Negash, Bennett, Wilson, Schneider, & Arnold, 2011).

It is important to note the discrepant results that were observed between models using linear slopes and those using quadratic slopes. It is likely that different health conditions and physical activity exhibit differential impacts on cognitive outcomes at different time points. A statistical approach, the Johnson-Neyman technique, may be best suited to analyzing this complex research question in the future (Johnson & Neyman, 1936). In this type of analysis, specific regions of significance for various predictors are identified. Recent work by Rast, Rush, Piccinin, and Hofer (2014) indicates that the Johnson-Neyman technique is useful for evaluating complex interactions in longitudinal data sets. Future work would benefit from using this technique to better understand the impact that hypertension, diabetes, and physical activity have on rate of change in cognition.

Although the results of this study did not strongly support the hypothesis that physical activity can reduce the risk of cognitive decline in individuals with diabetes and hypertension, this may be due to some of the limitations previously mentioned. Follow-up studies are recommended for evaluating this important research question. Future studies could benefit from examining energy expenditure specifically, so that we can better understand the optimal levels of physical activity that may be associated with a reduced risk of cognitive decline.

Additionally, future studies examining this research question would benefit from taking a coordinated analysis approach, whereby the same model is applied to multiple longitudinal studies (Hofer & Piccinin, 2009). This approach is useful in evaluating the replicability of findings and the extent to which differences may be observed in different cohorts of individuals. It is specifically recommended that this research question be evaluated with a sample of individuals who are younger at baseline, in order to see if physical activity interacts with mid-life hypertension to influence cognitive performance.

In summary, this study found that more physical activity was associated with less linear decline on three different cognitive domains. Hypertension had a largely protective association with mental status and episodic memory performance. Diabetes was largely unrelated to initial performance and rate of change, with the exception of immediate episodic memory performance. Although most interactions between physical activity and the two health conditions were non-significant, physical activity did appear to be associated with less steep declines in immediate episodic memory among individuals with diabetes, and this was true for both linear and quadratic growth models.

The findings from this study illuminate several important considerations when working with longitudinal data. First, results and interpretations can vary substantially depending on the

growth parameters selected. Studies that have many waves of data collection are likely better suited to a non-linear evaluation. This study also highlights the importance of considering multiple domains of cognition, given that many predictors were only associated with one or two out of four cognitive measures. In particular, mental status seemed susceptible to the protective effects of hypertension, and immediate episodic memory appeared especially sensitive to the negative effects of diabetes. More research is needed to better understand these complex associations. This line of research is particularly important given that these risk factors are amenable to lifestyle changes, and could potentially reduce the incidence and rate of cognitive decline in older adults.

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