MULTIMORBIDITY AND COGNITIVE DECLINE IN AGING ADULTS

by

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ABSTRACT

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This study explored longitudinal change in executive function (EF) and episodic memory (EM) related to multimorbidity, number of chronic conditions, change in chronic conditions overtime in a nationally representative sample of young, middle-aged, and older adults. Participants were from the second (2004-2006) and third (2013-2015) waves of the Survey of Midlife Development in the United States (MIDUS; N=2,532). Participants completed telephone interviews and questionnaires providing information on demographics and chronic conditions. The Brief Test of Adult Cognition by Telephone (BTACT) assessed cognitive function. The BTACT includes measures of EM (ex. word list recall) and EF (ex. digits backward, category fluency, etc.). Overall, only change in chronic conditions was associated with EF decline in the whole sample. In young adults multimorbidity and number of chronic conditions was significantly associated with both EF and EM decline, whereas only change in number of chronic conditions was significantly associated with EF decline in middle aged adults. Future research is needed to assess a broader range of chronic conditions to determine their overall burden on EF and EM over time.

INTRODUCTION

Aging is often accompanied by declines in cognitive function, but there is growing evidence that such declines are less related to aging *per se* than to the accumulation of chronic diseases that are associated with advancing age. Moreover, cognition is not a single entity but a set of mental processes that do not change uniformly with age or with chronic disease. Further, it is becoming more common for middle aged and older adults to be diagnosed with two or more chronic conditions (multimorbidity) that can vary in severity and impact on cognitive function. Given that the population continues to age and to experience cognitive declines, a better understanding of the factors that put them at greater risk for cognitive impairment can illuminate potential avenues for preserving cognitive function and quality of life.

As most studies to date have examined links between multimorbidity and cognitive function cross-sectionally, the first aim of this project is to determine if multimorbidity at one time is associated with adverse future cognitive function change. I then propose to examine change in number of chronic conditions over time and its potential association with the magnitude of cognitive decline. I hypothesize that not only will greater numbers of conditions increase risk of cognitive decline, but that larger increases in chronic conditions over time will be associated with accelerated cognitive decline.

Life expectancy has increased to over 75 years of age in most nations in the world (WHO, 2016). Evidence has shown that multimorbidity is strongly associated with age, with 55-98% of those 65 and older having two or more coexisting conditions (Marengoni et al., 2011). However, multimorbidity is also increasingly common in those under 65 years of age, with 50% experiencing multimorbidity (Quiñones, Markwardt, & Botoseneanu, 2016). This means that more people than ever are living longer with poor health.

Notably, multimorbidity has been shown to increase the risk of being diagnosed with cognitive impairment later in life (Vassilaki et al., 2015). In particular, the Helsinki Aging Study's five year follow-up of those 75 years and older showed 73% of those with cognitive decline had multimorbidity (Tilvis et al., 2004). Further, the Canadian Study of Health and Aging (65 years and older) found that over a 10 year period the predictive risk of dementia increased with the number of chronic conditions a participant had, regardless of whether they had a known factor in dementia, such as cardiovascular disease and diabetes (Song, Mitnitski, & Rockwood, 2014). These results indicate the importance of studying the relationship between multimorbidity's and the aging brain.

Two domains of cognition particularly vulnerable to cognitive decline are executive function and episodic memory. Executive function and episodic memory play critical roles in an adult's ability to function independently (Tun & Lachman, 2006). Executive function includes planning, working memory, attention, and task switching, and episodic memory comprises of unique events that can be consciously retrieved. Many chronic conditions are strongly associated with decline of cognitive function (Song et al., 2014), with cardiovascular disease and atrial fibrillation in particular known to contribute to executive function impairment (Eggermont et al., 2012). In addition to vascular diseases, neurological diseases, stroke, and depression have all been implicated in the decline of episodic memory (Budson & Price, 2005).

Slight but steady declines in executive function and episodic memory are considered normal cognitive aging (Chuang et al., 2014; Rugg & Vilberg, 2013). Multimorbidity could interfere with that normal cognitive aging, causing observable cognitive deficits at earlier points in the lifespan than cognitive decline would typically occur. Notably, one study has shown that pathological changes of the brain can start to occur years before clinical symptoms of dementia

arise. Rajan and colleagues (2015) performed a longitudinal study of 2,125 non-demented older adults (65 years and older). After 18 years of follow up 21% of participants developed clinical Alzheimer's disease (AD). Participants who went on to develop AD had significantly lower baseline cognitive scores than those who were not diagnosed. Since changes in cognitive performance begin to occur during middle age and development of multimorbidity is increasingly common during this time, longitudinal measurement of cognitive performance in this demographic could prove to be particularly useful in assessing if multimorbidity accelerates age-related cognitive decline.

There are limited studies examining longitudinal effects of change in number of chronic conditions and their impact on change in cognition. The lack of literature on cognition in middle aged adults is also problematic as pathological events, such as atrophy (a decrease in size) of the medial temporal lobe and hippocampi, which are associated with episodic memory loss, and of the prefrontal cortex associated with executive function loss (Harada, Natelson Love, & Triebel, 2013), can start to occur 10-15 years before clinical symptoms of dementia arise (Rajan, Wilson, Weuve, Barnes, & Evans, 2015). Studies that do exist focus on participants who are older adults (Fabbri et al., 2016; Loprinzi, 2016), and/or, the focus is on cognition that is already impaired, such as mild cognitive impairment or dementia (Loprinzi, 2016; Marengoni et al., 2011; Sanderson et al., 2002; Solomon, Dobranici, Kåreholt, Tudose, & Lăzărescu, 2011; Vassilaki et al., 2015; Villarreal, Grajales, Lopez, Britton, & Initiative, 2015). While two studies have examined mid- to late life differences of multimorbidity on cognitive decline, one was cross-sectional (Zahodne, Manly, Azar, Brickman, & Glymour, 2016), and the other focused only on vascular diseases (Gottesman et al., 2017). Thus, my study will evaluate the impact of diverse combinations of chronic conditions (multimorbidity) on executive function and episodic memory

over an 8-9 year period in middle aged to later life adults from the Mid-life in the United States study (MIDUS).

Normal Cognitive Aging

As adults age the ability to process information and remember personal events decreases. Normal cognitive change sees cognitive abilities slightly decline over time even when brain disease is absent (Harada et al., 2013). Although age-related cognitive declines are normal, age may not be the only driving force. As people live longer it's important to take into consideration factors such as disease, which also are highly associated with age and cognitive decline (Hugo & Ganguli, 2014; Loprinzi, 2016) .

Two main categories of cognitive function are executive function and episodic memory. Executive function includes planning, paying attention, or focusing for extended periods of time. Episodic memory includes memory for unique events and experiences that can be voluntarily retrieved. These two categories are important predictors of change from mild cognitive impairment to dementia (Brooks, Weaver, & Scialfa, 2006). Neuroimaging, particularly real time fluorodeoxyglucose-positron emission tomography (FDG-PET) measuring metabolic activation, is considered the gold standard for assessing cognitive changes in executive function and episodic memory, but is expensive and not often feasible in clinical settings (Prestia et al., 2013). However, neuropsychological assessments, pencil and paper and verbal tests, such as digit span, word list recall, and category fluency, are standard in most clinical practices and are considered reliable methods to measure cognitive function (Jutten et al., 2018; Lezak, Howieson, Bigler, & Tranel, 2012). Neuropsychological batteries are also helpful in tracking cognitive function in comparison to peers, before people report noticeable concerns in memory changes (Lezak et al., 2012).

Although neuroimaging can be diagnostically crucial for neurological diseases, neuropsychological assessments can show the extent of cognitive change in individuals over time. Single assessments can be highly predictive of future cognitive decline (Lezak et al., 2012). For instance, individual tests of delayed recall, a measure of how well an individual encodes information for later memory retrieval, can differentiate between older adults with mild AD and healthy older controls with up to a 90% accuracy (Salmon & Bondi, 2008). However, since many tests focus on one aspect of cognition, rather than global functioning, assessments are more reliable when included as a battery or set of tests (Harvey, 2012). Neurological assessments of learning and memory, executive function, and visuospatial skills performed on both older adult participants who had mild AD and age, gender, and education matched controls found tests successfully classified those with AD 96% of the time and those aging controls 93% (Salmon et al., 2002). This study will use a battery of established neuropsychological assessments, the Brief Test of Adult Cognition by Telephone (BTACT), to examine decline in multiple aspects of executive function and episodic memory.

Executive Function. Executive function refers to a set of cognitive processes that allow persons to control and direct purposive behaviour. This includes the abilities to problem-solve, think abstractly, and reason. Executive function skills are important as they play a critical role in an adult's ability to function independently (Tun & Lachman, 2006).

Over time, methodological differences in design and measurement have impacted our understanding of age associations in executive function. For instance, cross-sectional studies have found steady declines in executive function occurring as early as 25 years of age, with significant declines in reasoning occurring as early as the late 30's (Shroeder and Salthouse, 2004). In contrast, longitudinal studies show significant decline may be delayed until mid-life

(Schaie, 2005). The different research designs used to study declines in cognition are likely to explain much of the discrepancy (Salthouse, 2014). Cohort effects are a major concern in regard to cross-sectional data, in that comparison groups are from different generations and have different life influences. For example, younger cohorts are more likely than older to have more education and healthier lifestyles, both of which have been associated with better cognitive performance (Schaie, 2000). Longitudinal studies allow for study of both inter- and intra-individual changes. Not only can we observe behavioural and functional changes between cohorts, but we can also assess these changes within individuals over time (Schaie, 2000). This is particularly useful when comparing differences in those with and without multimorbidity over time. That said, longitudinal studies of cognitive performance have been criticized on the basis of potential practice effects. Specifically, repeated exposure to cognitive tests may yield better performance because of familiarity with the tests rather than preserved cognitive function (Salthouse, 2010).

Multiple facets comprise make up executive function. These facets, when impaired, can lead to disruptions in cognitive processing. Slowing processing speed – how long it takes a person to do a mental task – in particular can negatively affect problem-solving, attention, and working memory. Reduced processing speed usually manifests as longer response times during timed neuropsychological tests (Harada et al., 2013). Attention, the ability to concentrate and focus on specific task-relevant information, also declines with aging (Glisky, 2007). In addition to everyday tasks, such as talking in a noisy room or multitasking, attention is important for other cognitive abilities such as working memory (Glisky, 2007; Harada et al., 2013). The attention network test, for example, assesses an individual's ability to retain focus, inhibit response to distracting stimuli and speed of response to correct stimuli. Specifically, the participant is shown

an image above or below a small cross in the middle of a computer screen and must respond by pressing one of two buttons, that correspond with one or the other location, as quickly and accurately as they can. A study of young, middle aged, and older adults (mean ages 28, 51, 71, respectively) using the attention network test showed attentional decline starting in mid-life, particularly during more complex attentional tasks (Zhou, 2011).

Working memory – temporarily storing and manipulating information for tasks – is an important cognitive ability that serves long term memory, decision making, language, and problem solving (Baddeley, Eysenck, & Anderson, 2009). There are age-related differences in working memory, but they tend to be smaller than those for attention or executive function (Kirova, Bays, & Lagalwar, 2015). The hemispheric asymmetry reduction in older adults (HAROLD) model highlights age-related changes in working memory and attention in young (18-30 years of age) and older adults (60+; Cabeza, 2002). When performing specific working memory tasks, young adults activated either the left or right prefrontal cortex, the region of executive function, while older adults activated both the left and right prefrontal cortex (Cabeza, 2002). These results suggest that working memory processing becomes less efficient with age, making performance of complex tasks more difficult and thus requiring the recruitment of more brain regions for successful task completion.

Episodic Memory. Episodic memory is the memory of the time and place an event occurred and information about the event itself. These events could be as recent as a couple of minutes ago (e.g., remembering having taken medication), to weeks (e.g., remembering details of a company meeting), to years (e.g., remembering important life events). Episodic memory involves the ability to properly encode, store, and voluntarily retrieve information (Baddeley et al., 2009). Encoding entails receiving information and making it into a construct: visual, sound,

and/or meaning, so it can be stored and later retrieved from short-term and long-term memory. The next step, storing of memories, involves where the memory is stored, short-term or long-term, how long it should be stored, and how much of it should be stored. We do not have the capacity to remember everything from every day, thus, the mind filters out what it deems irrelevant. Lastly, memory retrieval is the process of accessing information previously encoded and stored. Recall – retrieving memories without being cued – and recognition – retrieving memories through cues such as associated words or smells – are the two most common modes of retrieval. Importantly, the three processes support one another. If there are impairments in the encoding or storage process, the retrieval process will be deficient (Baddeley et al., 2009).

Problems with episodic memory arise because the components can each be impacted individually. Decreased attention or emotional salience can negatively affect how information is encoded and stored, and poor contextual cues can negatively impact how that memory is retrieved. For instance, a comparison fMRI (functional magnetic resonance imaging) study of memory in healthy young and older adults (mean age 24 and 70, respectively) found older adults were significantly less likely to ignore new irrelevant information (Chadick, Zanto, & Gazzaley, 2014). While being scanned, the participants viewed faces, landscape, and/or overlapping images to distract (irrelevant information) and were asked if they recognized previous images. The distractions were found to interfere with their recognition of both faces and landscapes they had previously seen.

Standard measures of episodic memory use neuropsychological tests involving recall and recognition of words, faces, and pictures (Lezak et al., 2012). The California Verbal Learning Test—II (CVLT-II), a measurement of verbal memory through immediate word recall and delayed recall, is a common measure. A recent study of verbal episodic memory assessed a wide

range of adults (18-91 years of age) with the CVLT-II (Graves et al., 2017). Results showed that scores generally decreased with increasing age, but that women's scores stayed relatively stable until around the age of 60, whereas men saw linear declines starting in early in adulthood. This gender difference may have biological underpinnings. Evidence from previous studies has shown a positive effect of estrogen on verbal memory (Kramer, Yaffe, Lengenfelder, & Delis, 2003) and women having less atrophy of the hippocampus than men (Pruessner, Collins, Pruessner, & Evans, 2001). However, one study has shown that after the age of 70 these differences seem to diminish (Herlitz, Nilsson, & Bäckman, 1997). Nevertheless, studies have shown that individual changes across age groups are not always uniform and that some who are older perform as if they were cognitively younger and vice versa (Glisky, 2007).

Normal aging of episodic memory is characterized by poorer encoding and storing of information causing retrieved memories to be of poorer quality. In particular, with age memories become less detailed, and memories associated with fewer emotional details are more easily forgotten (Tromp, Dufour, Lithfous, Pebayle, & Després, 2015). As mentioned, cross-sectional and longitudinal studies have yielded different patterns of normative cognitive aging. As with executive function, cross-sectional studies of episodic memory suggest declines starting in an adults' twenties and thirties (Nilsson et al., 1997; Verhaeghen & Salthouse, 1997). In contrast, longitudinal studies of episodic memory suggest that, in comparison to executive function, it is highly stable over time, with declines occurring around the age of 60, even after controlling for practice effects (Gorbach et al., 2017; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). These longitudinal studies show decline in episodic memory occurring later in life than executive function. Since I plan to also use longitudinal data, I expect the same differential patterns of age-related change in executive function and episodic memory.

A major criticism of longitudinal studies is the of possible practice effects inflating prospective longitudinal performance. However, evidence has shown that practice effects diminish with increased retest intervals. Salthouse and colleagues (2004) assessed differing retest intervals of between 1 week and 35 years and found that after 7 years practice effects were no longer noticeable. There are eight to nine years between cognitive testing occasions in MIDUS. Thus, there should be minimal to null practice effects on the second cognitive testing occasion (MIDUS 3).

Links to health. Current research suggests that heterogeneity in cognitive aging may be due to multiple variables, not just age. While some individuals may see a rapid decline as they age, others may undergo normal change or even be considered high functioning late in life. In aging adults, poor health is becoming more of a concern due to its effects on cognitive decline. Studies addressing chronic illnesses, physical activity, and mental health have all found links to cognitive health (Cunningham & Hennessy, 2015; Loprinzi, 2016).

Chronic Conditions

Some diseases are more likely to occur as individuals age. Of those aged 45-54 years, arthritis, hypertension, asthma, depression, and diabetes were found to be the most prevalent chronic conditions (Koné Pefoyo et al., 2015). However, even though conditions may be common, some chronic conditions are more impactful on the neurological system than others. For instance, cardiovascular diseases damages the vascular system in the brain which can cause structural and functional changes leading to cognitive impairment, including dementia (Iadecola et al., 2016).

Single chronic conditions. The World Health Organization (WHO) has determined that the burden of chronic diseases, such as, cardiovascular diseases, respiratory diseases, and

diabetes mellitus, is rising each year (WHO, 2017). Single chronic diseases, especially cardiovascular ones, are associated with poorer cognitive function (Anstey, Sargent-Cox, Garde, Cherbuin, & Butterworth, 2014; Cheng, Huang, Deng, & Wang, 2012; Eggermont et al., 2012). Cardiovascular-related risk factors including hypertension and hypercholesterolemia are also known predictors of cognitive decline and dementia. When assessing middle aged adults over 20 years, data from the population-based Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study found that those diagnosed with dementia were likely to be older, less educated, and have vascular risk factors (hypertension, hypercholesterolemia, and obesity) than those who didn't (Kivipelto et al., 2001). These risk factors also significantly predicted dementia in the later years.

Some chronic conditions have been shown to promote a faster rate of cognitive decline. Chodosh and colleagues (2007) studied the effects of depression – considered by many to be a chronic condition – on cognitive decline in high functioning individuals 70-79 years of age over a 7-year period. Those with more depressive symptoms saw an increased rate of cognitive decline compared to those without depression. Another study found provisional evidence that some cardiovascular conditions, such as atrial fibrillation, hypertension, and angina, may also increase the rate of cognitive decline (Mielke et al., 2007). These results suggest that certain chronic conditions may be more impactful than others. Thus, this study elaborates on these ideas by determining whether increases in chronic conditions over time accelerate cognitive decline.

Multimorbidity. In the aging population, having multiple chronic conditions is becoming more common and assessing the cognitive impact of multimorbidity is important. Multimorbidity is defined as the coexistence of two or more disease conditions in a person (van der Zee-Neuen et al., 2016). Studies have shown that an increase in multimorbidity is strongly

associated with decreases in both executive function and episodic memory. A cross-sectional study of mid-life to older adults found that an increase in multimorbidity resulted in significantly worse performances of executive function and episodic memory, compared to those with one single chronic disease or no disease (Zahodne et al., 2016). Doraiswamy et al. (2002) found that after controlling for age, participants with higher multimorbidity had significantly lower scores on the mini-mental state examination (MMSE), a measure of global cognitive functioning. Lastly, a clinical study of patients 65 years and older showed that cognitive test scores were not significantly different between those with a family history of dementia and those without (Morrow, Snitz, Rodriquez, Huber, & Saxton, 2009). However, those patients with a high number (eight or more) of chronic conditions, including thyroid disorders, gastroesophageal reflux, sleep apnea, and chronic pain, had significantly decreased scores of executive function with trending scores for attention and episodic memory. To date, no study has examined change in chronic conditions over time and their impact on executive function and episodic memory.

Multimorbidity data typically come from self-reports, clinical assessments, or medical records data, and multimorbidity is typically measured as a simple summative count of the number of chronic illnesses (Vassilaki et al., 2015; Zahodne et al., 2016). Although this is the easiest way to measure multimorbidity, it does not account for differences in condition severity. Multimorbidity can also be weighted based on the risk of mortality or other outcomes associated with specific conditions; conditions can be precisely classified using the International Classifications of Disease (ICD) codes (Roffman, Buchanan, & Allison, 2016). The Charlson Comorbidity Index (CCI), for example, provides weights for specific conditions based on their likelihood of causing death. However, the CCI is sensitive to administrative errors in hospital data (Quan et al., 2011), and it does not account for change in disease severity, especially if

complications arise from the disease. The CCI also does not illuminate how specific conditions or combinations of conditions are linked to other relevant outcomes, such as physical function, that can have a significant impact on quality of life. More recent formulations of multimorbidity have begun to use other metrics of severity, including physical function (Solomon et al., 2011; Wei, Kawachi, Okereke, & Mukamal, 2016). These scales use self-reported disease diagnosis and impact of disease on diverse functional outcomes. For example, the cumulative illness rating scale-geriatric (CIRS-G) scores diseases by organ system and by severity of impact: none (0), mild problem or problem in the past (1), moderate disability or requiring treatment (2), severe/consistent significant disability (3), and extremely severe disability, organ failure (4) (Solomon et al., 2011). Although, there are limitations to this type of measure, such as self-report and under-analysis of rarer diseases, these measures avoid mis-diagnosis and recording errors, allow for interindividual disease severity, and recognizes the chronic nature of disease and not just its effect on mortality (Wei et al., 2016).

Although there are many measures of multimorbidity and its impact on function and mortality, a weighted risk or burden scale that determines which chronic conditions are most impactful on cognition has not yet been developed. Kivipelto et al. (2006) have created a score for the prediction of dementia risk over a 20-year period using cardiovascular related risk factors. Future dementia was predicted by age (47 years of age or more), hypertension, obesity, and hypercholesterolemia. However, this scale is limited in there is no weighted risk and its lack of disease inclusion. Creation of a scale or index similar to the severity scales would be helpful in highlighting diseases that are strongly associated with cognitive impairment and not just those diseases that are prevalent in aging. Given the absence of such a scale, however, the current study will employ an unweighted summative measure of multimorbidity.

Variability in cognitive decline in aging adults is not uncommon. Studies have shown that although there are general trends, interindividual differences exist. For instance, cognitive decline in those already diagnosed with dementia accelerates in the presence of other disease. In the Kungsholmen Project, a population-based cohort study of adults 75 and older with dementia, those with increased multimorbidity had a faster rate of cognitive function decline than those with no multimorbidity (Melis et al., 2013). Medication can also affect the rate of age-related cognitive decline. Nonsteroidal anti-inflammatory drugs (NSAIDs) that are often prescribed for chronic arthritis have been shown to slow the rate of cognitive decline, but other joint disorder medications do not (Cunningham & Hennessy, 2015; Wallin et al., 2012). Lastly, healthy behaviors can affect the impact of multimorbidity on cognitive performance. A study of older adults (60 years and over) revealed that those with multimorbidity who were also achieving the minimal 2.5 hours a week of recommended physical activity saw decreased cognitive decline compared to those with multimorbidity and less physical activity (Loprinzi, 2016). In sum, multimorbidity can negatively impact cognitive performance in both executive function and episodic memory. Nevertheless, the impact of even severe conditions can be moderated, positive or negatively, by additional factors such as medication and health behavior.

In conclusion, slight cognitive decline in both executive function and episodic memory are common as individuals age, with evidence suggesting greater declines often being attributed to chronic conditions. Additional evidence suggests that increases in chronic conditions are associated with changes in cognition over time. However, the available literature examining the relationship between multimorbidity and cognitive function, particularly in middle age, is limited in important ways.

CURRENT STUDY

The current study investigated the relationship between multimorbidity and cognitive function, particularly executive function and episodic memory. A unique feature of this study is its focus on longitudinal relationships between multimorbidity on executive function and episodic memory, separately, over an 8-9 year period. Due to limited research on the association between multimorbidity and cognitive decline, my first objective was to assess change in the smple as a whole (ages 33-83). In addition to these assessments, I conducted analyses after stratifying the sample into young, mid-life and later life (33-49, 50-64, and 65-83, respectively) for all research questions. Utilizing two waves of data from the Midlife in the United States study (MIDUS 2, 2002-2004 and MIDUS 3, 2012-2013) on mid to late life adults, I addressed two research questions:

Research Question 1. Previous cross-sectional research has demonstrated poorer executive function and episodic memory in adults aged 40 years and older with multimorbidity compared to those with a single or no chronic condition (Zahodne et al., 2016). The first research question used longitudinal data to extend this earlier work by addressing the question: Are greater numbers of chronic conditions and multimorbidity status related cognitive performance over time?

Hypothesis 1a: Declines in executive function will be larger in adults with multimorbidity, compared to adults with one or no chronic illnesses.

Hypothesis 1b: Declines in episodic memory will be larger in adults with multimorbidity, compared to adults with one or no chronic illnesses.

Hypothesis 1c: Greater numbers of chronic conditions will be associated with greater declines in executive function.

Hypothesis 1d: Greater numbers of chronic conditions will be associated with greater declines in episodic memory.

Hypothesis 1e: Declines in executive function will be greater than declines in episodic memory, due to their differing normative decline trajectories.

Research Question 2. Fabbri et al. (2016) observed, in the Baltimore Longitudinal Study of Aging (mean age 74 years), an association between faster accumulation of chronic illnesses and increased cognitive decline. However, the study included only older adult participants and measured cognition and multimorbidity only over a three-year period of time. Therefore, the second research question asks: In mid to late life adults, are increases in the number of chronic conditions over time (8-9 year follow up) related to the magnitude of cognitive decline?

Hypothesis 2a: Greater increases in chronic illnesses over time will be associated with accelerated decline in executive function compared to those with little or no change in numbers of conditions over time.

Hypothesis 2b: Greater increases in chronic illnesses over time will be associated with accelerated decline in episodic memory compared to those with little or no change in numbers of conditions over time.

Hypothesis 2c: Greater declines will be seen in executive function compared to episodic memory, due to their differing normative decline trajectories.

METHODS

Participants

Participants were from the second (2004-2006; MIDUS 2) and third (2013-2015; MIDUS 3) waves of MIDUS, including a Milwaukee oversample of Black participants. MIDUS is a nationally representative longitudinal study of health and well-being. At MIDUS 2 the participants were English-speaking, non-institutionalized adults aged 33-83 years of age.

The first wave of MIDUS comprised a national probability sample of non-institutionalized English-speaking adults (N = 3,487) living in the co-terminus United States and recruited by random digit dialing (RDD). A sample of monozygotic and dizygotic twin pairs (N = 1,914) were also recruited from a national twin registry. The first wave of MIDUS data collection (MIDUS 1) was completed in 1995-1996, and two follow-up studies (MIDUS 2 and MIDUS 3) were completed in 2004-2006 and 2013-2014, respectively. Mortality-adjusted retention was 75% from MIDUS 1 to MIDUS 2 and 77% from MIDUS 2 and MIDUS 3; a total of 1,108 of the original sample of 7,108 have died since study inception. All respondents completed telephone interviews and self-administered questionnaires at all three waves. The time elapsed between MIDUS 1 and MIDUS 3 participation ranged from 17-19 years with a mean of 18.02 years.

Participants at all MIDUS waves completed a 30-minute telephone interview and two mail-in self-administered questionnaires. The interviews and questionnaires provided information on sociodemographics and chronic conditions; chronic illnesses were included if they had symptoms or were diagnosed by a physician in the last 12 months. Cognitive assessments were completed by telephone at MIDUS 2 and MIDUS 3 (longitudinal sample =

2,532). At MIDUS 1 the total number of participants was 7,108 with 950 being siblings and 1,914 being twins.

Cognitive Assessment

Cognitive function was assessed using the Brief Test of Adult Cognition by Telephone (BTACT; Lachman & Tun, 2011; Tun & Lachman, 2006, 2008). The BTACT consists of six tests including word list recall and delayed recall (testing episodic memory), and digits backward, category fluency, number series, 30 seconds and counting task, and Stop and Go Switch Task (testing executive function). The battery in its entirety takes less than 20 minutes to perform.

Word list recall. The BTACT uses the Rey Auditory Verbal Learning Test (RAVLT) to assess episodic auditory-verbal learning and memory (Rey 1964, Lezak 1995). The immediate recall portion includes one trial of a list of 15 random words that the administrator reads out loud at the rate of one word per second. Participants are to recall as many words as they can in one minute. The delayed recall has the participant recall as many words as they can from the immediate recall trial without list prompting from the administrator. There is approximately 15 minutes required between immediate recall and delayed.

Digits backwards. The digits backward test from the WAIS-III (1997) tests work memory span. Participants are told numerical digits at one digit per second and are to repeat them back to the administrator in reverse order. Each trial has the participant repeat two series of digits the same length. The initial series starts with only two numbers going up to eight digits long. The test is finished when a participant gets two series wrong in the same trial. The final score is the largest sequence length that the participant was able to correctly recall.

Category fluency. A test of verbal fluency includes category fluency. This test has been shown to measure the "central executive component of working memory" (tech report BTACT pg. 3). Participants are to generate as many words as they can from the semantic category "Animals" in one minute. The score results from how many words can be generated, with repetitions and intrusions being considered.

Number series. To measure reasoning the study uses the number series completion task. Participants are given a series of numbers, such as "3,6,9,12,15…" and are asked to complete the sequence. Five series with increased difficulty, with one trial at the easiest level, one trial at the more complex level, and three trials at the most complex level. Scoring is determined by number of completed trials with a total possible score of five.

30 seconds and counting. To test speed of processing the participant is given 30 seconds to count backwards from 100 using only ones. Scored by number of correct, skipping and repeated numbers are also taken into account.

Stop and go switch task. This attention switching task asks participants to task switch when given cues. At baseline participants are asked to say "stop" when they hear "red" and "go" when they hear "green". The reverse condition requires participants to go against inhibition and when they hear "red" to say "go" and when they hear "green" to say "stop". The final trial is a more complex alternating condition, for when the participant is given cues they must switch between the two modes of response. Previous to each condition participants are given practice trials.

The BTACT is administered over the phone to non-demented adults. To ensure that participants can hear and understand the examiner a series of numbers are spoken, and the participant is asked to repeat each number aloud. The participant is then asked not to write

anything down, but to close their eyes to pay better attention. Test-retest reliability studies have shown that there were no significant differences between individuals given the BTACT over the phone or in person (Tun & Lachman, 2006).

Composite scores, the average of standardized z -scores for the total six measures, the total of the four executive function tests and the total of the two episodic memory tests are used. Researchers and clinicians find these composite scores useful to examine participant results across several domains, rather than each individual test score (Tun & Lachman, 2006).

Multimorbidity

Multimorbidity was assessed using a simple count variable. Participants were asked by questionnaire if they had experienced or been treated for any of a set of 12 conditions in the past 12 months. Conditions included diabetes, hypertension, arthritis, asthma, neurological problems, and autoimmune disorders. In addition, high cholesterol levels were determined from responses to an item about cholesterol medication use and obesity (>30 BMI) was derived from participant-reported height and weight. Finally, history of heart problems and cancer (excluding skin cancer) were determined from items in the telephone interview. Self-reported conditions typically match data from medical records (Katz et al., 1996). All “yes” responses were put into one cumulative continuous variable with a range of 0-12. A dichotomous multimorbidity status variable (0-1 conditions = 0; 2+ conditions =1) was used to test the impact of multimorbidity compared to single or no conditions.

Covariates

Participants were asked their age, sex, race, highest level of educational attainment, whether they were employed, and marital status. Unemployment, particularly retirement, is often

accompanied by decreased cognitive performance due to the lack of preservation and challenge of cognitive processes (Mazzonna & Peracchi, 2012). This loss increases with each year not employed. Being married or living with a partner has shown to provide a protective effect against decline in executive function (Lipnicki et al., 2013) and episodic memory (Håkansson et al., 2009; Mousavi-Nasab, Kormi-Nouri, Sundström, & Nilsson, 2012).

Age was used as both scale data, as well as stratified by young (33-49), mid-life (50-64) and later life (65-83) at MIDUS 2. Responses for education were initially grouped into 12 categories, ranging from "no school/some grade school" to "PhD, MD, JD, or other professional degree". These categories were aggregated into three categories ranging from those who had a high school diploma or General Educational Development (GED), some college, and college degree or more (Friedman, Christ, & Mroczek, 2015). Demographic covariates used in the analysis were age (scale data), sex (male and female), race (White, Black, Other), and current employment (employed, unemployed, retired).

Analyses

Data were analyzed using STATA 15. Bivariate associations among key variables were initially determined. Linear regression models were estimated to determine whether or not multimorbidity was associated with executive function and episodic memory decline over time. Executive function and episodic memory were assessed in independent models, with all models adjusted for age, race, sex, education, employment, marriage status, and baseline cognitive performance. Further, to determine whether cognitive decline was different for older individuals who have multimorbidity compared to those who are younger, a sensitivity analysis was performed on all models.

Research Question 1. Are greater numbers of chronic conditions and multimorbidity status related to cognitive performance over time? Hypothesis 1a-d: Multimorbidity will be negatively associated with executive function and episodic memory. The dichotomous variable for multimorbidity status was used to assess if there was a threshold relationship between having a multimorbid status and declines in executive function and episodic memory. Covariates were included as controls. The continuous variable of chronic conditions was entered to determine if multimorbidity affected executive function and episodic memory over and above control variables. For all regressions performed executive function and episodic memory were assessed in separate models. Statistically significant outcomes were determined by a significant ($p < .05$) change in R^2. Hypothesis 1e: A post-hoc analysis compared the effect sizes of executive function and episodic memory. For both model types standardized outcomes were used for comparison. Both the multimorbidity status variable and the multimorbidity continuous variable assessed difference between executive function and episodic memory by comparing the amount of standard deviation unit change in the outcome for one additional chronic condition. All were conditioned on the covariates included.

Research Question 2. Does an increase in multimorbidity over time increase the magnitude of decline of cognitive performance? Hypothesis 2a-b: There will be increased negative associations between greater chronic illness accumulation and cognition compared to those with no change in their chronic condition status over time. Change scores were calculated to determine changes in numbers of chronic conditions. As with Research Question 1, a model of residualized change was used to measure the outcome of executive function and episodic memory at MIDUS 3, adjusted for MIDUS 2 cognitive scores. For all regressions performed executive function and episodic memory were assessed in separate models. Statistically

significant outcomes were determined by a significant ($p < .05$) change in R^2. Hypothesis 2c: A post-hoc analysis compared the effect sizes of executive function and episodic memory. These continuous outcomes were standardized and assessed by comparing the standard deviation unit change for each additional chronic condition conditioned on the covariates included.

RESULTS

Descriptive statistics for the study can be found in Table 1. The participants were aged 33 to 83 (mean age 55 ± 11.3) at MIDUS 2 and the majority was female (57.23%); and White (86.06%). Of the total sample, 42.06% had at least a college degree and 46.25% had at least two chronic conditions at MIDUS 2. Those with multimorbidity at MIDUS 2 were more likely to be older, female, Black, less educated, retired or employed, and not married.

From MIDUS 2 to MIDUS 3 mean number of chronic conditions increased from 1.7 ± 1.57 to 2.27 ± 1.74. Multimorbidity increased from 46.25% to 62.09%. Overall executive function scores decreased from a mean of 0.15 ± 0.95 to 0.03 ± 0.98. Episodic memory scores decreased from a mean of 0.11 ± 0.96 to 0.02 ± 0.99. Bivariate correlations among all variables are shown in Table 2.

Hypothesis 1

Multimorbidity status. To determine whether those people with multimorbidity also had greater declines in executive function and episodic memory after an 8-9 year follow up, linear regression models were estimated. Results are shown in Table 3. After adjusting for baseline cognitive performance and covariates, multimorbidity did not significantly predict greater decline in executive function over time compared to those with 0 or 1 chronic condition. Similarly, multimorbidity did not predict greater declines in episodic memory over time in the adjusted model (Table 3).

Number of chronic conditions. Number of chronic conditions was associated with larger longitudinal declines in episodic memory, although this association was statistically

marginally significant [*b*=-0.02 [95% CI: –0.04, 0.00], *p*=.08). In contrast, number of chronic conditions was not associated with change in executive function (Table 4).

Effect size differences. The last sub-hypothesis predicted that multimorbidity status and increased chronic conditions would have a greater association with executive function compared to episodic memory. As hypothesized, after adjustments, in participants with multimorbidity executive function performance decreased 0.02 standard deviation units, with episodic memory performance decreasing 0.018 standard deviation units. In contrast, models involving a continuous measure of chronic conditions, a one standard deviation increase in chronic conditions predicted a 0.02 standard deviation decrease in executive function performance and a 0.03 decrease in episodic memory performance, holding all else constant.

Hypothesis 2

Hypothesis 2 focused on potential associations between change in number of chronic conditions over time and declines of executive function and episodic memory (Table 5). As predicted, larger increases in number of chronic conditions over time were significantly associated with larger declines in executive function (*b*=-.03 [95% CI: -0.04, -0.01], *p*=.01). In contrast, change in numbers of chronic conditions were not associated with declines in episodic memory (Table 5).

Effect size differences. As with hypothesis 1, this last hypothesis predicted that changes in chronic conditions over time would affect executive function more than episodic memory, after adjustments. Consistent with this hypothesis, for each additional chronic condition increase, executive function performance decreased by 0.03 standard deviation units compared to a 0.025 standard deviation decrease in episodic memory, holding all else constant.

Covariate Analysis

As expected, executive function scores at MIDUS 2 significantly predicted executive function performance at MIDUS 3 (*b* = .68 [95% CI: 0.65, 0.71], p < .001,). Advancing age was associated with greater executive function decline (*b* = -.01 [95% CI: -0.02, -0.01], p < .001,). Compared to those who completed high school only, those who completed at least a college degree (*b* = .11 [95% CI: 0.05, 0.17], p < .001) performed significantly better. Being Black significantly predicted greater decline in executive function performance than being White (*b* = -.17 [95% CI: -0.25, -0.08], p < .001). Participants who were unemployed or retired both showed statistically significantly larger declines in executive function compared to those who were employed (*b* = -.13 [95% CI: -0.21, -0.06], p < .001 and *b* = -.17 [95% CI: -0.23, -0.10], p < .001, respectively). Being married was associated with better executive function performance (*b* = -.06 [95% CI: 0.01, 0.12], p < .001). Sex was not significantly associated with change in executive function in these models.

Analyses of episodic memory revealed slightly different associations in the models of multimorbidity, chronic conditions, and change (Table 3-5). Better episodic memory performance at MIDUS 2 was associated with improvements in episodic memory over time (*b* = .43 [95% CI: 0.39, 0.46], p < .001). Greater age was associated with greater declines in episodic memory over time as was being male (*b* = -.02 [95% CI: -0.02, -0.02], p < .001 and *b* = .33 [95% CI: 0.26, 0.40], p < .001, respectively). In this model only those who had a college degree or more performed significantly better (*b* = .17 [95% CI: 0.09, 0.25], p < .001) than those with only a high school education. Being Black predicted poorer episodic memory performance than being White (*b* = -.16 [95% CI: -0.27, -0.05], p = .005). Those who were retired had marginally significant greater declines in episodic memory compared to those who were employed (*b* = -.09 [95% CI: -0.19, -0.00], p = .05,); being unemployed was not associated with

change in episodic memory. Similarly, being married was not predictive of change in episodic memory performance.

Sensitivity Analysis

To examine potential variability in key associations across age groups, I repeated all of the analyses after stratifying the sample by age: young (33-49 years of age), middle-aged (50-64), and older adults (65-83). Results showed that MIDUS participants of the youngest age category saw multimorbidity and number of chronic conditions having a significant impact on executive function (*b* = -.11 [95% CI: -0.19, -0.03], p = .008, and *b* = -.03 [95% CI: -0.06, -0.01], p = .02, respectively, Table 6). In this youngest age category episodic memory, multimorbidity, and number of chronic conditions also saw associations (*b* = -.12 [95% CI: -0.24, -0.0002], p = .05, and *b* = -.05 [95% CI: -0.09, -0.003], p = .04, respectively). Change in chronic conditions over time was not significant. The middle aged group only saw significant associations between executive function and change in chronic conditions (*b* = -.04 [95% CI: -0.07, -0.01], p = 0.003). Lastly, older participants only saw marginally significant results between episodic memory and number of chronic conditions (*b* = -.04 [95% CI: -0.08, 0.004], p = 0.08). All other models were nonsignificant.

DISCUSSION

The broad aim of the current study was to examine the relationship between chronic conditions and longitudinal change in cognitive function in a national sample of mid-life and older adults. I hypothesized that worse health at baseline assessment (multimorbidity; greater number of chronic conditions) and larger increases in chronic conditions over time would predict greater declines in executive function and episodic memory over the 8-9 year follow-up. The results for the full sample provided mixed support for my hypotheses, although sensitivity analyses showed important variability in these associations by age. In all of the models involving the full sample, the relationships were in the hypothesized directions, but most of these associations were not statistically significant. Baseline multimorbidity, for example, was not significantly associated with greater declines in executive function or episodic memory over time (Hypotheses 1a, 1b). Similarly, greater numbers of chronic conditions at baseline were not significantly associated with greater declines in executive function over the follow-up period (Hypothesis 1c), although there was a marginally significant inverse association between numbers of chronic conditions and declines in episodic memory (Hypothesis 1d). Overall, these results suggest a weak relationship between chronic condition burden at a single point in time and subsequent trajectories of change in cognitive function.

The second hypotheses concerned how dynamic change in chronic conditions over time would be associated with executive function and episodic memory performance over time. Results of these analyses showed that increases in chronic conditions were significantly associated with greater declines in executive function over the 8-9 year follow-up. There was no significant association between change in chronic conditions and episodic memory. These results

suggest that worsening health over time may be worse for cognitive function, and specifically for executive function, than absolute numbers of chronic conditions.

Finally, across both of the main hypotheses, I predicted that the magnitude of key associations would be greater for executive function than episodic memory. Although I am unsure of how meaningful the effect size differences are, the results from post hoc assessments generally supported this prediction. The clearest support came from analyses involving change in chronic conditions, where larger increases in number of conditions were significantly associated with change in executive function but not with change in episodic memory. In contrast, and contrary to my hypothesis, there was a greater impact on episodic memory compared to executive function for number chronic conditions. Lastly, sensitivity analysis of age performed on all models showed that older participants performed significantly worse than the younger age groups, irrespective of cognitive domain. Nevertheless, the youngest age group's executive function and episodic memory performance were highly associated with multimorbidity and increased chronic conditions.

Many of the covariates were significant predictors of cognitive change over time. Not surprisingly, previous cognitive performance was the greatest predictor of later performance. As age increased performance was more likely to decline over time. Essentially, being White, better educated and employed led to better cognitive outcomes. Similar to previous findings, women performed better than men in regard to episodic memory. Marriage saw advantage on executive function, but not on episodic memory performance compared to those who were single.

Several trends emerged from these findings that support and further previous results on contributions to cognitive decline. For example, Fabbri et al. (2016) observed a greater decline in executive function, but not episodic memory, when there was increased accumulation of chronic

conditions in older participants. My results support these findings, as well as extend this to younger and middle aged adults. The sensitivity analyses on age strata within the sample showed the association in middle aged adults between executive function and change in chronic conditions to be especially strong, implicating increases in chronic conditions over time to be a main driver in executive function decline as opposed to normal cognitive aging.

There was significant evidence to suggest that associations between multimorbidity and number of chronic conditions with executive function and episodic memory across all ages should have been observed (Doraiswamy et al., 2002; Vassilaki et al., 2015; Zahodne et al., 2016). However, only the youngest age group saw cognitive decline associated with multimorbidity and greater chronic conditions. Although there is an observable relationship between multimorbidity and chronic conditions and cognitive decline in younger adults, this study is unable to explain why. Additional research on the biological mechanisms is warranted. The nonsignificant results from the analyses involving the full sample and cognitive decline are likely due to the relatively young age of the sample, especially considering research in cognitive aging that has shown that longitudinal declines in executive function and episodic memory start to occur around middle age and late middle age, respectively (Gorbach et al., 2017; Schaie, 2005).

In general, this study produced results resembling previous studies of greater executive function decline than episodic memory, with the exception of number of chronic conditions. When considering why there was a marginally significant association between episodic memory and number of chronic conditions and not multimorbidity and both cognitive domains, it could be that by creating a dichotomous multimorbidity variable I wasn't able to fully examine the effect of incremental changes. Also, fairly prevalent vascular diseases, including atrial

fibrillation, hypertension, and cardiovascular diseases, have all been found to be associated with executive function decline (Eggermont et al., 2012). However, in addition to vascular diseases, depression and more severe, conditions such as neurological conditions and stroke are associated with episodic memory decline. Therefore, due to the greater amount of chronic conditions associated with episodic memory versus executive function, increased accumulation of conditions may become more impactful on episodic memory.

While this study extends our understanding of the relationship between multimorbidity and cognitive function in aging adults, the mechanisms underlying the association between increased chronic conditions and cognitive decline remain unclear. Evidence suggests that having a chronic condition is more likely to produce poorer health behaviours, such as physical inactivity and functional decline, which are associated with poorer cognitive outcomes (González, Fuentes, & Márquez, 2017; Loprinzi, 2016). In addition to poorer cognitive outcomes, reduced physical activity is associated with increased blood pressure, high cholesterol, diabetes, obesity, and cardiovascular diseases (Booth, Roberts, & Laye, 2012). Biological mechanisms, such as inflammation, have also been linked to chronic conditions and multimorbidity. Greater chronic inflammation, particularly neuroinflammation, may be a factor contributing to executive function and episodic memory declines over time. Inflammation occurs when the body's immune system tries to fight an illness, infection, injury, etc. by releasing pro-inflammatory factors. Prior work has documented higher levels of inflammatory proteins in adults with multimorbidity compared to those without (Friedman, Mroczek, & Christ, 2018) along with a dose-response relationship between greater numbers of chronic conditions and higher circulation levels of inflammatory markers (Friedman & Ryff, 2012). Importantly, studies have found that chronically increased inflammatory factors, as opposed to acute, impact

executive function and episodic memory (Grigoleit et al., 2010; Simen, Bordner, Martin, Moy, & Barry, 2011; Tampubolon, 2016).

Consistent with other studies age and race were significantly associated with cognitive decline in all models. As with other literature on normal cognitive aging, this study's results showed that as participants aged there were greater declines in both executive function and episodic memory (Salthouse, 2009; Schaie, 2000, 2005). Additionally, research has shown that Blacks are more likely to develop chronic conditions at much younger ages than Caucasians (Weuve et al., 2018). If those of colour are living with chronic conditions for longer periods of time this may partially explain the greater declines in cognitive performance compared to Whites in mid-life.

Individuals with greater educational attainment were more likely to have better executive function and episodic memory performance when compared to individuals with less education. This relationship persisted even when accounting for chronic conditions, race, age, and employment. One possibility is that advanced education can help individuals develop a cognitive reserve to draw from later in life (Stern, 2002). When insults occur to the brain, individuals with high reserve are able to cope with decline through compensation. Another possibility is that higher educational attainment often reflects better early-life environments which have been shown to impact cognitive function (Case & Paxson, 2008).

Lastly, being employed was found to be protective of executive function and episodic memory decline. These results are consistent with Bonsang, et al. (2012) who found a negative association between retirement and cognitive functioning. This is supported by the disuse hypothesis: the work environment is cognitively stimulating, and unemployment or retirement

result in the loss of that cognitive stimulation potentially leading to declines in cognitive performance (Salthouse, 2016).

There are several limitations that warrant consideration. As with many studies of this size many of the variables used in this study were self-reported. When considering reporting of chronic conditions, participants are more likely to omit chronic conditions than report conditions that they do not have (Bowlin et al., 1993), thus the current data may reflect conservative estimates of the impact chronic conditions have on cognitive performance. Moreover, since the follow-up questionnaires only asks the participant if they had experienced or been treated for the chronic conditions in the prior 12 months participants could be underreporting chronic conditions that were in remission or reporting conditions too recently diagnosed to affect changes in cognition. Further, the chronic conditions measure was a summative count. Although this is one of the most common ways of determining multimorbidity, it does not account for variability in the severity of the component conditions.

Despite the above limitations, there are notable strengths to this study. First, it assessed subclinical levels of cognitive function in an age-diverse sample of adults without dementia through a large nationally representative longitudinal study of aging across the United States. Indeed, the broad age range in this sample, spanning six decades of life, permitted sensitivity analyses involving three different age categories, young, mid-life, and older adults, that revealed significant variability in key associations across the different age groups. Secondly, this study also included prevalent chronic conditions, including arthritis and asthma, that are not often included in studies of cognitive aging. Lastly, it uniquely assessed whether change in chronic conditions over time was associated with cognitive decline in a non-demented age-diverse sample.

In conclusion, although evidence suggests that multimorbidity and chronic conditions, should have observable cognitive effects, particularly on executive function performance in middle-aged and older adults, the current study's results do not support this. However, the relationship between increases in chronic conditions over time and executive function was supported. Moreover, and consistent with existing literature, those who are Black, have lower education, and are unemployed or retired are at greatest risk of both executive function and episodic memory decline. The observed link between executive function performance and multimorbidity status, chronic conditions, and change in chronic conditions adds novel data to a larger literature showing a driving role of chronic conditions in cognitive decline beginning in mid-life. In earlier literature specific chronic conditions were treated as covariates, something only controlled for. The current study joins a growing body of research highlighting a role for chronic conditions in cognitive decline, independent of age.

Additional studies should test the association of a broader range of chronic conditions and their overall burden on executive function and episodic memory. This study only assessed common chronic conditions, but there may be others that are not as prevalent but may have a great effect on cognition. Also, assessing specific combinations may provide better understanding of synergistic effects of multimorbidity on cognition. A better understanding of determinants of cognitive decline in mid-life is important given the rising rates of multimorbidity and the lack of effective treatments for dementia. Early preventative efforts may be more effective if we are able to catch those in mid-life who are at increased risk.

Table 1. *Descriptives of Study Population (N = 2,532)*

Variables	Mean (SD)	Range	%
Age	55 (11.3)	33 – 83	
Sex (Female)			57.23
Race			
White			86.06
Black			9.91
Other			4.03
Education			
High School			29.78
Some College			28.16
College +			42.06
Work			
Employed			66.51
Unemployed			11.18
Retired			22.31
Married			69.63
Multimorbid			
MIDUS 2			46.25
Young			28.9
Middle			50.4
Older			64
MIDUS 3			62.09
Young			40.98
Middle			68.35
Older			77.16
Chronic Conditions			
MIDUS 2	1.70 (1.57)	0 – 9	
Young	1.11 (1.27)		
Middle	1.85 (1.61)		
Older	2.27 (1.61)		
MIDUS 3	2.27 (1.74)	0 – 9	
Young	1.50 (1.51)		
Middle	2.49 (1.75)		
Older	2.86 (1.66)		
Change in Conditions	0.62 (1.27)	-6 – 6	
Young	0.46 (1.16)		
Middle	0.71 (1.27)		
Older	0.64 (1.37)		
EF at MIDUS 2	0.15 (0.95)	-4.62 – 3.36	
EF at MIDUS 3	0.03 (0.98)	-7.00 – 2.92	
EM at MIDUS 2	0.11 (0.96)	-2.59 – 3.83	
EM at MIDUS 3	0.02 (0.99)	-2.87 – 3.71	

Note. Asian American, Latinos/-as, Native-American, and Pacific Islander were collapsed into “Other”. EF is executive function and EM is episodic memory.

Table 2. *Bivariate Correlations Between Multimorbidity, Executive Function, Episodic Memory, and Covariates (N = 2,532)*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Age	1																		
2. Sex	.00	1																	
3. High School	.11***	.06***	1																
4. Some College	-.03*	.05**	-.48***	1															
5. College +	-.09***	-.11***	-.54***	-.48***	1														
6. White	.10***	-.05***	-.12***	-.02	.14***	1													
7. Black	-.09***	.06***	.14***	.01	-.15***	-.83***	1												
8. Other	-.03*	-.01	-.00	.02	-.01	-.48***	-.09***	1											
9. Employed	-.48***	-.12***	-.16***	.02	.13***	.03*	-.04*	.02	1										
10. Unemployed	-.12***	.17***	.10***	-.01	-.09***	-.09***	.10***	.00	-.51***	1									
11. Retired	.64***	.00	.10***	-.02	-.08***	.04*	-.03*	-.02	.73***	-.21***	1								
12. Married	-.05***	-.17***	-.07***	-.03	.10***	.26***	-.28***	-.02	.07***	-.06***	-.04**	1							
13. Multimorbid	.31***	.05*	.13***	.02	-.13***	-.08***	.09***	.01	-.27***	.06***	-.25***	-.07***	1						
14. Chronic	.32***	.05***	.15***	.01	-.16***	-.10***	.11***	.02	-.31***	.09***	.27***	-.09***	.80***	1					
15. Change	.05*	-.00	.01	.02	-.03	-.03	.03	.01	-.01	-.01	.01	.01	-.17***	-.23***	1				
16. EF MIDUS 2	-.40***	-.12***	-.34***	-.04*	.37***	.24***	-.25***	-.04**	.32***	-.06***	-.31***	.16***	-.26***	-.29***	-.03	1			
17. EF MIDUS 3	-.39***	-.12***	-.22***	-.05*	.35***	.29***	-.29***	-.05**	.32***	-.09***	-.30***	.16***	-.27***	-.30***	-.07***	.78***	1		
18. EM MIDUS 2	-.32***	.21***	-.20***	.02	.17***	.11***	-.10***	-.04*	.20***	.03*	-.25***	.05**	-.16***	-.18***	.00	.43***	.34***	1	
19. EM MIDUS 3	-.34***	.23***	-.18***	-.00	.17***	.09***	-.10***	-.01	.19***	.01	-.23***	.02	-.16***	-.18***	-.04*	.35***	.43***	.54***	1

Note. Change is the change in number of chronic conditions from MIDUS 2 to MIDUS 3, EF is executive function and EM is episodic memory.
*p < .05. **p < .01. ***p < .001.

Table 3. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Multimorbidity Status (N = 2,532)*

	Multimorbidity							
	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Age	-0.01	0.001	-0.17***	-0.02, -0.01	-0.02	0.002	-0.24***	-0.02, -0.02
Sex (Male)								
Female	-0.006	0.02	-0.003	-0.05, 0.04	0.33	0.03	0.17***	0.26, 0.40
Education (High School)								
Some College	0.03	0.03	0.02	-0.03, 0.10	0.03	0.04	0.01	-0.05, 0.11
College +	0.11	0.03	0.05***	0.05, 0.17	0.17	0.04	0.09***	0.09, 0.25
Race (White)								
Black	-0.17	0.04	-0.05***	-0.25, -0.08	-0.16	0.06	-0.05**	-0.27, -0.05
Other	-0.03	0.06	-0.01	-0.15, 0.09	-0.001	0.08	0.00	-0.16, 0.16
Work (Employed)								
Unemployed	-0.13	0.04	-0.04***	-0.21, -0.06	-0.07	0.05	-0.02	-0.17, 0.03
Retired	-0.17	0.04	-0.07***	-0.23, -0.10	-0.09	0.05	-0.04*	-0.19, -0.001
Married	0.06	0.03	0.07*	0.01, 0.12	0.004	0.04	0.00	-0.07, 0.07
Multimorbid	-0.04	0.02	-0.02	-0.09, 0.01	-0.04	0.03	-0.02	-0.10, 0.03
EF MIDUS 2	0.68	0.02	0.66***	0.57, 0.88				
EM MIDUS 2					0.43	0.02	0.42***	0.39, 0.46

Note. Multimorbid is having 2 or more chronic conditions. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001

Table 4. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Chronic Conditions (N = 2,532)*

	Chronic Conditions							
	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Age	-0.01	0.00	-0.17***	-0.02, -0.01	-0.02	0.00	-0.23***	-0.02, -0.02
Sex (Male)								
Female	-0.01	0.02	-0.00	-0.05, 0.04	0.33	0.03	0.17***	0.27, 0.40
Education (High School)								
Some College	0.03	0.03	0.02	-0.03, 0.09	0.03	0.04	0.01	-0.06, 0.11
College +	0.11	0.03	0.05**	0.05, 0.17	0.17	0.04	0.08***	0.09, 0.25
Race (White)								
Black	-0.17	0.04	-0.05***	-0.25, -0.08	-0.15	0.06	-0.04**	-0.26, -0.04
Other	-0.03	0.06	-0.01	-0.15, 0.09	-0.001	0.08	-0.02	-0.15, 0.16
Work (Employed)								
Unemployed	-0.13	0.04	-0.04**	-0.21, -0.06	-0.06	0.05	-0.03	-0.17, 0.03
Retired	-0.16	0.04	-0.07***	-0.23, -0.10	-0.09	0.05	-0.04	-0.18, 0.003
Married	0.06	0.03	0.03*	0.01, 0.12	0.01	0.04	0.01	-0.07, 0.07
Chronic	-0.01	0.01	-0.02	-0.03, 0.004	-0.02	0.01	-0.03	-0.04, 0.002
EF MIDUS 2	0.68	0.02	0.65***	0.58, 0.89				
EM MIDUS 2					0.43	0.02	0.41***	0.39, 0.46

Note. Chronic is chronic conditions. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

Table 5. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Change in Chronic Conditions (N = 2,126)*

	Chronic Conditions							
	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Age	-0.02	0.00	-0.18***	-0.02, -0.01	-0.02	0.00	-0.25***	-0.02, -0.02
Sex (Male)								
Female	-0.01	0.03	-0.01	-0.06, 0.04	0.34	0.04	0.17***	0.25, 0.39
Education (High School)								
Some College	0.02	0.03	0.01	-0.03, 0.10	0.03	0.05	0.01	-0.05, 0.11
College +	0.09	0.03	0.05**	0.03, 0.16	0.18	0.04	0.09***	0.08, 0.24
Race (White)								
Black	-0.25	0.08	-0.04**	-0.41, -0.09	-0.35	0.11	-0.06**	-0.25, -0.03
Other	-0.03	0.06	-0.01	-0.16, 0.10	-0.04	0.09	-0.01	-0.06, 0.26
Work (Employed)								
Unemployed	-0.15	0.04	-0.05***	-0.24, -0.07	-0.09	0.06	-0.03	-0.30, 0.02
Retired	-0.18	0.04	-0.08***	-0.25, -0.10	-0.08	0.05	-0.03	-0.19, -0.01
Married	0.08	0.03	0.04**	0.02, 0.13	0.02	0.04	0.01	-0.05, 0.09
Change	-0.03	0.01	-0.03*	-0.04, -0.01	-0.02	0.01	-0.03	-0.04, 0.00
EF MIDUS 2	0.69	0.02	0.65***	0.64, 0.70				
EM MIDUS 2					0.43	0.02	0.41***	0.39, 0.46

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

Table 6. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Multimorbidity and Chronic Conditions for Young Adults (N=854)*

	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Sex (Male)								
Female	0.00	0.04	0.00	-0.07, 0.08	0.30	0.06	0.16***	0.18, 0.41
Education (High School)								
Some College	0.10	0.05	0.05	-0.001, 0.20	-0.03	0.08	-0.02	-0.18, 0.12
College +	0.13	0.05	0.07**	0.03, 0.23	0.09	0.07	0.05***	-0.05, 0.23
Race (White)								
Black	-0.28	0.06	-0.11***	-0.41, -0.16	-0.14	0.09	-0.05	-0.32, 0.04
Other	-0.07	0.10	-0.02	-0.26, 0.12	0.33	0.14	-0.07*	0.05, 0.61
Work (Employed)								
Unemployed	-0.08	0.05	-0.07**	-0.19, 0.02	-0.04	0.08	-0.02	-0.20, 0.11
Retired	-0.20	0.31	-0.10***	-0.81, 0.42	-0.43	0.46	-0.03	-1.34, -0.47
Married	0.04	0.04	0.04	-0.05, 0.12	0.02	0.06	0.01	-0.10, 0.14
Multimorbid	-0.11	0.04	-0.002**	-0.19, -0.03	-0.12	0.06	-0.06*	-0.24, -0.0002
Chronic Conditions	-0.03	0.02	-0.04*	-0.06, -0.01	-0.05	0.02	-0.06*	-0.09, -0.003
EF MIDUS 2	0.69	0.02	0.71***	0.64, 0.73				
EM MIDUS 2					0.43	0.03	0.43***	0.37, 0.50

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001

Table 7. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Multimorbidity and Chronic Conditions for Middle Aged Adults (N = 1,103)*

	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Sex (Male)								
Female	-0.01	0.04	-0.01	-0.09, 0.06	0.41	0.05	0.22***	0.31, 0.51
Education (High School)								
Some College	0.06	0.05	0.03	-0.03, 0.15	0.11	0.06	0.06	-0.01, 0.24
College +	0.15	0.05	0.08**	0.06, 0.24	0.24	0.06	0.13***	0.13, 0.36
Race (White)								
Black	-0.08	0.06	-0.03	-0.21, 0.04	-0.14	0.08	-0.04	-0.30, 0.03
Other	-0.06	0.08	-0.01	-0.22, 0.10	-0.30	0.11	-0.07**	-0.52, -0.09
Work (Employed)								
Unemployed	-0.19	0.05	-0.07**	-0.30, -0.08	-0.14	0.08	-0.05*	-0.29, 0.01
Retired	-0.25	0.05	-0.10***	-0.35, -0.16	-0.06	0.06	-0.03	-0.19, 0.06
Married	0.07	0.04	0.04	-0.01, 0.15	0.01	0.05	0.01	-0.10, 0.12
Multimorbid	-0.00	0.04	-0.002	-0.07, 0.07	-0.02	0.05	-0.01	-0.11, 0.08
Chronic Conditions	-0.01	0.01	-0.01	-0.03, 0.02	-0.01	0.02	-0.02	-0.04, 0.02
EF MIDUS 2	0.69	0.02	0.70***	0.64, 0.73				
EM MIDUS 2					0.43	0.03	0.43***	0.37, 0.48

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

Table 8. Regressions for Executive Function and Episodic Memory at MIDUS 3 on Multimorbidity and Chronic Conditions for Older Adults (N = 575)

	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Sex (Male)								
Female	0.03	0.06	0.00	-0.09, 0.15	0.27	0.08	0.14***	0.12, 0.42
Education (High School)								
Some College	-0.08	0.07	-0.05	-0.22, 0.06	-0.02	0.08	-0.01	-0.19, 0.14
College +	-0.01	0.07	-0.01	-0.16, 0.13	0.17	0.08	0.09*	0.01, 0.33
Race (White)								
Black	-0.00	0.12	-0.00	-0.24, 0.23	-0.17	0.14	-0.04	-0.43, 0.10
Other	0.15	0.17	0.03	-0.19, 0.48	0.30	0.20	0.05	-0.10, 0.69
Work (Employed)								
Unemployed	-0.06	0.14	-0.02	-0.33, 0.20	-0.02	0.16	-0.01	-0.33, 0.29
Retired	-0.08	0.06	-0.05	-0.21, 0.04	-0.11	0.07	-0.06	-0.26, 0.03
Married	0.10	0.06	0.05	-0.02, 0.22	0.02	0.07	-0.01	-0.16, 0.12
Multimorbid	-0.02	0.02	-0.01	-0.14, 0.10	-0.06	0.07	-0.03	-0.20, 0.07
Chronic Conditions	-0.01	0.02	-0.02	-0.04, 0.03	-0.04	0.02	-0.06	-0.08, 0.00
EF MIDUS 2	0.67	0.04	0.64***	0.64, 0.73				
EM MIDUS 2					0.44	0.04	0.47***	0.37, 0.51

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

Table 9. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Change in Chronic Conditions for Young Adults (N = 654)*

	Chronic Conditions							
	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Sex (Male)								
Female	-0.01	0.04	-0.01	-0.09, 0.08	0.28	0.07	0.15***	0.16, 0.41
Education (High School)								
Some College	0.02	0.06	0.04	-0.05, 0.19	-0.08	0.09	-0.04	-0.25, 0.10
College +	0.09	0.06	0.07*	0.00, 0.22	0.10	0.08	0.06	-0.05, 0.25
Race (White)								
Black	-0.25	0.13	-0.06*	-0.51, -0.02	-0.48	0.18	-0.09**	-0.85, -0.12
Other	-0.03	0.11	-0.03	-0.36, 0.09	0.26	0.17	0.05	-0.08, 0.59
Work (Employed)								
Unemployed	-0.15	0.06	-0.07**	-0.28, -0.04	-0.02	0.09	-0.01	-0.20, 0.16
Retired	-0.18	0.37	-0.02	-1.04, 0.43	-0.43	0.56	-0.03	-1.53, 0.67
Married	0.08	0.05	0.02	-0.05, 0.13	0.05	0.07	0.03	-0.09, 0.19
Change	-0.03	0.02	-0.03	-0.05, 0.02	-0.03	0.03	-0.03	-0.08, 0.03
EF MIDUS 2	0.69	0.03	0.65***	0.63, 0.74				
EM MIDUS 2					0.44	0.04	0.43***	0.37, 0.51

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

Table 10. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Change in Chronic Conditions for Middle Aged Adults (N = 951)*

	Chronic Conditions							
	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Sex (Male)								
Female	-0.03	0.04	-0.02	-0.10, 0.05	0.43	0.05	0.23***	0.32, 0.54
Education (High School)								
Some College	0.06	0.05	0.03	-0.04, 0.15	0.12	0.07	0.06	-0.01, 0.25
College +	0.14	0.05	0.08**	0.04, 0.24	0.24	0.06	0.13***	0.12, 0.36
Race (White)								
Black	-0.31	0.12	-0.06**	-0.55, -0.08	-0.30	0.16	-0.05	-0.62, 0.02
Other	-0.04	0.08	-0.01	-0.20, 0.13	-0.30	0.11	-0.07**	-0.53, -0.08
Work (Employed)								
Unemployed	-0.18	0.06	-0.06**	-0.30, -0.06	-0.19	0.08	-0.07*	-0.35, -0.03
Retired	-0.27	0.05	-0.12***	-0.37, -0.18	-0.07	0.07	-0.03	-0.20, 0.07
Married	0.11	0.04	0.05*	0.02, 0.19	0.03	0.06	0.02	-0.08, 0.15
Change	-0.04	0.01	-0.06**	-0.07, -0.01	-0.01	0.02	-0.01	-0.05, 0.03
EF MIDUS 2	0.72	0.02	0.69***	0.67, 0.76				
EM MIDUS 2					0.42	0.03	0.43***	0.36, 0.48

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

Table 11. *Regressions for Executive Function and Episodic Memory at MIDUS 3 on Change in Chronic Conditions for Older Adults (N = 521)*

	Chronic Conditions							
	EF				EM			
	B	(SE)	β	95% CI	B	(SE)	β	95% CI
Sex (Male)								
Female	0.06	0.06	0.03	-0.07, 0.18	0.28	0.08	0.15***	0.12, 0.43
Education (High School)								
Some College	-0.10	0.08	-0.05	-0.24, 0.05	0.01	0.09	0.01	-0.16, 0.19
College +	-0.09	0.07	-0.00	-0.15, 0.14	0.20	0.08	0.10**	0.04, 0.36
Race (White)								
Black	-0.07	0.19	-0.01	-0.44, 0.30	-0.22	0.22	-0.04	-0.65, 0.21
Other	0.13	0.18	0.02	-0.22, 0.47	0.35	0.21	0.06	-0.06, 0.75
Work (Employed)								
Unemployed	-0.15	0.14	-0.01***	-0.31, 0.23	-0.03	0.16	-0.01	-0.35, 0.29
Retired	-0.18	0.07	-0.05***	-0.22, 0.04	-0.12	0.08	-0.06	-0.27, 0.03
Married	0.08	0.07	0.05**	-0.03, 0.23	-0.04	0.08	-0.02	-0.19, 0.11
Change	-0.03	0.02	-0.01	-0.05, 0.04	-0.03	0.03	-0.05	-0.08, 0.02
EF MIDUS 2	0.67	0.04	0.63***	0.60, 0.75				
EM MIDUS 2					0.45	0.04	0.47***	0.37, 0.52

Note. Change is change in number of chronic conditions from MIDUS 2 TO MIDUS 3. EF is executive function and EM is episodic memory.
*p ≤ .05. **p < .01. ***p < .001.

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