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THE EFFECTS OF MENTAL WORK DEMANDS ON COGNITIVE AGING AND DEMENTIA

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ABSTRACT

As the population is rapidly aging, staying mentally sharp into old age is an increasingly important public health issue. A growing body of empirical research highlights the importance of engaging in mental activities for maintaining cognitive health in later life. Because a person's occupation is a major source of mental activities during a large segment of an individual's life, it is important to identify occupational characteristics that impact long-term cognitive health. The overarching goal of this dissertation was to examine the associations between mental work demands and late-life cognitive outcomes in both cognitively normal individuals and those with dementia.

Using data from the longitudinal Einstein Aging Study, Aim 1 examined whether mental work demands predicted the likelihood and onset of incident dementia (*N*=496). To calculate dementia onset, we used three temporal anchors: birth, baseline assessment, and retirement. Results indicated that individuals with greater mental work demands showed a significantly lower likelihood of incident dementia. Further, work demands were associated with delayed onset of dementia (as indexed by time since retirement), even after controlling for education, genetic risk, and other covariates. Aim 2 examined whether mental work demands were associated with levels and rates of change in cognition among older adults without dementia (*N*=1,118). Cognitive change was represented using two time metrics (i.e., retirement, baseline) for aligning individual trajectories. In the "time from retirement model", mental work demands were associated with higher levels of cognitive performance and faster rates of decline. Despite faster cognitive loss, the protective effect of mental work demands persisted for 24 years after retirement. The relationship between mental work demands and rate of cognitive change, however, was not significant in the "time from baseline" model.

Overall, results from this dissertation are consistent with prior work indicating that greater mental work demands in midlife confer protective effects for late-life cognition. In addition, the seemingly paradoxical result that greater mental work demands predicted faster cognitive decline in later decades of healthy older adulthood is in line with the cognitive reserve hypothesis (Stern, 2002), such that protective factors for cognitive health are associated with delayed onset but more rapid cognitive decline afterwards. Public attention as well as individuals' efforts should be directed to continued mental engagement through midlife into old age.

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Chapter 1. Introduction

Due to increased life expectancy and decreased mortality rates, the U.S. population of older adults has been dramatically increasing. The number of people aged 65 years or older is expected to increase from 48 million (15 percent of the population) in 2015 to 98 million in 2060, which will comprise nearly one in four U.S. residents (US Census Bureau, 2017). Preservation of cognitive health is important for individuals to maintain a sense of purpose, a high quality of life, and importantly, their autonomy and independence into old age. Both cognitive aging and age-related neurodegenerative disease, such as Alzheimer's disease, threaten cognitive health in the older segments of the population. Cognitive decline in older adults is a public health concern because it influences everyday functions such as driving or making financial decisions and may also be an early sign of dementia (Blazer, Yaffe, & Liverman, 2015). Dementia, which is characterized by a decline in mental ability severe enough to interfere with independence and daily life (American Psychiatric Association, 2013), can lead to a heavy familial, societal, and economic burden (Hurd, Martorell, Delavande, Mullen, & Langa, 2013). Thus, identifying modifiable risk and protective factors to maintain cognitive health and prevent dementia in later life is increasingly important.

Some estimates suggest that up to fifty percent of dementia cases worldwide reflects the influence of preventable causes (Barnes & Yaffe, 2011). For example, fewer years of education in early life are associated with lower levels of cognitive function in late life (Wilson et al., 2009) as well as increased dementia risk (Caamaño-Isorna, Corral, Montes-Martínez, & Takkouche, 2006; Meng & D'Arcy, 2012). Engaging in mentally challenging activities during adulthood can also impact cognitive health and alter risk for dementia. Occupation is a major source of a person's mentally challenging activities across the adult lifespan, considering about seventy percent of the adult population in OECD countries (OECD, 2018) spends a substantial amount of time in the workplace. The nature of work tasks during midlife may influence normative cognitive aging as well as dementia risk in later life (Nexø, Meng, & Borg, 2016; Then, Luck, et al., 2013). Moreover, because midlife is the time when late-life health issues start to emerge, identifying the modifiable risk and protective factors during this period is important to minimize, delay, or prevent negative health consequences that happen in later life (Lachman, 2004). The overall aim of the proposed studies is to examine the effects of mental work demands in midlife on both healthy and diseased cognition in late life. The cognitive reserve hypothesis (Stern, 2002) provides a potentially useful framework to examine the protective effect of midlife occupation on late life cognition.

Cognitive reserve hypothesis

This hypothesis was originally proposed to account for the individual differences in disjunction between brain pathology and the cognitive or functional impairment that is expected to result from the pathology; for example, some older adults who had shown normal cognitive functioning prior to death indicated advanced AD pathology in their brains during autopsy (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001). Cognitive reserve reflects the brain's resilience to pathology; despite equivalent levels of brain pathology, individuals with greater resilience to pathology (i.e., high cognitive reserve) maintain unimpaired functioning whereas individuals with poorer resilience (i.e., low cognitive reserve) show impairment. Functional differences by cognitive reserve are attributable to an acquired set of skills or repertoires as well as the brain itself such that higher cognitive reserve reflects better brain networks (i.e., synaptic density), increased brain volume and neurogenesis, and slower accumulation of pathology. It is expected that individuals with higher cognitive reserve can use pre-existing cognitive processes more efficiently or use alternative cognitive strategies to compensate for damage (Stern, 2002, 2009). As will be discussed in later sections, cognitive reserve may impact the manifestation of both cognitive decline associated with normal aging as well as with progressive dementia. Before we delve into the consequence of cognitive reserve in demented as well as non-demented brains, we first suggest a heuristic model, in the next section, that illustrates a life-span perspective on the cognitive reserve hypothesis and describes measures of cognitive reserve that have been widely used in epidemiological studies.

A Life-span perspective on cognitive reserve

Numerous genetic and environmental factors contribute to and are used as proxy variables for cognitive reserve (e.g., intelligence score, years of education, occupational complexity, and leisure activity). Figure 1 describes a heuristic model that delineates factors to contribute to cognitive reserve across the life span (Fratiglioni, Paillard-Borg, & Winblad, 2004, Whalley et al, 2006). Diverse genetic components influence innate intelligence and determine baseline cognitive reserve that manifests throughout adulthood. Exposure to different environmental factors (e.g., parental resources, education) early in development also directly and/or indirectly influences brain structure. Moreover, various environmental conditions start to influence cognitive reserve even after early developmental periods. The influence of occupation typically starts during young adulthood, whereas the importance for leisure activities becomes relatively stronger in older adulthood (Fratiglioni, Paillard-Borg, & Winblad, 2004; Vemuri et al., 2014; Wang, MacDonald, Dekhtyar, & Fratiglioni, 2017). The effects of environmental conditions that allow individuals to engage in mentally challenging activities may be accumulated throughout life and contribute to development and maintenance of cognitive functioning with increasing age. However, when there are changes in the environmental conditions that reduce participation in mental activities, this “disuse” (Salthouse, 1991) may lead to deterioration of cognitive processes and strategies and, eventually, cognitive decline. Thus, mental activities at any point in one’s lifetime can accumulate and influence the maintenance of cognition, but changes in the activity patterns can result in concomitant change in cognitive decline (Whalley, Deary, Appleton, & Starr, 2004; Hultsch, 2004; Hackman et al., 2010; Fratiglioni, Paillard-Borg, & Winblad, 2004).

It is likely that genetic and environmental factors which contribute to cognitive reserve relate to each other. Indeed, genetic factors, parental resources, and education may all influence or relate to occupational opportunities and choices, and these factors may themselves influence late-life cognition directly. This view is in line with the perspective of cumulative advantage/disadvantage (Dannefer, 1987); individuals’ cognitive reserve resulting from contextual conditions early in the life course becomes more pronounced with age as initial advantages or disadvantages early in life accumulate across the lifespan. Lack of parental resources in childhood limits opportunities for education, which, in turn, negatively influences employment options and adulthood income. Indeed, studies have found that childhood socioeconomic status (SES) factors, such as parental economic resources or parents’ education, were associated with late-life cognitive functioning, partially mediated through individuals’ own education levels and mid-late life financial status (González, Tarraf, Bowen, Johnson-Jennings, & Fisher, 2013; Horvat et al., 2014; Luo & Waite, 2005) and these SES advantages/disadvantages seem to accumulate to influence late-life cognitive health outcomes (Luo & Waite, 2005; Turrell et al., 2002). Thus, taking a life-span perspective into account is crucial to examine complex linkages among factors that contribute to cognitive reserve and late-life cognition.

However, favorable circumstance at later points in the lifespan may compensate for the effect of earlier disadvantages. Previous studies have found SES mobility influenced late-life cognitive outcomes, such that the negative impact of low childhood SES (i.e., parents' education or occupation, financial status) was partly ameliorated through mobilization to higher SES (i.e., education, household income) in adulthood (Luo & Waite, 2005; Turrell et al., 2002). Moreover, the effect of adult SES on late-life cognition was greater for individuals with low childhood SES than for those with more advantaged childhoods (Luo & Waite, 2005). Although little is known about the mechanisms through which SES influences late-life cognition, it is plausible that being in a high SES at any stage of the life course is associated with greater exposure to cognitively stimulating environments. Indeed, findings from both experimental and observational studies suggest that the detrimental effects of deprived environments may be reversible at least partially by providing a cognitively demanding environment (Oltmanns et al., 2017; Winocur, 1998). Winocur (1998) found that old rats transferred from impoverished environment to enriched environment showed significantly improved maze performance. In a case-control study, Oltmanns and colleagues (2017) found that constant changes of the work task among assembly line workers, which involve repeated need to learn across the work life, were associated with better cognitive performance as well as with greater regional gray matter volume. However, there has been little and conflicting evidence regarding the unique contribution of midlife occupation on late-life cognitive function over and above early and mid–late life factors. Identifying the unique contribution of midlife occupation could have significant implications for both individuals and public policy to deal with cognitive health disparities in late adulthood.

Operationalization of mental work demands

Researchers have used various terms to describe the cognitive demands of occupational roles. For example, mental stimulation (Grotz et al., 2017; Marquié et al., 2010), mental work/occupational demands (Bosma et al., 2003; Fisher et al., 2014; Smyth et al., 2004), intellectual demands (Potter, Helms, & Plassman, 2008), intellectually challenging work (Gow, Avlund, & Mortensen, 2012), and substantive complexity of work (Schooler, Mulatu, & Oates, 1999) all represent job behaviors and tasks that require cognitive and mental efforts. In this study, we use the term "mental work demands" to represent these various terms. Specifically, we utilize the factor score of substantive complexity of work derived from the fourth edition of the Dictionary of Occupational Titles (DOT)(Roos & Treiman, 1980) to represent mental work demands. This score involves complexity of work with data, an aptitude regarding verbal, mathematics, and intelligence, interests for abstract/creative activities, and vocational preparation.

Indeed, mental work demands score derived from the DOT indicate both job contents and an applicant's traits. The DOT was first developed during the Great Depression and modified throughout World War and postwar economic recovery. The purpose of the DOT was to match workers to jobs on the basis of job contents as well as an applicant's potential traits. The DOT classification of work characteristics includes various ratings for "workers function" (e.g., complexity of work with data/people/things), which is made upon specific occupational contents, and "worker traits" (e.g., interests for abstract/creative/non-routine activities), which are made upon workers in carrying out a specific job (Cain and Treiman, 1981). Therefore, when researchers examine the effects of job characteristics from the DOT score, it would be hard to distinguish between the effects of occupations per se and the effects of individuals who select themselves into the specific occupation. In this dissertation, we make an assumption that the mental work demands score, derived from DOT, represents mentally demanding work contents in a given job that delivers protective effects against negative cognitive health consequences and regards it as a proxy for cognitive reserve. However, alternative explanations (i.e., people select into a specific job) will be provided later in the discussion section.

Aim 1: Mental work demands and dementia

Cognitive reserve in demented brains

The cognitive reserve hypothesis (Stern, 2002) implies three empirical effects in demented brains: cognitive reserve predicts *delayed* onset of cognitive impairment, *reduced* risk of developing dementia, and *accelerated* rates of decline after impairment. Figure 2 depicts the cognitive trajectory of two hypothetical individuals (one with high and one with low reserve) as a function of disease progression. AD pathology starts to develop decades before the initial expression of disease and becomes more severe over time. First, the cognitive reserve hypothesis (Stern, 2009, 2009) predicts that the disease-related cognitive decline will commence later for high compared to low reserve individuals. Individuals with higher cognitive reserve, compared to those with lower reserve, can tolerate more brain pathology because they can process tasks more efficiently with the remaining neural structures and/or can recruit and utilize alternative brain networks. Because of these individual differences in capacity to process cognitive demands, the amount of pathology required for initial expression of disease and the subsequent diagnosis varies by levels of cognitive reserve. For example, in the figure, high reserve people have more AD pathology when dementia is clinically diagnosed (Stern, 2002). Because high reserve people require more pathology to exhibit clinical symptoms of disease, the onset of disease-related decline is postponed relative to low reserve people. Second, because the onset of dementia is delayed among high compared to low reserve people, higher reserve would be related to lower risk for incident (i.e., newly developed) dementia during a specific time interval.

Third, the cognitive reserve hypothesis predicts that, after cognitive decline begins to accelerate, high reserve people will exhibit faster decline than low reserve people (Stern, 2002, 2009). This somewhat counterintuitive effect is related to two points shown in Figure 2. The onset of cognitive impairment emerges at later time among people with higher, compared to lower, cognitive reserve as was described above. The point of complete loss of function, which refers to the timing of final endpoint in which pathology is so severe that individuals cannot function anymore, may be equivalent regardless of levels of cognitive reserve. The slopes of the lines that connect these two points indicate different rates of cognitive decline in high versus low reserve people, such that individuals with higher reserve show more rapid cognitive decline (i.e., steeper slope) after the change point and those with lower reserve show slower decline. Because of delayed onset of impairment and accelerated decline among high, compared to low, reserve people, individuals with higher reserve are expected to die sooner, with shortened period of cognitive and functional disability, after dementia diagnosis (compression of morbidity; Fries, 1980; Langa et al., 2008).

The primary goal of Aim 1 was to examine whether high levels of mental work demands in midlife, one of a proxy measure for cognitive reserve, would predict lower risk and delayed onset of dementia. Because investigating individual difference in dementia onset inevitably requires special attention to the reference time point from which the onset of dementia diagnosis is calculated, various temporal anchors (i.e., birth, baseline assessment, retirement timing) to dementia were compared to examine whether greater mental work demands delay dementia onset from the given reference point. We also examined whether mental work demands in midlife would have a unique contribution to the risk and onset of dementia after accounting for other lifespan factors including education and late-life income. Additionally, to explore which aspects of mental work demands drive the protective effect, the relation of dementia risk/onset with each subcomponent of mental work demands (e.g., aptitude, interests, complexity of work with data) were examined.

Epidemiologic and neuroimaging evidence

There has been ample evidence from epidemiological studies suggesting that proxies of cognitive reserve, such as education (Caamaño-Isorna et al., 2006; Meng & D'Arcy, 2012; Paradise, Cooper, & Livingston, 2009), occupation (Fisher, Chaffee, Tetrick, Davalos, & Potter, 2017; Then, Luck, et al., 2013), and cognitively or socially engaging leisure activities and lifestyle (Fratiglioni et al., 2004; Yates, Ziser, Spector, & Orrell, 2016), predict lower risk of developing dementia probably because the clinical expression of the pathology is delayed. Although disease progression could not be directly measured in those epidemiological studies, evidence from neuroimaging studies supports that individuals with higher cognitive reserve can endure brain damage for a longer time. Stern and colleagues (Stern, Alexander, Prohovnik, & Mayeux, 1992; Stern et al., 1995) examined whether high levels of education and mentally demanding occupation were associated with the severity of AD pathology, measured by resting regional cerebral blood flow, in AD patients. They found that, among individuals with AD matched for clinical severity, those with more years of education (Stern et al., 1992) or higher levels of mental, social, and physical work demands (Stern et al., 1995), compared to their counterparts, exhibited more advanced underlying damage, reflected by greater deficits in parietal blood flow. More advanced pathology among high reserve people in AD patients indicates that they have tolerated more brain damage and have maintained intact cognition longer than lower reserve people prior to clinical diagnosis of dementia. Similarly, other neuroimaging studies found that, among AD participants with similar clinical severity, individuals with higher education had lower glucose metabolism in the brain area typically influenced by AD pathology (Perneczky et al., 2006).

Importance of time reference in investigating dementia onset

Further evidence also suggests that measures of cognitive reserve are associated with dementia onset (Paradise et al., 2009; Then, Luck, et al., 2013) and cognitive impairment (Hall et al., 2007, 2009). Hall and colleagues identified that accelerated memory decline (i.e., change point) begins on average 5 years prior to clinical diagnosis of dementia (Hall, Lipton, Sliwinski, & Stewart, 2000) by modeling cognitive trajectory with the date of dementia diagnosis as time zero and looking backwards in time that preceded diagnosis. By applying this model, Hall and colleagues tested individual differences in the onset of cognitive impairment regarding whether years of formal education (Hall et al., 2007) or participation in cognitively stimulating leisure activities in late life (Hall et al., 2009) were associated with differential onset of dementia-related accelerated memory decline. They found that one year increase in years of formal education and one day increase in self-reported cognitive activity per week delayed the time of accelerated memory decline by 0.21 years and 0.18 years respectively. It should be noted, however, that the time reference that Hall and colleagues (2007, 2009) selected to align individuals’ cognitive trajectories on (i.e., clinical dementia diagnosis) was not identical to the selection of time that the cognitive reserve hypothesis proposed (i.e., same amount of pathology as shown in Figure 2), and this difference may influence the interpretation of the results. Based on the cognitive reserve hypothesis, aligning high and low reserve people on the time axis at which individuals diagnosed with dementia, as Hall and colleagues’ studies did, will result in different amount of pathology between high and low reserve people; that is, at the reference point of diagnosis, high reserve people have more advanced pathology compared to low reserve people. Therefore, the small differences in the onset of cognitive impairment that Hall and colleagues (2007, 2009) observed between high and low reserve people were likely to be underestimated compared to the differences if these individuals' cognitive trajectories were aligned on the progress of pathology. Because it is almost impossible to repeatedly assess biological disease progression in longitudinal studies using currently available methods, we can only approximate individual differences in the relationships between disease progression and the onset of cognitive impairment.

One of the more common approaches to examine individual differences in dementia risk and onset is modeling the risk of developing dementia with a function of time elapsed from a particular point (i.e., looking forwards in time) until diagnosis. If there is no convincing argument to choose a specific point in time, researchers typically use an arbitrary or convenient start time such as year of birth or baseline assessment (Singer & Willett, 2003). In the studies examining the association between occupation and dementia, a few studies used time from baseline assessment to dementia diagnosis as a timescale (Karp et al., 2009), and found that high scores in work complexity with data and people were associated with lower risk of dementia (Karp et al., 2009). Indeed, most previous studies utilized the participant's age as the reference point for the relative timing of each diagnostic evaluation (Kröger et al., 2008; Potter, Helms, Burke, Steffens, & Plassman, 2007; Stern et al., 1994; Then et al., 2017). These studies showed that education- and occupation-based hierarchies (Stern 1994) or specific work characteristics were associated with decreased risk and delayed onset of dementia.

No studies so far, however, have chosen participant's retirement as the reference point for the relative timing of dementia diagnosis to examine the association between dementia onset and mental work demands. The benefit of cognitive challenging activities can be lost if those activities are not continued (Salthouse, 1991). Several studies found that retirement is associated with a drop in cognitive functioning (Bonsang, Adam, & Perelman, 2012; Mazzonna & Peracchi, 2012; Rohwedder & Willis, 2010) close to 10% decrease compared to the sample average (Bonsang et al., 2012). Therefore, retirement timing may be an appropriate temporal anchor for investigating individual differences in dementia onset.

Current study

In the current study, we tested whether greater mental work demands would be associated with reduced risk of developing dementia and later dementia onset. To investigate the association between mental work demands and dementia onset, we compared three time references: delay in dementia onset from birth (i.e., chronological age), baseline assessment, and retirement timing. The following hypotheses were tested.

H1a. Higher levels of mental work demands predict lower likelihood of incident dementia.

H1b. Higher levels of mental work demands predict later onset of dementia.

We also explored two additional research questions. Based on previous studies that found education (Caamaño-Isorna et al., 2006; Ngandu et al., 2007) and late-life income (Anttila et al., 2002; Evans et al., 1997; Scazufca, Almeida, & Menezes, 2010) as important factors predicting dementia, we examined whether the effects of mental work demands persisted after accounting for education and late-life income. Also, because some types of work demands may be particularly more effective in reducing dementia risk and delaying dementia onset than others

(Potter et al., 2007; Then et al., 2017; Then, Luppa, et al., 2013), we examined which sub-components of mental work demands (i.e., aptitude, creative activities) would be associated with risk and onset of dementia.

Aim 2: Mental work demands and normal cognitive aging

Cognitive reserve in cognitively normal individuals

In the cognitive reserve literature, most empirical evidence as well as theory is framed around brain damage in general with a special focus on AD. In demented brains, the cognitive reserve hypothesis proposes that greater cognitive reserve is associated with higher levels of cognition, delayed onset of cognitive impairment, and accelerated cognitive decline after the onset of impairment. Although it is less clear what the cognitive reserve hypothesis predicts regarding normal cognitive aging without clinical diagnosis, the same logic that the cognitive reserve hypothesis suggests for the demented brains can be applied to the normal aging brains. Previous literature has suggested that cognitively healthy older adults are affected by both age-related neural insults and accumulation of pathologies (Park & Reuter-Lorenz, 2009; Rodrigue, Kennedy, & Park, 2009; Whalley, Deary, Appleton, & Starr, 2004). Although overall numbers of neurons are relatively well-preserved, reduced ability in remodeling synaptic connections seems to attribute to age-related cognitive aging. Moreover, the aging brain in the absence of overt dementia is also influenced by Alzheimer neuropathology (mostly amyloid plaques) as well as cerebrovascular pathology (Whalley et al., 2004). It has been suggested that 20-30% of clinically normal, healthy older adults (age 65-90) exhibits significant amyloid deposition (Rodrigue et al., 2009). Also, there seems to be no clear threshold of pathological features (e.g., plaques, vascular pathology) that distinguish clinical dementia from normal cognitive aging (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001). This increasing burden of subclinical Alzheimer and vascular pathologies as well as the reductions in synaptic plasticity can affect accelerated cognitive decline among cognitively healthy individuals (Whalley 2004).

In the face of neuro-aging and pathologies, the aging brain is capable of decreasing the cognitive effects of neurological/neuropathological burden by engaging in compensatory neural processes and flexible cognitive strategies (Reuter-Lorenz & Park, 2014; Richards & Deary, 2005; Schmitt et al., 2000; Whalley, 2015). There is also substantial inter-individual variability in these compensatory abilities; for example, people who experienced more intellectually stimulating activities across the lifespan can better capitalize on these protective capacities against aging and pathologies compared to those with less intellectually stimulating activities (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014; Stern, 2009). Thus, high reserve people will show higher levels of cognition and slower rates of cognitive aging relative to low reserve people until the brain reaches the point of severe neuro-aging and/or brain pathology. When the intact brain reaches the point of advanced neuro-aging and/or brain pathology, however, cognitive reserve in the later stages of normal aging may act similarly as in the brains with dementia. That is, a greater burden of pathologies and neuro-aging would be required for high compared to low reserve people to exhibit cognitive decline. But once the magnitude of neural insults that the brain can sustain is much more advanced, greater cognitive reserve is likely to be associated with more *rapid* cognitive decline among high reserve people to keep with their more severe pathology or neuro-aging. In line with this prediction, Fotenos and colleagues (Fotenos, Mintun, Snyder, Morris, & Buckner, 2008) found that, for non-demented older adults, higher levels of SES, measured by both education and occupation, were related to smaller whole brain volumes, faster volume loss, and more rapid functional decline over time when levels of baseline functioning (i.e., Clinical Dementia Rating; CDR) were equivalent (i.e., no dementia). They also observed that reduced brain volume was associated with increased amyloid plaques. It appears that high reserve people showed more rapid functional decline (e.g., CDR rating from no dementia to very mild dementia) due to advanced brain changes, which related to increased amyloid accumulation in the normal brains. However, there has been little empirical evidence regarding rates of cognitive decline associated with measures of cognitive reserve (e.g., education, occupation) in later stages of the non-demented brains.

Epidemiological evidence

Although it is relatively well-established that engaging in cognitively stimulating activities at any point in one's lifetime is associated with higher levels of cognition (Jefferson et al., 2011; Opdebeeck, Martyr, & Clare, 2016; Then, Luck, et al., 2013), conflicting results have been reported when examining the association of cognitively stimulating activities with cognitive *change* (Anstey & Christensen, 2000; Fratiglioni et al., 2004; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). In terms of cognitively engaging activities in the workplace, greater mental work demands have been consistently associated with higher levels of cognition in late life (Bosma et al., 2003; Fisher et al., 2014; Gow et al., 2012; Grotz et al., 2017; Marquié et al., 2010; Pool et al., 2016; Potter et al., 2008; Then et al., 2015). There have been, however, only handful of studies that examined whether engaging in mentally stimulating activities in the workplace prospectively predicted the rates of cognitive decline in late life (Fisher et al., 2014; Gow et al., 2012; Grotz et al., 2017; Marquié et al., 2010; Pool et al., 2016). Some studies found that greater mental work demands, compared to lesser mental demands, were associated with slower cognitive decline (Fisher et al., 2014; Marquié et al., 2010; Pool et al., 2016; Then et al., 2015), other studies did not find significant associations between mental work demands and rates of cognitive decline (Gow et al., 2012; Grotz et al., 2017), and others found more rapid cognitive decline associated with higher occupation-based SES (Singh-Manoux Archana et al., 2011).

Likely explanations for these inconsistent findings may relate to 1) heterogeneity in participants' age range, 2) being unable to filter out individuals who developed dementia in later assessments, and 3) different selection of time basis to aggregate cognitive trajectories across individuals to describe the pattern of longitudinal change. First, heterogeneity in participants' age range among studies may account for different results if cognitive aging shows a non-linear pattern within older adulthood. Indeed, previous longitudinal studies found nonlinear increase in the average rate of cognitive decline with advancing baseline age in older adulthood (Wilson et al., 2002). Then, studies that restrict samples in midlife and early old age (i.e. fifties or early- to mid-sixties) may be able to identify only part of the pattern in cognitive aging but ignore what happens in the latter part of older adulthood. As such, the role of protective factors against cognitive deficit may differ with advancing age in older adulthood. For example, previous studies found that slower rates of cognitive decline were associated with greater mental work demands among individuals in their mid- to early old age (Fisher et al., 2014), but this pattern might not hold (or could even reverse) among individuals with more advanced age. In the present study, participants were older individuals in their later stages of life during which the effects of accumulative brain aging and pathologies were more likely to impact cognitive function, even among high reserve individuals. Investigating the current sample at this period will help us understand whether the effect of a protective factor holds the same or changes throughout older adulthood.

Second, some studies excluded participants with dementia at baseline (Grotz et al., 2017), others excluded participants who developed dementia at any point of assessment (Finkel, Andel, Gatz, & Pedersen, 2009), whereas other studies did not exclude participants based on cognitive status (Fisher et al., 2014; Lane, Windsor, Andel, & Luszcz, 2017; Marquié et al., 2010; Pool et al., 2016; Then et al., 2015). Because the cognitive reserve hypothesis predicts earlier onset of developing dementia among individuals with low, compared to high, reserve people (Stern, 2002), it is possible that larger percentage of participants in low reserve group compared to high reserve group developed dementia over time. Failure to distinguish cognitively healthy people from those who developed dementia during follow-up might have biased the results and would have erroneously resulted in rapid cognitive decline among individuals with lower mental work demands (Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003; Sliwinski, Lipton, Buschke, & Stewart, 1996). One possible way to deal with this issue is to exclude participants who developed dementia at any point of assessment.

Third, different time indices across studies may have resulted in inconsistent findings. Most of the studies used time from baseline assessment (Lane et al., 2017; Marquié et al., 2010; Then et al., 2015) and a few studies used time in relation to retirement (Finkel et al., 2009; Fisher et al., 2014) to examine age-related longitudinal changes in rate of cognitive decline. Indeed, the choice of time index in longitudinal studies is a critical issue to formulate a descriptive model of intraindividual change. Time index needs to reflect underlying processes such as age-graded change, disease progression, or changes in the environment that relates to cognitive stimulation or engagement. If one fails to select appropriate time indices, the true pattern for intraindividual change would be distorted (Sliwinski & Mogle, 2008). Although time from baseline is a commonly used index to aggregate data to estimate average intraindividual change, describing change from an arbitrary time point may provide little or even distorted information about underlying causal processes if there are multiple age-graded and non-age-graded factors that drive change. Importantly, when certain changes in the environment significantly influence cognitive functioning, the selection of a time basis needs to incorporate such changes as well as factors driving aging processes. Retirement implies major changes in individuals' lifestyle in a way that impacts involvement in cognitively stimulating activities. Previous studies have suggested the critical impact of retirement timing on a subsequent cognitive decline (Bonsang et al., 2012; Mazzonna & Peracchi, 2012). To examine the effect of mental work demands on cognitive decline, the length of exposure to retirement may be a better indicator to represent both normative age-related change and the retirement effect than the time of enrollment into a longitudinal study (i.e., baseline).

Current study

Aim 2 of the current study was to test the hypothesis that greater mental work demands in midlife would predict higher levels of cognition but faster rates of cognitive decline among older adults in later stages of life. Due to the sample age range in this study (mean age at baseline=79.2, SD=5.4), it is plausible that participants in the current study without clinical dementia experienced advanced neuro-aging and/or brain pathology over time. Cognitive reserve in this later stages of normal cognitive aging may act similarly as in the demented brain. Then, higher mental work demands, which are regarded as a protective factor for cognitive aging, are likely to be associated with higher levels of cognition but more rapid cognitive decline in the later older adulthood. Thus, two specific hypotheses were tested.

H2a. Greater mental work demands in midlife predict higher levels of cognition in late life.

H2b. Greater mental work demands in midlife predict faster rates of cognitive decline in late life.

To address limitations from previous literature, participants who developed dementia at any assessment were excluded from the study sample. Moreover, two time indices (i.e., time from baseline, time from retirement) were compared to examine whether the choice of time index changes the description of longitudinal changes over time. Additionally, we explored whether the effects of mental work demands were independent of early life education and late-life income, and whether there was interactive effect between mental work demands and education. The associations between sub-components of mental work demands (e.g., aptitude, creative activities) and late-life cognition were also explored.

Chapter 2. Method

Overview

This study is based on data from the Einstein Aging Study (EAS), a longitudinal study of cognitive aging and dementia. Study details are described elsewhere (Katz et al., 2012). Briefly, diverse adults sample has been systematically recruited from Bronx County, NY from 1993 through 2015. Individuals were mailed introductory letters, telephoned to complete a brief screening interview, and potential participants were invited for further screening at the EAS clinical research center to determine final eligibility. Eligible participants were at least 70 years of age, Bronx residents, non-institutionalized, and fluent in English speaking. Exclusion criteria included visual or auditory impairments, active psychiatric symptomatology, and non-ambulatory status. Participants received comprehensive annual assessments including demographics and health status, psychosocial status, clinical evaluations, a neuropsychological battery, and medical histories. Written informed consent was obtained in the initial clinic visit. The study protocol was approved by the Institutional Review Board of the Albert Einstein College of Medicine.

Analyses for Aims 1 and 2 are based on data from individuals who were working for pay in their primary job, were retired after the ages of 50, and who did not develop dementia at baseline. Among 2,357 individuals in original EAS data, 248 (10.5%) participants had to be excluded because of incomplete or missing occupational information, 9 (0.4%) because the mental work demands score, derived from the fourth edition of the US Dictionary of Occupational Titles (DOT), was not available for some occupations coded by 1970 census code. Furthermore, 534 (22.7%) participants had to be excluded because of missing dementia diagnosis information, 145 (6.2%) because of missing information of the retirement timing, and 122

(5.2%) because individuals were retired before age 50. Seventy one (3.0%) participants were also excluded as they were diagnosed with dementia at baseline. Among the remaining participants, 579 (24.6%) participants were excluded from the analytic sample of Aim 1 because of incomplete apolipoprotein (APOE) ε4 information and 153 (6.5%) were excluded because of no follow-up assessments. The final sample for Aim 1 comprised a total of 496 participants (n=423 for dementia-free, n=73 for incident dementia). Compared to individuals who were excluded from the analyses, individuals who were included in the analytical sample in Aim 1 were significantly more likely to be older (mean age=78.5 years at baseline vs. 79.2 years; *p*=.008), have more education (12.9 years vs. 13.4 years; *p*=.012), and have incomes above the poverty level (72.9% vs. 77.7%; *p*=.038) but did not differ in terms of gender and ethnicity. For Aim 2, 110 (4.7%) participants were also excluded as they developed incident dementia, and the final sample comprised a total of 1,118 participants (see Figure 3). Compared to individuals who were excluded from the analyses, individuals who were included in the analytical sample in Aim 2 were significantly more likely to be older (mean age=78.2 years at baseline vs. 79.2 years; *p*=<.001) and be Caucasian (62.7% vs. 68.6%; *p*=.010) but did not differ in terms of education, gender, and income.

Measures

Mental work demands

Participants' primary occupations (i.e., occupation of longest duration over their lifetime) were identified from self-reports at the initial visit of the EAS. Trained coders assigned each participant's job to the three-digit 1970 U.S. Census Occupational Classification System (U.S. Bureau of the Census, 1970). Then, we applied mental work demands scores developed by Roos and Treiman (1980) for each occupation category. Because mental work demands scores were already assigned to each 3-digit 1970 Census occupational codes (Roos & Treiman, 1980, pp. 365–386), each occupation in EAS could be directly linked with the mental work demands scores as well as occupational description scores that constitute mental work demands variable.

Measures of mental work demands were based on the factor score (Roos & Treiman, 1980) from the 4th edition of DOT (US Department of Labor, 1977) ratings and data from the April 1971 Current Population Survey (CPS) for each occupation category (Roos and Treiman, 1980). Occupational analysts performed on-site ratings for 46 occupation-related descriptions for more than 12,000 different occupational titles coded with DOT occupations. Occupational descriptions include complexity of work (with data/people/things), the education and training required, the aptitudes, interests, and temperaments appropriate for the occupation, the physical demands of the occupation, and the physical conditions under which the work is performed (Table 1)(Roos & Treiman, 1980). With these items of occupational descriptions, Roos and Treiman (1980) conducted factor analysis using data from the April 1971 CPS, which include information for more than 60,000 workers and were coded with both DOT codes and 1970 Census occupational codes. Before conducting factor analysis, some variables, originally coded as dichotomies in the DOT sample, were recoded as proportions in the Census sample. Then, the fourth edition DOT codes were aggregated with weights proportional to the number of individuals holding each DOT occupation, to create scores of each occupational description for more than 500 Census occupational categories. Among four factors (substantive complexity, motor skills, physical demands, and undesirable working conditions) found in Roos and Treiman (1980), we opted to use the substantive complexity factor to operationalize mental work demands. The factor score of mental work demands reflects general educational development (reasoning, mathematics, and language), specific vocational preparation, complexity of functioning with data, intelligence, numerical aptitude, verbal aptitude, interests for abstract and creative activities, and temperament for non-repetitive or non-continuous processes (Table 1). These items were standardized and summed to form mental work demands scale, and for ease of interpretation, the scale was converted to a 0-10 range.

Occupational descriptions

Although the mental work demands score was the main focus of our interest, ten specific DOT occupational descriptions were also used in the supplementary analyses. These occupational descriptions included: 1) complexity of work with data, 2) general educational development (GED): reasoning, 3) GED: mathematics, 4) GED: language, 5) specific vocational preparation, 6) intelligence aptitude, 7) verbal aptitude, 8) numeric aptitude, 9) repetitive or continuous processes, and 10) interests for abstract and creative versus routine, concrete activities. These variables were selected as they were sub-components of the factor scale of mental work demands.

Complexity of work with data

These measures reflect the levels of complexity at which a worker in a particular occupation functions in relation to data (Miller, Pamela, Patricia, & Roos, 1980). Complexity of work with data was rated from highest level 0 to lowest level 6: Synthesizing (0), coordinating (1), analyzing (2), compiling (3), computing (4), copying (5), and comparing (6). Complexity scores were reversed so that higher scores indicate greater complexity. Each GED measure was standardized and the scale was converted to a 0-10 range.

General educational development (GED): Reasoning, mathematics, and language

GED indicates the aspects of formal and informal education which are required of the worker for satisfactory job performance. This measure includes the worker's reasoning development, ability to follow instructions, and acquisition of language and mathematical skills. Education in this measure reflects learning experiences of a general nature that does not have a particular occupational purpose (U.S. Department of Labor, 1972). However, it should be also noted that this is not an actual measure of educational attainment but how the job demands correspond expected educational requirements to support the specific cognitive domains. GED scores ranged from 1 to 6 for reasoning, 1 to 6 for math, and 1 to 5 for language (Appendix 1). Each complexity measure was standardized and the scale was converted to a 0-10 range.

Specific vocational preparation (SVP)

SVP indicates the amount of lapsed time required by a typical worker to learn the techniques, acquire the information, and develop the facility needed for average performance in a specific job-worker situation. SVP includes training acquired in a work, school, institutional, or avocational environment but excludes schooling without specific vocational contents. Original scales ranged from lowest level 1 to highest level 9: Short demonstration only (1), anything beyond short demonstration up to and including 30 days (2), over 30 days up to and including 3 months (3), over 3 months up to and including 6 months (4), over 6 months up to and including 1 year (5), over 1 year up to and including 2 years (6), over 2 years up to and including 4 years (7), over 4 years up to and including 10 years (8), over 10 years (9) (Cain & Treiman, 1981; U.S. Department of Labor, 1972). Scales were standardized and converted to a 0-10 range.

Intelligence, verbal aptitude, and numerical aptitude

Aptitudes are the abilities that workers can facilitate the learning of job tasks. Scores of 1 (high) to 4 (low) were assigned to indicate the level of intelligence, mathematical aptitude, and language aptitude required for satisfactory performance of specific job. Although Level 5 was assigned if the aptitude was not required to perform the job for mathematical and language aptitude, 5 could not be assigned on the intelligence aptitude because it was assumed that every job requires at least a 4 level of intelligence (Roos & Treiman, 1980; U.S. Department of Labor, 1972). Scales were reversed so that higher score indicates higher aptitude, standardized, and converted to a 0-10 range.

Interests in abstract and creative versus routine, concrete activities

This measure reflects a preference for activities of an abstract and creative nature that are entailed in job performance compared to a preference for activities of a routine, concrete, organized nature (Roos & Treiman, 1980; US Department of Labor, 1972). This variable, originally coded as -1, 0, 1, was recoded as proportions, standardized, and converted to a 0-10 range.

Temperaments for repetitive or continuous processes

This measure reflects adaptability to working with repetitive and continuous processes. This variable, originally coded as dichotomies, was recoded as proportions, reverse coded, standardized, and converted to a 0-10 range.

Neurocognitive outcomes

Nine neurocognitive tests, including Free and Cued Selective Reminding Test (FCSRT), Logical Memory, Trail Making (Part A), Trail Making (Part B), Digit Symbol–Coding, Block Design, Letter Fluency, Category Fluency, and Boston Naming, were administered throughout the entire longitudinal assessments in EAS. Scores for Trail making A and B were reverse-coded, so that higher scores for all cognitive tests indicate higher cognitive function. To create an invariant definition of cognitive outcomes at each wave of testing, raw scores of all cognitive measures were standardized relative to the respective means and variances at the baseline assessment. Moreover, principal components analysis (PCA) was used to construct a composite cognitive score from nine individual tests; the loadings from the PCA conducted at baseline assessment were used to construct the composite cognition component. Loadings ranged from .43 (FCSRT) to .80 (Digit Symbol) and the component explained 45% of the variance. All cognitive scores including individual and composite cognitive outcomes were centered at 50 with 10 SD to enhance the interpretability of the results.

Free and Cued Selective Reminding Test (FCSRT) with Immediate Recall

The FCSRT (Buschke, 1984) measures deficits in episodic memory. The test begins with a study phase to identify 16 pictured items (e.g., guitar) in response to category cues (e.g., musical instrument). In the test phase, participants were asked to recall the items they learned during separate three test trials (i.e., free recall). Participants were given the category cues to prompt recall of items not correctly answered by free recall (i.e., cued recall). The sum of free recall score (range 0–48) was used in analyses.

Logical Memory Subtest of the Wechsler Memory Scale-Revised (WMS-R) with Immediate Recall

The Logical Memory subtest Story A and Story B (Wechsler, 1987) measures deficits in prose recall. Two independent stories (A and B) were read to the participants and participants were asked to recall each story immediately after listening to each story. Word-for-word recall was encouraged because scores were given by the number of story units that were accurately retold (range 0–50).

Digit Symbol-Coding Subtest of the Wechsler Adult Intelligence Scale III

This is an index of processing speed. Participants were provided a code table displaying pairs of digits and symbols at the top of the page. The participant was asked to copy as many symbols under the corresponding digits as possible using a code table. The number of symbols correctly drawn in a 120-second time period determines the score (range 0–133). Previous literature suggested that this test had good sensitivity to identify small cognitive changes among participants with normal cognition rather than cognitively impaired participants (Proust-Lima, Amieva, Dartigues, & Jacqmin-Gadda, 2006).

Block design Subtest of the Wechsler Adult Intelligence Scale III

This is an index of visuospatial constructional ability. The participant was required to replicate models or pictures of two-color designs with blocks in a limited time period (starts off with 1 min and moves onto 2 min with task difficulty; range 0–68). Each block has two white sides, two red sides, and two half-red and half-white sides. The test consists of a set of 14 printed geometric designs. The difficulty of the designs ranged from simple two-block designs to more complex, nine-block designs.

Trail Making Test

The Trail Making Test (Reitan, 1958) includes two parts: A and B. In Trail Making Test Part A, the participant was given a sheet with the numbers 1–25 and the participant has to connect the numbers in sequence as quickly as possible within a maximum of 150 seconds. This test requires processing speed and visual searching and sequencing. The score indicates the amount of time in seconds required for task completion. Final scores were reversed so that higher scores indicate better cognitive functioning. In Trail Making Test Part B, the participant was given a sheet with number 1–13 and letters A–M. The participant had to connect the numbers and letters in alternating sequences (e.g., 1, A, 2, B, etc.) as quickly as possible within a maximum of 300 seconds. This task measures executive functioning, cognitive flexibility, and visual searching and sequencing. The score indicates the amount of time in seconds required for task completion. Final scores were reversed so that higher scores indicate better cognitive functioning.

Letter Fluency Test for F-A-S

The Verbal Fluency Test (FAS)(Benton, Hamsher, & Sivan, 1989) measures timed phonemic verbal fluency. The participant was given a letter (F, A, and S) and in 1 minute produces as many words as possible that begin with the letter. The score is the total number of correctly listed items.

Category fluency

Category fluency (Monsch et al., 1992) measures timed semantic verbal fluency. The participant had 1 minute to name as many words that belong to a particular category (animals, vegetables, and fruits). The score is the total number of correctly listed items during the 3-min period.

The Boston Naming Task

The Boston Naming Task (Mack, Freed, Williams, & Henderson, 1992) is a measure of confrontation naming. The participant had to name pictures that range from common objects to rare ones (range 0–60). Semantic and phonemic cues were given if the participant had difficulty naming any particular object; however, no score was given if the phonemic cue was used.

Dementia diagnosis

Dementia diagnosis was based on standardized clinical criteria from the DSM-IV (American Psychiatric Association, 1994), which requires impairment in memory and at least one additional cognitive domain, accompanied by evidence of functional decline. Diagnoses were assigned at consensus case conferences, which involved comprehensive review of neurocognitive test results, neurologic symptoms, and functional impairment. Memory impairment was defined as a score of 24 or less on the FCSRT−Free Recall (Buschke, 1984) or scores of 1.5 SDs or more below the age-adjusted mean for the Logical Memory test (Wechsler, 1987). Clinical evaluation, informant questionnaires, and the Lawton Brody Scale (Lawton & Brody, 1970) determined functional impairment. To ensure uniformity of diagnosis over time, all individuals evaluated before DSM-IV was released in 1994 were reconferenced retrospectively according to DSM-IV criteria.

Other items

Time from retirement was calculated by subtracting retirement year from the year that each assessment was conducted. *Retirement age* was calculated based on the information about birth date and date of retirement and centered at its mean. Demographic characteristics, including *baseline age* (years; centered at baseline mean), *gender* (reference: female), *years of education* (centered at mean), and *late-life income* (poverty level vs. above poverty level) were obtained at the time of the baseline survey. Because carriers of the APOE ε4 allele are known to be at increased risk for AD and dementia and many previous studies have considered the influence of risk factors in the context of APOE ε4 genotype (Farrer et al., 1997; Slooter et al., 1998), *APOE ε4 carriers* were also identified (at least one APOE *ε*4 allele vs. others).

Analytic plans

Aim 1: Logistic regression and Cox proportional hazards regression

We investigated the effect of mental work demands on (1) the likelihood of incident dementia using logistic regression and (2) dementia onset using Cox proportional hazards regression. First, logistic regression using SAS PROC GENMOD was used to model the probability of incident dementia as a function of mental work demands score. The relative risks (RRs) were estimated using log-binomial regression (DIST=BINNOMIAL, LINK=LOG). When convergence problems occurred with binomial regression models due to the inclusion of covariates, the modified Poisson method with a robust error variance was used (DIST=POISSION, LINK=LOG)(Fang, 2011; Zou, 2004). Education, gender, baseline age, study duration, and APOE ε4 were controlled for as covariates.

Second, Cox proportional hazards regression using SAS PROC PHREG was used to model survival hazards (i.e., time until dementia diagnosis) as a function of mental work demands. Years to dementia onset was the outcome variable and mental work demands were a predictor variable. Three time scales were compared in separate models: Participants' age at dementia diagnosis, time from baseline assessment to dementia diagnosis, and time from retirement to dementia diagnosis. Education, gender, baseline age, and APOE ε4 were controlled for in time from baseline models and time from retirement models. Education, gender, and APOE ε4 were controlled for in participants' age at dementia models.

Continuous scores of mental work demands and years of education were used in all analyses. The analyses were then replicated with categorical variables of mental work demands (high vs. low based on a median split) and years of education (high vs. low based on a median split), in which the high groups were the reference categories. Supplemental analyses were conducted on each of the mental work demand components (i.e., complexity with data, GED reasoning, GED mathematics, GED language, specific vocational preparation, intelligence aptitude, verbal aptitude, numeric aptitude, non-repetitive processes, abstract/creative activities). All statistical analyses were performed using SAS 9.4 software.

Aim 2: Mixed models

To examine Aim 2, which investigated whether mental work demands predict both levels and rates of change in cognition among cognitively normal older adults, mixed models using

SAS PROC MIXED (version 9.4) were used to account for the nested structure of the data (i.e., multiple assessment occasions within persons). Full maximum likelihood was used for model estimation and robust standard errors were used for fixed effects hypothesis testing. Cognition was modeled as a function of mental work demands and a within-person time index (i.e., time from baseline, time from retirement). We opted not to use a time index regarding chronological age due to the age convergence issue (Sliwinski, Hoffman, & Hofer, 2010). Briefly, in age-heterogeneous longitudinal studies like this study, parameters of change using chronological age as a within-person time index can be correctly estimated only under the assumption that cross sectional age differences and longitudinal age changes converge onto the same trajectory. Although the time effect would be uninterpretable without confirming this convergence assumption, this is often difficult to test because baseline age difference is much larger than the duration of follow-up (Sliwinski et al., 2010).

Mental work demands were used as a main predictor variable and a composite cognitive score, constructed from PCA of nine different neurocognitive test scores, was used as a main outcome variable. Supplemental analyses were conducted on nine separate cognitive scores (i.e., FCSRT, Logical Memory, Trail Making Part A, Trail Making Part B, Digit Symbol–Coding, Block Design, Letter Fluency, Category Fluency, and Boston Naming) and each of the mental work demand components (i.e., complexity with data, GED reasoning, GED mathematics, GED language, specific vocational preparation, intelligence aptitude, verbal aptitude, numeric aptitude, non-repetitive processes, abstract/creative activities). Covariates were education, baseline age, and gender. To minimize potential biases from individuals who develop dementia over time, participants who developed dementia at any point of assessment were excluded.

Shown below is the mixed model in which cognition is modeled as a function of mental work demands and a within-person time index.

Level 1: $Cognition_{ij} = b_{0j} + b_{1j}(Linear\ time_{ij}) + \ b_{2j}(Quadratic\ time_{ij}) + e_{ij}$

Level 2: $b_{0j} = \ \beta_{00} + \ \beta_{01}(Mental\ work\ demands_{.j}) + \ \beta_{02}(Education_{.j})$

$$+\beta_{03}(Gender_{.j}) + \ \beta_{04}(Baseline\ age_{.j}) + \beta_{05}(Practice\ effect_{.j}) + u_{0j}$$

$$b_{1j} = \ \beta_{10} + \ \beta_{11}(Mental\ work\ demands_{.j}) + u_{1j}$$

$$b_{2j} = \ \beta_{20}$$

Time indicates either time from baseline or time from retirement. We also controlled for practice/retest effects. Modeling practice effect on cognitive performance is not a simple issue, and there are a variety of ways to account for practice effects (Ferrer, Salthouse, Stewart, & Schwartz, 2004; Wilson et al., 2002). Following prior research (Finkel et al., 2009; Fisher et al., 2014), we opted to use one of the simpler methods for modeling practice effect; practice effects were controlled for by constructing a dummy-coded variable that was coded as a 0 (baseline cognitive measure) and 1 (all assessments following baseline). In the equation, β_{01}indicates the main effect of mental work demands on levels of cognition. We predict this to be significant and positive, which indicates that levels of cognition will be higher among individuals with higher compared to lower mental work demands (H2a). β_{11} indicates the interaction term between time and mental work demands and represents the effect of mental work demands on rates of cognitive change. We predict this to be significant and negative, which indicates that rates of cognitive decline will be faster among individuals with higher compared to lower levels of mental work demands (H2b).

Chapter 3. Results and Discussion

Results for Aim 1

Study characteristics

The analysis was based on 496 individuals (mean age at baseline=79.2, SD=5.2; mean follow-ups=4.5 years; mean retirement age=65.2). As a result of data linkage, 132 unique occupation categories were identified based on 3-digit 1970 Census occupation codes. With this occupation coding, eight broader occupation categories were created to represent types of occupation that individuals had (Table 2). Among 496 participants, 73 were diagnosed with dementia at follow-up, with 33.2 new cases of dementia per 1,000 persons per year. Table 3 shows the baseline characteristics of the study participants between high versus low levels of mental work demands. High mental work demands group was more likely to have higher years of education (*p*<.001), be Caucasian (*p*=.03), and have incomes above the poverty level (*p*<.001). There were no significant differences in baseline age, retirement age, mean follow-up time, being female, and being APOE ε4 carriers by levels of metal work demands.

The effect of mental work demands

Tables 4 and 5 present findings from logistic regression and Cox proportional hazards regression. First, results from logistic regression showed that individuals with higher scores in mental work demands had a significantly lower dementia risk in the univariate model (RR=0.89, 95% CI=0.79-0.99). After controlling for education, gender, baseline age, study duration, and APOE E4, the effect of mental work demands remained significant (RR=0.86, 95% CI=0.77-0.98)(Table 4). Second, results from Cox proportional hazards regression suggested that greater mental work demands were associated with delayed dementia onset in the univariate models regardless of selection of time references (HR=0.87, 95% CI=0.77-0.98 for chronological age at dementia diagnosis; HR=0.87, 95% CI=0.76-0.98 for time from baseline to dementia; HR=0.87, 95% CI=0.75-0.98 for time from retirement to dementia)(not presented in the table). When education, gender, APOE ε4, and baseline age were adjusted for, the effects of mental work demands on dementia onset varied across time references. Greater mental work demands were significantly associated with later onset of dementia only in the model of time from retirement to dementia (HR=0.83, 95% CI=0.71-0.96)(Table 5).

Using categorical variables of mental work demands (high/low) and education (high/low) did not change the main findings. The Kaplan-Meier curve comparing the risk of dementia for those in high and low mental work demands is shown in Figure 4. Low mental work demands, compared to high demands, were associated with a higher RR of incident dementia (RR=1.63, 95% CI=1.04-2.55) and faster dementia onset from retirement timing (HR=1.94, 95% CI=1.15-3.27) in fully adjusted models. The effects of education were not significant by itself in a univariate model as well as in any models above. Further adjustment for late-life income did not significantly alter the pattern of findings. The effects of late-life income were not significant in any models. We also examined whether there were interactive effects between mental work demands and education/income. Results from logistic regression and Cox proportional hazards regression showed no significant interaction effects between mental work demands and education, and mental work demands and late-life income.

Sub-components of mental work demands

We also tested which specific aspects of mental work demands and work characteristics were associated with dementia risk and onset. Table 6 presents findings from both logistic regression and Cox proportional hazards regression in fully adjusted models. Results from logistic regression indicated that higher scores in GED language (RR=0.87, 95% CI=0.77-0.98) and abstract/creative activities (RR=0.87, 95% CI=0.78-0.96) were significantly associated with lower dementia risk. In addition, results from Cox proportional hazards regression similarly indicated that higher scores in GED language (HR=0.83, 95% CI=0.71-0.97), intelligence aptitude (HR=0.87, 95% CI=0.75-1.00), verbal aptitude (HR=0.85, 95% CI=0.74-0.97), and abstract/creative activities (HR=0.83, 95% CI=0.73-0.95) were significantly associated with a later dementia onset in fully adjusted models. The results were similar in univariate models. Using categorical variables of each item did not change the pattern of findings.

Discussion for Aim 1

We aimed to examine whether mental work demands in midlife were associated with the likelihood of incident dementia and onset of dementia from multiple temporal index variables. We observed significant association between high levels of the mental work demands and a reduced risk of dementia; high compared to low mental work demands group showed decreased dementia risk by 41%. This effect remained significant after controlling for education, gender, follow-up times, and APOE ε4. Moreover, greater mental work demands predicted later onset of dementia with regard to retirement timing.

Mental work demands and dementia

In the current study, we found evidence of reduced likelihood of incident dementia and delayed onset related to greater mental work demands, lending support to the cognitive reserve hypothesis (Stern, 2002, 2009). The cognitive reserve hypothesis suggests that there are individual differences in the ability to deal with pathology. When a certain percentage of the brain has been affected by a pathological process, individuals with higher cognitive reserve have better synaptic connectivity and more efficient use of alternative brain networks compared to those with low reserve. Different aspects of life experience, including midlife work experiences, can modulate cognitive reserve. Thus, greater mental stimulation may prevent individuals with advanced pathology from expressing the symptoms, postpone the onset of dementia, and reduce the rates of incident dementia. Support for this view was also found in the study cited earlier, which found the relationship between higher mental work demands and advanced pathology among AD patients after controlling for dementia severity (Stern et al., 1995). Andel and colleagues (2006) also found that, among AD patients, higher mental work demands were associated with faster cognitive decline, suggesting that brain structures among those with higher, compared to lower, mental work demands may have been affected by dementia pathology to a greater extent at dementia onset (Andel, Vigen, Mack, Clark, & Gatz, 2006). Moreover, if higher levels of cognitive reserve postpone the threshold that marks clinical diagnosis, clinical manifestations of dementia may even be prevented. Previous studies also found that some older adults with extensive pathological AD-related lesions in the brain did not show clinical manifestation of cognitive impairment (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001).

In addition, mental activities may alter the pathologic progression of dementia (Coyle, 2003). Although AD neuropathology, such as neurofibrillary tangles and neuropil threads, progressively and slowly develops over approximately five decades (Ohm, 1997), persistent engagement in mentally challenging activities strengthens existing synaptic connections and generates new ones, and stimulates neurogenesis. Indeed, reduced neuronal activation, rather than cell loss, occurs early in the disease process and may underlie the clinical dementia symptoms (Swaab et al., 2002). However, mental activities even in the later decades of life may increase neuronal activation, and the activated neurons may remain intact in old age (Schooler et al., 1999; Stern, 2002; Swaab et al., 2002). These plastic changes can circumvent the pathology underlying dementia symptoms and delay clinical manifestation of disease (Coyle, 2003; Swaab et al., 2002).

Retirement timing and dementia onset

Importantly, we observed significant associations between greater mental work demands and delayed onset of dementia after controlling for covariates only when dementia onset was calculated from retirement rather than birth or baseline assessment. The cognitive reserve hypothesis makes predictions that, for high compared to low reserve people, clinical diagnosis as well as the point of inflection, where cognition begins to be influenced by dementia pathology, will be reached later when pathology is more severe. Thus, the theory supposes delayed onset in terms of disease progression (i.e., accumulation of pathology). However, it would be challenging to test these predictions due to the limitations in biological measurement (i.e., frequent longitudinal assessments of neuropathology biomarkers). Instead, some studies examined whether cognitively challenging activities in early or midlife postpone clinical diagnosis of dementia from baseline assessment (e.g., Karp et al., 2009) or in terms of chronological age (Kröger et al., 2008; Potter et al., 2007; Stern et al., 1994; Then et al., 2017), and others investigated whether individuals with high reserve show shortened duration between accelerated cognitive impairment and dementia diagnosis (Hall et al., 2007, 2009). Retirement timing may be another important time index to investigate individual differences in dementia onset especially among those who had maintained their primary lifetime occupation.

Because dementia diagnosis is determined not entirely by pathologic processes but the complex interactions among pathology and various genetic and environmental factors contribute to the clinical expression of symptoms (Stern, 2002), it would be important to consider those underlying factors in order to determine individual differences in dementia onset. Moreover, the benefit of mental activities can be lost if those activities are not maintained (Bielak, 2010; Salthouse, 2006). Although many researchers appear to assume that effect of mentally challenging activities, such as education or mental work demands, accumulate over a period of decades before it influences late-life cognition, there also might be relatively immediate and concomitant effects of initiating or terminating such activities (Hultsch, Hertzog, Small, & Dixon, 1999; Salthouse, 2006). Indeed, several studies found that retirement amplified the rate of cognitive decline (Bonsang, Adam, & Perelman, 2012; Mazzonna & Peracchi, 2012; Rohwedder & Willis, 2010); the loss was not one-time but increased with the length of the retirement spell (Mazzonna & Peracchi, 2012). Given that retirement timing may have both concomitant and cumulative effects and that mental activities in the workplace influence pathologic progression as well as manifestation of disease, it would be reasonable to investigate the onset of dementia from the point at which people stop accumulating such mental activities (i.e., retirement).

We compared three time reference points (i.e., birth, baseline assessment, retirement timing) to calculate the relative duration until diagnostic evaluation, and found the stable and significant results only when retirement timing was used as a temporal anchor. Indeed, Sliwinski and colleauges (2003) found that, compared to chronological age, time to incident diagnosis provided a better representation of memory decline among preclinical subset of the sample, probably because the time index better represents non age-graded influences, i.e., progression of pathology. Although a few studies have emphasized the importance of selection of time basis when modeling cognitive change (Sliwinski et al., 2003), there had been little research in dementia literature that examined the importance of choosing the right time metrics. The current finding highlights the importance of selecting the appropriate time metrics that can properly describe the influences of causal processes when investigating dementia onset. An outcome variable representing the time to diagnosis changes its value depending on the choice of temporal anchor when examining survival function. By using chronological age as a time anchor, as most previous studies did, researchers assume that individuals with the same age are at the equivalent stages in aging and pathologic progression that causes cognitive loss. However, the present finding suggests that elapsed time from retirement may better represent the temporal dimensions of the underlying process (i.e., pathologic progression) and thus provides a more accurate representation of its time course (Sliwinski et al., 2003; Sliwinski & Mogle, 2008).

The unique effect of mental work demands

Despite high correlation between early-life and adulthood factors, we found a unique effect of midlife occupation on incident dementia after accounting for early education or late-life income. The present findings are consistent with previous studies suggesting mental work demands as a more robust predictor of dementia risk and a better indicator of cognitive reserve than education (Andel et al., 2005; Dekhtyar et al., 2015; Potter et al., 2007). Because formal education ends in young adulthood for most individuals, the workplace is important in preserving and developing the protective effects of earlier mental activity into the middle and older stages of adulthood. However, other studies did not find significant effects of occupation after controlling for early education and/or late-life income (Evans et al., 1997; Karp et al., 2004). Different measures of occupation (Evans et al. measured perceived occupational prestige; Karp et al. did not used mental work demands score but used separate complexity scores) may account for the different results.

Moreover, neither education nor late-life income was significantly associated with risk/onset of dementia. Lack of protective effects of education in the current study is in contrast with some (Meng & D’Arcy, 2012; Stern et al., 1994) but not all (Bonaiuto et al., 1995; Cobb, Wolf, Au, White, & D’agostino, 1995; Dekhtyar et al., 2015) prior studies. The current measure of education (i.e., years of education) may not properly represent the degree/magnitude of mental activities during school years and we may need a better measure for levels of mental activities in school. The measure to indicate late-life income (poverty vs. non-poverty level) was also crude. Moreover, because late-life income may be a consequence of the disease process rather than a risk factor for dementia (Anttila et al., 2002), future studies could test whether individuals’ own income levels in midlife or changes in income levels from mid to older age change the effect of mental work demands.

Furthermore, although we did not have measures for early intelligence or childhood cognitive abilities, those factors may be more important to control for when investigating unique contribution of mental work demands to rule out the possibility of reversed causation. Dekhtyar and colleagues (2015) found that school performance at age 10, but not education (elementary vs. senior high vs. professional and university), was significantly associated with dementia risk when they were included with work complexity variable in the same model. In the Nun study, Snowdon and colleagues (1996) found that linguistic ability in early adulthood was a strong predictor of poor cognitive function and AD in late life. Linguistic ability in early adulthood may be an important marker of cognitive ability and neurological development as a result of both genetic and educational factors in earlier period.

We also found that APOE ε4 carriers showed higher likelihood and earlier onset of dementia as expected. Regarding the effect of baseline age, however, we found a somewhat counterintuitive result in the time from retirement model (Table 5, Model 3). Although the baseline age effect on dementia onset was in the expected direction in time from baseline model (i.e., higher baseline age associated with earlier onset), we found that higher baseline age was associated with later onset in time from retirement to dementia model. We cannot fully explain it from this study alone. However, when retirement timing was used as a temporal anchor to investigate dementia onset, selection bias might have occurred such that people who retired later than other people may be in better health conditions compared to those who retired relatively earlier.

Which types of mental work demands are more protective?

We also examined whether the effects of mental work demands on the likelihood and onset of dementia differ in regard to the specific types. We found significant associations between higher levels of language development, interests in abstract/creative activities and a reduced dementia risk; those who had high scores in abstract/creative activities and language development had a 52% and 43% reduction in risk of developing incident dementia respectively compared to those who had lower scores. Our results also showed significant associations between high levels of interests in abstract/creative activities, language development, intelligence/verbal aptitude and a delayed dementia onset from retirement timing even after adjusting for education, gender, age, and APOE ε4. However, the effects of complexity with data, reasoning, mathematical development, and vocational training were not significant.

The present findings that revealed the protective effects of specific types of work characteristics are in line with some studies (Andel et al., 2005; Kröger et al., 2008; Potter et al., 2007; Then et al., 2017) but not others (Karp et al., 2009; Potter et al., 2007; Then, Luppa, et al., 2013). Different sources of database from which work scores were derived (1970s DOT vs. 2010 O*NET) may have influenced this discrepancy. Although the database from the 4th edition of DOT (US Department of Labor, 1977) was relevant to describe work characteristics among the current sample, work scores from 2010 O*NET database (www.onetonline.org/) that other study utilized (Then et al., 2017; Then, Luppa, et al., 2013) may have different scores in corresponding items due to shift in work contents over time (e.g., computerization). Different selection of sample (e.g., male twin pair in Potter et al., 2007) or lack of power due to a small sample size in the current study may be another possible explanation. However, Kröger and colleagues (2008) found that individuals with high complexity of work with data showed enhanced risk of developing dementia for those who held their principal occupation for more than 23 years. It is possible that deleterious effects of work overload and stress from work complexity may counteract the protective aspects of work complexity. Then, it may be other features of mental work demands (e.g., abstract/creative activities) that drive protective effect of mental work demands rather than work complexity itself.

Importantly, interests for abstract/creative activities showed strong and consistent protective effects on both dementia risk and onset. Work tasks conducted under abstract and ill-defined contingencies require individuals to have skills for independent judgement, problem solving intuition, and creativity (Schooler et al., 1999). Previous imaging studies found that occupational experience that requires greater abstract/creative activities were associated with better neurological outcomes. Suo and colleagues found that supervisory and managerial experience during midlife was associated with reduced hippocampal grey matter loss in old age independent of premorbid IQ (Suo et al., 2012). Other studies found that older workers with repetitive work demands showed worse task-switching performance and reduced brain activity than those with mentally stimulating work demands (Gajewski et al., 2010), but workers who experienced continuous changes of the work task showed better cognitive performance and greater regional gray matter volume than workers who experienced less work-task changes (Oltmanns et al., 2017). In addition, the significant effect of language development may suggest that language skill, obtained through prior formal education, is an important component of cognitively stimulating job characteristics. This finding of which subcomponents of mental work demands drive the significant results may be useful to inform ways in order to prevent or delay disease onset and provide public health interventions.

Limitations and future direction

Several limitations should be noted for future research. First, we could not rule out the possibility of reserved causality. Innate intelligence might be underling factors for higher occupation to be associated with lower dementia risk. However, previous research of a co-twin control study, which could account for genetic and early-life environmental factors, showed similar findings (Andel et al., 2005; Potter et al., 2007), suggesting that these results cannot be entirely explained by genetic or familiar confounding. Second, it is unclear whether early retirement may be a subtle symptom that precedes dementia. However, even when we excluded from the analysis those who retired early because of mental and physical health problem, the significant protective effects persisted.

Third, due to the lack of detailed information on participants' occupational history, we could not investigate whether mental work demands in different period of lifespan are associated with dementia risk and onset. Previous studies have suggested that high level of mental work demands in specific period of life may be more important (Smyth et al., 2004). In the case-control study, Smyth and colleagues (2004) found significant mean differences in occupational demands among AD cases and control participants from their 30s through 50s but not in their 20s. However, it is unknown how mental work demands for older adults (i.e., age 60+), impacts the risk for and onset of dementia.

Fourth, due to the limited measures, the present study did not test or control for the effects of other lifespan factors such as parental resources, midlife income, or mid/late-life leisure activities. Fifth, this study did not test the psychological/behavioral/biological mechanisms through which mental work demands in midlife were associated with dementia. Previous studies found that in less educated people, cerebrovascular disease is a possible determinant of dementia through mechanisms such as deleterious smoking habits or other risk factors for stroke (Del Ser, Hachinski, Merskey, & Munoz, 1999; Fratiglioni & Wang, 2007; Snowdon et al., 1997). Future studies are needed to examine whether vascular risk or other mechanisms mediate the association between mental work demands and dementia.

Results for Aim 2

Descriptive statistics

The analysis was based on 1,118 individuals (mean age at baseline=79.2, SD=5.4; mean follow-ups=2.8 years; mean retirement age=64.9). As a result of data linkage, there were 197 unique occupation categories based on 3-digit 1970 Census occupation codes. Based on this occupation coding, eight broader occupation categories were created to represent types of occupation that individuals have (Table 2). Mental work demands score was normally distributed with a mean of 4.81 and a SD of 1.97. Average retirement duration (i.e., time from retirement) at baseline was 14.3 years (SD=6.9, range= −4.5~48.8). Table 7 shows descriptive statistics at the baseline assessment between high versus low levels of mental work demands (median-splitted). High metal work demands group had more years of education (*p*<.001), had a higher baseline composite cognitive score (*p*<.001), had incomes above the poverty level (*p*<.001), and was more likely to be female (*p*=.001) and Caucasian (*p*<.001). There were no significant differences in baseline age and retirement age by levels of mental work demands. Moreover, person-level correlation analyses were conducted among main variables. Education was positively correlated with mental work demands (*r*=.51, *p*<.001). The composite cognitive score was positively associated with both mental work demands (*r*=.34, *p*<.001) and years of education (*r*=.44, *p*=.001). Retirement age was not significantly associated with years of education, mental work demands, and composite cognitive score.

The effects of mental work demands on cognition: from retirement timing

We tested the hypotheses that greater mental work demands would predict higher initial levels but faster rates of change in cognition. Two separate analytic models were constructed using two time indices; one in which levels and changes in cognition were modeled as a function of time from retirement and the other with time from baseline assessment. Before testing our hypotheses with time from retirement, preliminary models were fit to test for the presence of a first-order autoregression process (AR(1)). Fitting an empty model resulted in evidence of significant lag 1 residual autocorrelation (*b*=.49, *p*<.001), which remained significant (*b*=.41, *p*<.001) after detrending the time series by including time from retirement. Thus subsequent models included first-order autoregressive correlation structures. The results from the mixed model, which examined the effects of covariates on the composite cognitive score, indicated that the composite score were lower in males (*b*= −1.30, *p*=.02), older participants (*b*= −.37, *p*<.001), and those with fewer years of education (*b*=1.28, *p*<.001). The linear effect of duration of retirement (i.e., time from retirement) was not significant, but the quadratic effect of time from retirement was significant (*b*= −.01, *p*<.01), indicating accelerated rates of decline in the composite cognitive score over time after retirement. The practice effect was significant (*b*=.82, *p*<.001), indicating that there was significant improvement in cognition after the first assessment. Random effect for time since retirement was significant (*p*<.001), indicating significant inter-individual variation in rates of cognitive change. All the covariates, random effect of time from retirement, and autocorrelation term were significant and included in subsequent analyses.

Results from the mixed model examining the association between mental work demands and the composite cognitive score from retirement timing are presented in Table 8, Model 1. As hypothesized, greater mental work demands were associated with higher levels of composite cognition at retirement (*b*=1.28, *p*<.001) and faster decline over time, indicated by the mental work demands × time interaction (*b*= −.03, *p*=.027). Analyses examining separate neurocognitive tests indicated that greater mental work demands were associated with higher levels in Logical Memory (*p*=.002), Trail making A (*p*=.0002), Trail Making B (*p*=.014), Digit Symbol (*p*<.0001), FAS (*p*=.0002), CAT (*p*=.043) and Boston Naming (*p*=.0075) but not with FCSRT and Block Design. For rates of cognitive decline, greater mental work demands were associated with more rapid decline in Logical Memory (*p*=.014), Trail Making A (*p*=.002), and Digit Symbol (*p*=.001). Further adjustment for late-life income did not significantly alter the pattern of findings for levels (*p*<.001) or rates of change (*p*<.02) in the composite cognitive score. The effect of late-life income was significant (*b*=4.29, *p*<.001).

Despite the pattern in cognitive decline among individuals with greater mental work demands, the magnitude of difference in levels of cognition at retirement may still have protective effects over time into later adulthood. The effects of mental work demands on cognition remained significant 24 years after retirement. Figure 5 illustrates initial levels and change in cognition after retirement between males in 75th percentile of mental work demands and males in 25th percentile.

Additional analyses were conducted to examine which aspects of mental work demands contributed to the cognitive outcome. After controlling for years of education and other covariates, higher initial levels of the composite cognitive score were significantly associated with most subcomponents that were included in the factor score of mental work demands (*p*=.001 for GED reasoning; *p*=.025 for GED mathematics; *p*<.001 for GED language; *p*=.005 for SVP, *p*<.001 for intelligence aptitude; *p*<.001 for verbal aptitude; *p*=.002 for numeric aptitude; *p*=.041 for non-repetitive processes; *p*<.001 for abstract and creative activities) except for complexity with data (Table 9). Regarding rates of cognitive change, faster rates of decline were associated with GED reasoning (*p*=.04), GED language (*p*=.005), intelligence aptitude (*p*=.019), verbal aptitude (*p*=.01), and interests for abstract/creative activities (*p*=.004). Complexity with data, GED mathematics, specific vocational preparation, numeric aptitude, and temperaments for repetitive processes were not significantly associated with rates of cognitive decline over time.

Next, we examined interactions between mental work demands and education on levels and rates of change in cognition. When a 2-way interaction term between education and mental work demands was included in the above Model 1, the interaction between education and mental work demands was significant (b=−.137, p<.005). Figure 6 illustrates this interaction effect on initial level of composite cognition. Individuals with lower levels of education benefitted more from higher levels of mental work demands compared to those with higher levels of education. The three-way education × mental work demands × time interaction, however, was not significant. Using categorical variables of education (high/low) and occupation (high/low) did not change the pattern of findings.

Several sensitivity analyses were conducted to confirm the associations between mental work demands and the composite cognitive score. First, we removed 7.9% of the sample who reported the reason of retirement as being either cognitively or physically sick. The effects of mental work demands on the initial levels of cognition (b=1.27, p<.001) and rates of cognitive decline (b= −.04, p=.033) remained significant. Second, based on quintiles of the retirement year, we removed lowest quintile (18.5% removed; retired before 1980) to minimize biases from potential cohort effects from shift in job contents (Autor & Price, 2013). The effects of mental work demands on both initial cognition (b=1.271, p<.001) and rates of change (b= −.048, p=.027) remained significant.

The effects of mental work demands on cognition: from baseline assessment

Another analytic model was constructed to examine the associations between mental work demands and late-life cognition as a function of time from baseline assessment. Before testing our hypotheses, preliminary models were fit to test for the presence of a first-order autoregression process (AR(1)). Lag 1 residual autocorrelation was significant (b=.35, p<.001) after detrending the time series by including time from baseline. Thus subsequent models included first-order autoregressive correlation structures. The results from the mixed model, which examined the effects of covariates on the composite cognitive score from the baseline assessment, indicated that the composite score was lower in male (*b*= −1.10, *p*=.06) and higher in those with higher education scores (*b*=1.29, *p*<.001). The association between being male and lower composite score was marginally significant (*p*=.06). Baseline age was not significantly associated with the composite score. Both linear (*b*=.33, *p*<.01) and quadratic effects (*b*=−.09, *p*<.001) of time from baseline were significant. The practice effect was not significant, probably because this effect was accounted for by both linear and quadratic time effects (i.e., time from baseline). Random effect for time from baseline was significant (*p*<.001). To make the results using time from baseline and using time from retirement comparable, all the covariates that were used for the above analytic model with time from retirement, as well as random effect of time from baseline and autocorrelation term, were included in subsequent analyses.

The results from the mixed model examining the association between mental work demands and the composite cognitive score from the baseline assessment are presented in Table 8, Model 2. Mental work demands were associated with higher levels of composite cognition at baseline (*b*=.74, *p*<.001). However, greater mental work demands were not significantly associated with rate of change in the composite cognitive score. Analyses examining separate neurocognitive tests indicated that greater mental work demands were associated with higher levels in Trail Making B (*p*=.008), Digit Symbol (*p*=.002), Block Design (*p*=.006), FAS (*p*<.001), and Boston Naming (*p*=.001), but not with FCSRT, Logical Memory, Trail Making A, and CAT. For rates of cognitive decline, none of the neurocognitive measure was significantly associated with mental work demands.

Discussion for Aim 2

The primary goal of this study was to examine the longitudinal association between individual's midlife occupation and late-life cognitive functioning, considering potential importance of retirement timing. In support of the first hypothesis, greater mental work demands were associated with higher levels of cognitive function. Regarding the second hypothesis, greater mental work demands were associated with faster rate of cognitive decline after retirement, but the protective effect of mental work demands, as reflected by better cognitive performance, persisted for 24 years. The effects of mental work demands on levels and rates of change in cognition were significant after controlling for education and late-life income. Moreover, individuals with lower levels of education derived greater cognitive benefit from mental work demands.

Cognitive reserve in cognitively normal individuals

Although the cognitive reserve hypothesis (Stern, 2002) and related evidence focus on cognitive declines a few years prior to and post dementia diagnosis, there has been less consideration of the role that cognitive reserve plays in the normal aging brain and in temporal progression of cognitive change (i.e., accelerated decline from early-old to old-old brains). Given the paucity of evidence, the present study extends the research on cognitive reserve by examining individuals 1) in the later stages of normal cognitive aging, 2) who did not develop dementia during follow-up, 3) with utilizing meaningful longitudinal time index (i.e., retirement timing).

We found a seemingly paradoxical result in terms of rates of cognitive decline such that greater mental work demands were associated with faster cognitive decline. Despite faster cognitive decline among individuals with higher mental work demands, it should be noted that the magnitude of the effect on rates was small relative to the overall shift in levels of cognition. Therefore, the protective effect of mental work demands is manifested as relatively higher cognition that is maintained over 24 years after retirement. Moreover, steeper cognitive decline appears to be in line with the cognitive reserve hypothesis (Stern, 2002) such that protective factors for cognitive aging may be associated with delayed onset but more rapid cognitive decline in the later stages of life as will be discussed below.

Although the biological mechanisms underlying cognitive aging are not fully understood, there has been good evidence that a continuum exists from normative cognitive aging to clinical dementia (Whalley et al., 2004). The aging brain even in the absence of dementia is associated with pathologies (e.g., amyloid plaques, cerebrovascular pathology) as well as reductions in synaptic plasticity (Hedden et al., 2012; Hof, Glannakopoulos, & Bouras, 1996; Whalley et al., 2004). However, the aging brain can adapt to minimize the cognitive consequences of impaired neuronal function and neuronal loss and to tolerate structural changes from pathologies (Reuter-Lorenz & Park, 2014; Schmitt, 2000; Whalley et al., 2004). Cognitive reserve accumulated from intellectually demanding activities can bolster these protective capacities against aging and pathologies by allowing efficient processing with better synaptic links (Stern, 2002, 2009). Thus, high reserve people may show similar or even slower rates of cognitive decline relative to low reserve people until the brain reaches the point of advanced neuro-aging and/or brain pathology. However, because a greater burden of neuro-aging and/or pathology is required for high compared to low reserve people, the rates of cognitive decline would be faster among high reserve people to keep with their more severe pathology or neuro-aging when they were to exhibit cognitive deficit. Indeed, this line of reasoning is in agreement with the theoretical accounts of cognitive reserve hypothesis for the demented brains and suggests that the same logic can be applied to the normal, old-old brains. The current finding that greater mental work demands were associated with faster cognitive decline supports this idea.

The current findings have implications for identifying risk and protective factors in cognitive aging. If researchers were to examine people at younger ages prior to having high levels of neuro-aging and pathology, people with high reserve may show slower rates of cognitive decline. However, as this study revealed, if researchers examine people at older ages who experience advanced neuro-aging and pathology, they may find different pattern such that protective factors are associated with <u>faster</u> cognitive decline, perhaps driven by changes in later life. Indeed, Fisher and colleagues (2014), with using time from retirement, found that greater mental work demands were associated with slower cognitive decline among relatively younger older adults (mean age at the baseline assessment= 55). Unlike the participants in the current study (mean baseline age = 79), participants in early old age are not likely to develop advanced neuro-aging and/or pathology. Therefore, it would be important to consider participants' age range and to examine both levels and rates of change in cognition when examining risk/protective factors for cognitive aging. It is possible that the same factor (e.g., mental work demands) that was associated with slower cognitive decline during one time period may be associated with faster decline later in older adulthood. If researchers examine levels of cognition only, without considering rates of cognitive decline, they are likely to miss the true association between risk/protective factors and cognitive aging.

Alternatively, the current finding may be explained by an inherent potential confound due to how dementia is diagnosed using neurocognitive test scores. High reserve people have higher cognitive scores and therefore are less likely to meet diagnostic thresholds for cognitive impairment on clinical tests. Because more pathology is required in those of high reserve to be diagnosed with clinical dementia, high reserve people with some amount of pathology may have not be diagnosed with dementia and included in the analyses. Conversely, low reserve people with the same amount of pathology may be diagnosed with dementia and excluded from this study analysis. But pathology in high reserve people are still associated with more rapid cognitive decline (Hedden, Oh, Younger, & Patel, 2013; Rodrigue et al., 2012), possibly resulting in faster cognitive decline among high compared to low reserve individuals. However, we did not find the evidence that either levels or rates of decline in FCSRT, which is a sensitive measure to predict future dementia (Grober, Lipton, Hall, & Crystal, 2000), varied by levels of mental work demands. Thus we consider this explanation unlikely.

The current study also examined specific variables that were included in mental work demands as well as other complexity variables. We found that variables reflecting educational development, vocational training, intelligence/verbal/numeric aptitude, and interests in abstract and creative activities were all protective by contributing to higher levels of cognition even after controlling for the effects of years of education. After the termination of education, the workplace may provide a context to preserve and bolster the protective effects of education into the later developmental stages. Moreover, abstract/creative activities, verbal/intelligence aptitude, and language/reasoning development were associated with faster cognitive decline, suggesting that these components may be a better indicator of cognitive reserve. Complexity with data was significantly associated with levels in cognition only when years of education were not included in the model, suggesting education as a potential prerequisite to obtain an occupation high in complexity with data (Finkel et al., 2009).

It would also be important to investigate whether and to what extent the cognitive benefits associated with mentally engaging activities endure in the absence of such mental engagement. Although cumulative influence of cognitively engaging activities during early and midlife may be related to subsequent cognitive change in late life (Stern, 2002), concomitant change in cognitive activities in late life may also influence changes in late-life cognition. That is, change from cognitively engaged to unengaged lifestyle is likely to influence cognitive decline (Hultsch, Hertzog, Small, & Dixon, 1999; Schooler, 1984). In the current study, retirement timing may represent an abrupt and major change in terms of cognitive stimulation, suggesting that retirement may be the time at which cognitive decline commences. In the next section, we will further discuss the importance of time selection in modeling longitudinal cognitive trajectories.

Retirement and the choice of the time base

The choice of the time to represent intraindividual change is an important issue in longitudinal studies. Although the selection of the time basis does not influence the rate of cognitive change for any given individual, the selection of the time basis influences how data are aggregated across individuals to estimate an average curve that describes the pattern of intraindividual change and how people deviate from that average. If the time index does not reflect the progression of the causal processes driving change, then the estimate of the typical curve will be distorted as will model-based representations of individual differences in change; on the other hand, use of an appropriate time index can improve precision and reduce error in estimates of individual differences in change (Sliwinski & Buschke, 2004; Sliwinski et al., 2003;

Sliwinski & Mogle, 2008). Although previous literature suggests chronological age or time from baseline as the time index to examine normative age effects such as development, maturation, or senescence (McArdle, Ferrer-Caja, Hamagami, & Woodcock, 2002; Wilson et al., 2002), retirement timing can reflect another process that drives abrupt cognitive change (Rohwedder & willis, 2010; Bonsang et al., 2012). It is reasonable to assume that there might be both age-graded (i.e., brain aging) and non-age-graded (i.e., retirement) processes that separately and interactively influence cognitive changes in the same individual. It makes more sense, then, to align individuals on the time index regarding retirement to correctly identify the pattern of intraindividual change related to occupational characteristics.

We compared two separate models; one in which cognitive decline was modeled as a function of mental work demands and time from retirement and the other with time from baseline assessment. Significant effects were found for the association between mental work demands and rate of cognitive change only when individuals' cognitive trajectories were aligned with reference to retirement timing. It should be noted that the estimates of rates of cognitive decline in two time indices were similar but the magnitude of differences in standard error was larger for the time from baseline model ($b = -.034$, SE=.015 for time form retirement; $b = -.031$, SE=.029 for time from baseline). Aligning individuals' trajectories on a meaningful time index (i.e., retirement timing), rather than using arbitrary time index (i.e., time from baseline), appears to reduce between-person variability in average rates of cognitive change associated with mental work demands. Remarkably, this was also the case when additional analysis was conducted with education predicting cognition; more years of education were associated with significantly steeper decline in composite cognition only when cognition was modeled as a function of retirement timing ($b = -.027$, SE=.009, p=.003), not time from baseline ($b = -.024$, SE=.015, *p*=.11). It is plausible that, even after a few decades, the influence of early education continued through cognitive activities in the workplace during midlife. The different result between time from retirement and time from baseline emphasizes the importance of time basis to examine longitudinal changes. It also reveals that the benefits in cognitive capacities may be attenuated in the absence of such environmental exposure (Hultsch et al., 1999; Schooler et al., 1999).

Interactive effects between mental work demands and education

We found a significant interaction effect between early education and midlife occupation on late life cognition, which suggests that the negative impact of earlier education on late-life cognition may be partly ameliorated if people from a lower education have greater mental work demands in midlife. This finding is in line with previous studies suggesting that earlier disadvantages, such as intellectual aptitude (Potter et al., 2008) or childhood SES (Luo & Waite, 2005; Turrell et al., 2002), could be partially overcome by mentally stimulating activities or adult SES in later life. It should be acknowledged, however, that innate intelligence might have played a role in the interactive effect between education and occupation on late-life cognition. That is, although lack of resources in childhood might have limited opportunities for better education, people with higher levels of innate intelligence might have a better chance to obtain cognitively stimulating occupation in midlife, which in turn influences late-life cognition. We were unable to disentangle the effect of innate intelligence from the effects of education/occupation. However, a previous study found unique contributions of education and occupation on late-life cognition after accounting for childhood mental ability and age-related pathological changes (Staff, Murray, Deary, & Whalley, 2004), suggesting the importance of mental activities across lifespan.

Limitations and future direction

There are some limitations to the present study. First, participants' age range in the current study does not cover the entire adulthood period; although present study suggests the role of cognitive reserve in the later decades of aging, patterns of cognitive decline and the role of cognitive reserve may be different from those in earlier older adulthood (Finkel et al., 2009; Fisher et al., 2014). Future studies are required to examine temporal progression of cognitive decline associated with cognitive reserve from early-old to old-old period. Second, reversed causality is possible such that individuals with higher innate intelligence select intellectually more demanding job. However, although cognitive function in youth accounts for approximately half of the variance of cognitive function in old age (Deary, Whalley, Lemmon, Crawford, & Starr, 2000), rodents models have emphasized the importance of understanding gene-environment interactions and experience-dependent plasticity (Nithianantharajah & Hannan, 2006; Van Praag, Kempermann, & Gage, 2000). Moreover, a large body of evidence shows that the association between environmental factors and cognition is bi-directional (Ceci, 1991; Neal & Johnson, 1996). Third, despite the importance of a life-span perspective in examining cognitive reserve and late-life cognition, the present study could not test the effect of parental resources, midlife income, or mid/late-life leisure activities. Fourth, we did not have information on individuals' job change or subjective mental demands in the workplace. Fifth, due to the effects of selective attrition, caution should be taken when interpreting the present study. Sixth, other competing risks may have influenced cognitive decline (e.g., mortality and terminal decline) and we could not separate those effects from the effects of neuropathology or normal brain aging.

Chapter 4. General Discussion

The primary goal of this dissertation was to examine the association between mental work demands and late-life cognition in both demented and non-demented older adults. This dissertation evaluated four hypotheses. Aim 1 hypothesized that higher levels of mental work demands would predict lower likelihood of developing incident dementia (Hypothesis 1a) and later onset of dementia (Hypothesis 1b). Among cognitively normal older adults who did not exhibit signs of dementia, Aim 2 hypothesized that greater mental work demands would predict higher levels of cognitive functioning (Hypothesis 2a) and faster rates of cognitive decline in later older adulthood (Hypothesis 2b).

Mental work demands and cognitive health in late life

The pattern of findings was broadly consistent with the cognitive reserve framework. This theory postulates that mental activities in a person's lifespan promote the development of cognitive reserve in the form of more efficient cognitive processes and more robust neural networks, which allows some individuals to cope more effectively and for a longer time with pathology than those with less cognitive reserve. Thus, a greater burden in the brain is required for high compared to low reserve people in order to express clinical symptoms of dementia. Once the magnitude of neural insults is much more advanced, however, greater cognitive reserve is likely to be associated with more rapid cognitive decline to keep with more severe pathology. As a consequent, three empirical effects related to higher cognitive reserve are expected; lower likelihood of incident dementia, later onset of cognitive impairment and dementia, and a more rapid decline once it begins. Our results are in line with these predictions. First, individuals with higher work demands had a lower chance for developing dementia and a delayed onset. Second, among those who never developed dementia, greater job demands were associated with higher levels, but faster rates of cognitive decline. Moreover, the protective effects of mental work demands were over and above the effects of education, while education did not predict the risk or onset of dementia. Together, this dissertation indicates that work demands seem to display the properties expected of an indicator of cognitive reserve and have a better predictive power than education regarding dementia.

One of the important findings was that greater mental work demands, that are usually considered to be a protective factor, were associated with faster rates of cognitive decline among cognitively normal individuals. Indeed, there has been inconsistent findings about the association between lifetime cognitive engagement (e.g., mental work demands, education) and rates of cognitive aging (Sharrett, 2012). This dissertation identified potential issues influencing many previous studies that arose from 1) failure to consider the timing of cognitive decline (i.e., participants' age range) and 2) misaligning individuals' cognitive trajectories. First, although previous studies have assumed uniform relations between protective factors and cognitive aging (e.g., slower rates of cognitive decline associated with higher levels of mental work demands or education) throughout older adulthood, this relation may be valid only until certain period of lifespan. The rates of cognitive aging are influenced by processes that impair neural health (Whalley et al., 2004), but these aging processes are not likely to be uniform throughout older adulthood. Also, the role that protective/risk factors plays in the aging processes may be different, depending on how much the processes are advanced. Therefore, studies may find slower cognitive decline associated with higher mental demands if participants are in earlier old age. However, the current study showed that greater mental work demands, a potential protective factor for cognitive health, were associated with faster cognitive decline once the decline commenced, probably to keep with more severe neuro-aging and pathology. Without considering the timing of cognitive decline in older adulthood, longitudinal studies may suffer from inconsistent associations of cognitive decline and risk/protective factors across studies.

Second, different time references across studies to align individuals’ cognitive trajectories on (e.g., study entry, chronological age, retirement timing) may affect the association between rates of cognitive decline and risk/protective factors. If individuals are misaligned on a time metric that does not reflect processes underlying cognitive change, then the average cognitive trajectories as well as individual differences in the trajectories will be distorted. Moreover, given that the average rates of cognitive decline are small compared to large differences in levels of cognition associated with risk/protective factors (Glymour & Dufouil, 2012; Sharrett, 2012), misaligning individuals' cognitive trajectories will make it hard to find true associations of rates of cognitive decline while the associations between levels of cognition and risk/protective factors would be less biased from misaligning. The importance of time metrics is discussed more in the later section.

Specific types of mental work demands that are protective

Although mental work demands contain several different aspects of workers’ functions and traits including levels of complex mental activities, aptitudes, temperaments, and interests, only a few studies have investigated specific components of mental work demands that predict late-life cognitive outcomes. In this dissertation, we investigated whether there were specific types of metal work demands associated with dementia and cognitive aging. In cognitively healthy individuals (Aim 2), most components of mental work demands, including educational development (reasoning/math/language), vocational preparation, intelligence/verbal/numeric aptitude, non-repetitive processes, and interests for abstract and creative activities, were associated with enhanced levels of cognition. Among those sub-components, only a few components – e.g., interests in abstract/creative activities, language development, and verbal aptitude – were associated with faster rates of cognitive decline. Interestingly, these components overlapped with sub-components of mental work demands that predicted later dementia onset (Aim 1). It is probable that (interests for) abstract/creative activities and language/verbal aspects are the features most indicative of cognitive reserve.

We found consistent and strong effects of language development and interests for abstract/creative activities above and beyond the effects of education; moreover, these were more robust predictors of dementia risk and onset than education. Language development indicates the levels of reading/writing/speaking skills that workers had obtained in prior education so that they can follow the instructions and acquire and update knowledge for the successful completion of work tasks (U.S. Department of Labor, 1991). From the current dataset, example occupations high in language development included judges, lawyers, clergymen, teachers, social workers, and editors, and occupations low in language development included garbage collectors, fishermen, bus driver, and machine operatives. It appears that prior learning and education in language abilities may be a prerequisite to obtain an occupation that is cognitively engaging. Moreover, considering the significant and strong protective effects of this component after accounting for education, further language abilities that individuals develop through workplace tasks and experiences may be pathways through which the protective effects of earlier experiences could be preserved and even strengthened into the middle and older adulthood.

Interests for abstract and creative activities were another facet of mental work demands that predicted late-life cognitive outcomes. In the original rating system of DOT, this measure indicates preferences for work activities of an abstract, creative, and non-routine nature, which was ambiguously defined compared to other job characteristics (Roos & Treiman, 1980), and thus it is not clear from DOT measure which specific components in this measure predicted late-life cognitive outcomes. However, based on previous literature (Autor & Price, 2013; Kohn & Schooler, 1978; Schooler et al., 1999), this abstract/creative/non-routine facet of mental work demands may be further defined as, 1) work activities that require strategic planning, persuasion, independent thinking, and decision making in ill-defined and abstract situations (e.g., examples from the current data are judges and clergymen), 2) creative and artistic work that requires cognitive flexibility and novelty seeking (e.g., musicians/composers, painters, photographers), and 3) non-routine manual work, in which the core tasks do not follow concrete procedures and require situational adaptability and in-person interaction (e.g., hair designers/barbers, person service apprentices). There has been little and mixed evidence regarding whether these components are associated with better cognitive health outcomes in later life. Although some studies found that working in abstract and ill-defined situation (Suo et al., 2012; Then, Luck, et al., 2013), novelty seeking (Bielak, Hughes, Small, & Dixon, 2007; Fritsch, Smyth, Debanne, Petot, & Friedland, 2005; Oltmanns et al., 2017), and creativity (Then et al., 2017) in the workplace were associated with lower risk of dementia, better cognitive functioning, and more grey matter volume in the brain, others found conflicting results (Then et al., 2017; Then, Luppa, et al., 2013). Moreover, there is lack of evidence regarding causal associations between occupational components and cognitive health outcomes. Most of the previous studies, including the current study, are based on observational studies and it is not clear whether it is pre-existing conditions of workers that enable them to obtain a specific job (e.g., interests and preference for abstract and creative activities) or activities that workers perform in the job (e.g., activities for abstract and creative tasks) that contributes to late-life cognition. To reveal the direction of the relationship as well as specific components of mental work demands associated with cognitive health would be essential to develop effective preventive programs or intervention studies.

Although both language abilities and interests for abstract/creative/non-routine activities may relate to cognitive reserve by contributing to efficient cognitive processing and adaptive reorganization of neural circuits, the potential protective effects of both components may be conveyed through different mechanisms. That is, occupations high in language development may support the preservation of already established cognitive and neural pathways (i.e., crystallized cognition) and confronting abstract and ill-defined, novel situations at work may support the development of new kinds of pathways (i.e., fluid cognition)(Bowen, Noack, & Staudinger, 2011; Sternberg, 1985). The empirical evidence supporting this idea is lacking and the potential different mechanisms require further investigation.

Selection of time metrics and retirement

This dissertation also provides insights into selecting the appropriate time metrics in longitudinal studies. In Aim 1, dementia onset was calculated using three time anchors—birth (i.e., chronological age), baseline, and retirement. Work demands were associated with delayed onset of dementia as indexed by “time from retirement” even after controlling for education and other covariates. In Aim 2, cognitive change was represented using two time metrics for aligning individual trajectories: time from retirement and time from baseline. Mental work demands were associated with higher levels of cognitive performance and with faster rates of decline in the “time from retirement model”. However, the association between mental work demands and rate of cognitive decline was not significant for the “time from baseline” model. In both studies, time index regrading retirement, rather than chronological age or baseline assessment, appears to do a better job describing individual differences in cognitive impairment and changes as it may represent aging/pathologic progression and environmental changes driving cognitive changes.

Selecting appropriate time metrics that represent intraindividual cognitive and psychological change has been an important yet often neglected issue in longitudinal studies (c.f., Sliwinski & Buschke, 2004). Because selection of time metrics influences how data are aggregated to describe an average cognitive change, misaligning data with a time metric that does not reflect underlying causes (e.g., biological aging, disease progression) will distort the typical and average cognitive trend (Sliwinski & Mogle, 2008). Although time from baseline has been a frequently used temporal index to examine individual differences in rates of cognitive change, baseline is an arbitrary point of time and has little significance to account for aging and development. On the other hand, retirement represents an important normative aging event, which may be more closely associated with the progress of neurological and pathologic aging and with the individual differences in the progress than arbitrary time points (i.e., baseline). Indeed, aligning people with respect to baseline could mislead the correct identification of change trajectories especially when variability in retirement duration across individuals is substantially large at baseline. Due to the heterogeneity in retirement duration at the study entry of Aim 2 (range of retirement duration at baseline = –4~49 years), it would have been hard to reveal whether and how changes in mental activity patterns lead to individual differences in rates of cognitive change if individual’s cognitive trajectories were aligned on each individual’s baseline (see Figure 7a). However, using a meaningful time index that reflects causal processes driving change (i.e., retirement) could result in more precise identification of average cognitive trajectories and individual differences in change (Figure 7b).

The significance of retirement timing associated with changes in cognitive function is based on “use it or lose it” or “disuse” perspective (Hultsch et al., 1999; Salthouse, 1991). This view accounts for the changes in cognitive performance in terms of changes in the mental activity patterns performed by people across the life span. In the absence of such activities, the benefit in cognitive capacities are attenuated or even lost (Bielak, 2010; Salthouse, 2006; Hultsch et al., 1999; Schooler et al., 1999). Thus, it would be important to distinguish between accumulated (or lagged) and concomitant (or immediate) effects of mental (in)activity on subsequent cognitive change to examine individual differences in cognitive change. In the current study, retirement may represent abrupt changes in a person’s lifestyle, which can result in disuse of cognitive processes and skills. Therefore, retirement may have relatively immediate or concomitant effects on cognitive deterioration. However, the protective effects of mental work demands are likely to accumulate over a period of decades, preserve and promote cognitive health in later life, and possibly endure for years even after retirement. In line with this reasoning, the accumulated effects of cognitively demanding activities in the workplace were protective for 24 years after retirement (Aim 2) and associated with later dementia onset (Aim 1).

Although it was probable that retirement induced concomitant effects on cognitive deficit, the present study was limited by being unable to examine cognitive changes immediately prior to and following retirement, which would be required to more precisely disentangle the effects of retirement from “aging”. It has been suggested that honeymoon effect of retirement may attenuate the negative effect of retirement on cognitive decline due to an immediate reduction in psychological or physical job stress (Bonsang et al., 2012; Celidoni, Dal Bianco, & Weber, 2017). In line with this prediction, Celidoni and colleagues (2017) found that retirement had an immediate positive effect on cognition at first. In contrast, Bonsang and colleagues (2012) found that there was almost an immediate negative effect of retirement on cognition and the effect was more salient about one year after retirement. Moreover, although Bonsang and colleagues found that the cognitive functioning tended to stabilize about one year after retirement, Mazzonna and Peracchi (2012) found that retirement duration amplified cognitive decline. Given these heterogeneous findings, it is important to examine the long term trajectories associated with retirement. Future study needs to examine how quickly the effects of current mental disengagement emerge, how long the effects of past mental activity remain, and whether the effects are equivalent across individuals with different levels of mental demands. These questions may be elucidated by longitudinal research designs such as measurement burst designs (Stawski, MacDonald, & Sliwinski, 2015), which will allow examining both the short-term and long-term associations between cognition and (dis)engaging in mental activities.

Alternative explanations and future directions

Although the results from this dissertation suggests that mental work demands in midlife are associated with cognitive health consequences in late life, our observational study design does not allow to determine causality. Moreover, it is beyond the scope of this study to confirm whether it is people’s mentally challenging experiences in the workplace or preexisting factors related to the choice of occupation that predicts late-life cognitive health. In this section, we offer alternative explanations for the association between occupation and late-life cognition. First, individual differences in personal traits including cognitive abilities, interests, and personality may influence one’s career choice (Ackerman & Beier, 2003). People initially showing higher intellectuality or interests in novelty are more likely to select themselves into mentally demanding jobs that require higher cognitive functioning or novelty-seeking. Because the current measure of mental work demands derived from DOT reflects both workers’ traits and work contents, it is hard to distinguish whether the protective effects of mental work demands score were from occupation per se or from preexisting differences of people's traits. It is also possible that there is a reciprocal relationship between people's traits and mentally-demanding work contents, such that people initially exhibiting higher cognitive functioning and interests for mental activities select themselves into mentally demanding job, and in turn, mental work activities provide better intellectual functioning (Kohn & Schooler, 1978). In order to confirm the causal process of mental work demands on late-life cognition, it would be important to confirm these results in a randomized controlled trial or intervention study.

Second, earlier life factors can independently and interactively influence the choice of occupation and late-life cognition. For example, childhood SES may increase the risk of being exposed to perinatal insult, nutritional deficiencies, and/or toxic environments (Katzman, 1993; Plassman et al., 2010), which may result in negative cognitive health consequences. Moreover, innate intelligence as well as parents' education and financial resources may have significant influence on individuals' future life choices (e.g., educational and occupational opportunities) associated with late-life cognitive functioning (González et al., 2013; Horvat et al., 2014; Luo & Waite, 2005). A few studies have controlled for premorbid cognitive abilities (Gow et al., 2014; Van der Elst & van Boxtel, 2012) in an effort to establish the direction between mental work demands and cognition, but the results have been conflicting. Moreover, it is hard to test the influence of early life factors due to the lack of early or midlife data in longitudinal studies. However, considering early life experiences may have enduring effects on cognitive, studies on later life cognitive health need to adopt the lifespan approach.

Third, there may be other mediating or confounding variables that underlie the associations reported here. One example would be health behaviors. Gottfredson and Deary

(2004) found that psychometric intelligence in childhood predicted adult morbidity and mortality and suggested health behaviors as a possible underlying mechanism. Intelligence is related to efficient learning, reasoning, problem solving, and abstract thinking; specifically, fluid intelligence, which is manifested when tasks are novel or situations are ambiguous, appears to play an important role in health self-care demands. Differences in health behavior to prevent or slow the progression of disease and to adhere to appropriate treatment regimens among individuals between high and low intelligence may contribute to unfavorable health among people with low intelligence (Gottfredson & Deary, 2004). In the current study, mental work demands may represent a proxy for intelligence in health matters, with higher mental work demands providing better skills for health self-care.

Another potential mediator would be the vascular pathway, which may be not exclusive but may act at the same time as cognitive reserve (Fratigloino et al., 2004). Evidence from epidemiological (Kivipelto et al., 2001; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005) and pathological studies (Attems & Jellinger, 2014) has identified vascular risk factors for dementia, including AD, and for cognitive decline. It appears that vascular factors may lower the threshold for the clinical expression of dementia and increase the risk of AD pathology (i.e., amyloid beta plaque and neurofibrillary tangle)(Attems & Jellinger, 2014; O’Brien & Markus, 2014). Several population-based studies have shown that midlife cardiovascular risk factors, including smoking, cholesterol, diabetes, hypertension, and systolic blood pressure predict higher risk of AD and dementia in later life (e.g., Kivipelto et al., 2001; Whitmer et al., 2005). If individuals with lower mental work demands have less resources to deal with work stress and thus carry greater job strain than those with higher mental demands, they may be at increased risk of cardiovascular disease (Belkic, Landsbergis, Schnall, & Baker, 2004; Karasek, Baker, Marxer, Ahlbom, & Theorell, 1981), which, in turn, may increase the risk of dementia (Andel et al., 2012).

Implications and conclusion

The current findings emphasize the importance of midlife occupation for preserving cognitive health into old age. Although age-related cognitive decline becomes apparent after mid-50s or 60s (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012) and prevalence and incidence of dementia rise only after age 70 (Fratiglioni & Wang, 2007), disease pathology develops slowly and insidiously across the span of several decades. Then it is possible that lifestyle features in midlife may afford protections or confer risk for long-term brain health outcomes. Results from this dissertation raise the possibility that those who enjoy occupations that are mentally demanding may have reduced risk of cognitive impairment and dementia. Specifically, individuals in jobs that foster language skills and support creative and novel activities may be particularly beneficial. In contrast, individuals who work in occupations related to routine cognitive and production activities (e.g., data entry, repetitive production tasks performed on an assembly line), full-time housewives or individuals who quitted their job in their midlife, or those working in traumatic and toxic environment may be at increased risk of cognitive deficit and dementia. Some of these individuals with low mental work demands may even face double jeopardy because hazardous working environments, work strain, and low SES in earlier life that potentially limits individuals’ occupational choices, are risk factors of dementia and cognitive impairment (Andel et al., 2012; Clouston et al., 2016; Genuis & Kelln, 2015).

Providing further workplace training or adult educational programs may be one way to convey protective effects of mental activities to the vulnerable population subgroups. However, the most qualified workers tend to participate in training more than the less qualified, indicating the pattern of accumulated advantages/disadvantages (Bowen et al., 2011; Dannefer, 1987). Thus, workplace training to enhance worker's ability should become an essential part of working life across the life span so that individuals enter in positive loops. Specifically, we found that language development and creative/abstract/non-routine activities were the most critical components of mental work demands that may promote cognitive health and prevent dementia. This finding may inform ways to provide workplace training that involves problem-solving skills, intuition, and creativity, and to widen opportunities for formal/informal education to develop language skills. Moreover, training programs designed to help people re-enter the workforce or retain new skills would be also helpful, considering changing skill requirements and updated technological skills would challenge individuals seeking employment.

Recent studies found a significant decrease in the prevalence of dementia in the United States, with increases in educational attainment among later-born cohort partly accounting for this result (Langa et al., 2017). It is also possible that changes in the nature of occupation contributed a decrease in dementia rate. In this study, we found that greater mental work demands promoted cognitive health and prevent dementia in later life. The present findings also suggest that, even after retirement, seeking out new environments that support their insights and creativity may be beneficial to cognitive outcomes. Creating environmental and social support to allow individuals to maintain mental engagement throughout their life is potentially important.

Table 1. Worker functions and traits from the Dictionary of Occupational Titles (DOT), Fourth edition.

Variable	**Description**
Worker functions	
Data*+	complexity of function in relation to data
People+	complexity of function in relation to people
Things+	complexity of function in relation to things
Training times	
GED reasoning*	general educational development: reasoning
GED math*	general educational development: math
GED language*	general educational development: language
SVP*	specific vocational preparation
Aptitudes	
Intell*+	intelligence
Verbal*+	verbal aptitude
Number *+	numerical aptitude
Spatial	spatial perception
Form	form perception
Clerical	clerical perception
Motor	motor coordination
Fingdex	finger dexterity
Mandex	manual dexterity
Eyehand	eye-hand-foot coordination

Colordis	color discrimination

Temperaments

DCP	direction, control, and planning
FIF	feelings, ideas, or facts
INFLU	influencing people
SJC	sensory or judgmental criteria
MVC	measurable or verifiable criteria
DEPL	dealing with people
REPCON*+	repetitive or continuous processes
PUS	performing under stress
STS	set limits, tolerances, or standards
VARCH	variety and change

Interests

DATACOM	communication of data versus activities with things
SCIENCE	scientific and technical activities versus business contact
ABSTRACT*	abstract and creative versus routine, concrete activities
MACHINE	activities involving processes, machines, or techniques versus social welfare
TANGIBLE	activities resulting in tangible, productive satisfaction versus prestige, esteem

Physical demands

STRENGTH	lifting, carrying, pulling, pushing
CLIMB	climbing, balancing

STOOP	stooping, kneeling, crouching, crawling
REACH	reaching, handling, fingering, feeling
TALK	talking, hearing
SEE	seeing
Working conditions	
LOCATION	outside working conditions
COLD	extreme cold
HEAT	extreme heat
WET	wet, humid
NOISE	noise, vibration
HAZARDS	hazardous conditions
ATMOSPHR	fumes, odors, dust gases, poor ventilation

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* indicates items included in the factor score of mental work demands.

+ indicates that scales have been reserved from the original DOT scales so that higher score represents more complex worker's function or traits.

Table 2. Occupational categories of the study sample

Occupation categories	Aim 1 (n=496)	Aim 2 (n=1,118)
Professional, technical	24.8%	24.4%
Managers and administrator, sales workers	19.2%	18.4%
Clerical	31.1%	29.9%
Craftsmen	6.7%	5.9%
Operatives; Transport equipment operatives	6.9%	9.4%
Laborers; farmers	1.4%	1.4%
Service workers	8.9%	9.2%
Private household	1.2%	1.3%

Note. Occupational categories were created based on the first digit of 1970 Census occupation codes.

Aim 1: study with individuals with dementia; Aim 2: study with cognitively normal individuals.

Table 3. Baseline demographic by level of mental work demands for Aim 1

	Total (n=496)	Low mental work demands (n=246)	High mental work demands (n=250)	*p*
Baseline age, mean (SD)	79.2 (5.2)	79.1 (5.1)	79.3 (5.2)	0.66
Retirement age, mean (SD)	65.2 (5.7)	65.3 (6.0)	65.2 (5.4)	0.75
Years of education, mean (SD)	13.4 (3.5)	11.7 (2.9)	15.1 (3.2)	<.001
Mental work demands, mean (SD)	4.9 (1.9)	3.4 (1.2)	6.4 (0.9)	<.001
Female, %	57.9%	56.1%	59.6%	0.43
Ethnicity, %	Caucasian=66.9%; African American=27%; Others=6%	Caucasian=62.2%; African American=31.3%; Others=6.5%	Caucasian=71.6%; African American=22.8%; Others=5.6%	0.03
Low income, %	22.2%	32.4%	12.5%	<.001
APOE ε4 allele, %	23.6%	22.0%	25.2%	0.39

Note. To compare the significance between low and high mental work demands group, t-test was used for continuous variables and Chi-square test was used for categorical variables.

Table 4. Results from logistic regression examining the effects of mental work demands on dementia risk

	Model 1: unadjusted			Model 2: adjusted		
	RR	95% CI	*p*	RR	95% CI	*p*
Mental work demands	0.89	0.79-0.99	0.030	0.86	0.77-0.98	0.019
Education				1.02	0.95-1.10	0.523
Baseline age				1.06	1.02-1.10	0.002
Gender (ref: female)				0.84	0.54-1.30	0.427
APOE ε4 (ref: 0)				2.34	1.53-3.56	<.001
Study duration				1.14	1.08-1.22	<.001

Note. Continuous variables were used for mental work demands and education. Reference: gender (female), APOE ε4 (non-carrier).

Table 5. Results from Cox proportional hazards regression examining the effects of mental work demands on dementia risk

	Model 1: Chronological age at dementia			Model 2: Time from baseline to dementia			Model 3: Time from retirement to dementia		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mental work demands	0.89	0.77-1.03	0.125	0.87	0.75-1.01	0.072	0.83	0.71-0.96	0.015
Education	0.99	0.91-1.07	0.746	1	0.92-1.10	0.939	1.05	0.96-1.15	0.257
Gender	0.9	0.55-1.48	0.673	0.93	0.57-1.53	0.771	0.78	0.47-1.28	0.324
APOE ε4	2.87	1.78-4.63	<.001	2.67	1.65-4.32	<.001	2.06	1.27-3.35	0.004
Baseline age	-	-	-	1.11	1.05-1.17	<.001	0.92	0.88-0.97	0.003

Note. Continuous variables were used for mental work demands and education. Reference: gender (female), APOE ε4 (non-carrier).

Table 6. The effect of each job description on dementia risk and dementia onset

	Dementia risk*		Dementia onset (Time from retirement)**	
	RR (95% CI)	*p*	HR (95% CI)	*p*
Complexity with data	0.95 (0.83, 1.08)	0.418	0.90 (0.77, 1.06)	0.207
GED: reasoning	0.92 (0.79, 1.07)	0.255	0.88 (0.72, 1.07)	0.186
GED: mathematics	0.90 (0.79, 1.03)	0.117	0.89 (0.76, 1.05)	0.152
GED: language	0.87 (0.77, 0.98)	0.021	0.83 (0.71, 0.97)	0.020
Specific vocational preparation	0.92 (0.82, 1.03)	0.161	0.89 (0.78, 1.02)	0.095
Intelligence	0.90 (0.80, 1.01)	0.070	0.87 (0.75, 1.00)	0.043
Verbal aptitude	0.91 (0.81, 1.01)	0.073	0.85 (0.74, 0.97)	0.017
Numeric aptitude	0.93 (0.79, 1.09)	0.355	0.92 (0.75, 1.12)	0.379
Repetitive processes (-)	0.95 (0.88, 1.03)	0.237	0.94 (0.85, 1.03)	0.190
Abstract and creative activities	0.87 (0.78, 0.96)	0.008	0.83 (0.73, 0.95)	0.008

* adjusted for education, gender, baseline age, APOE ε4, and study duration

** adjusted for education, gender, baseline age, and APOE ε4

Table 7. Descriptive statistics at the baseline assessment for Aim 2

Variable	Mean (SD)	Low mental work demands (*N*=581)	High mental work demands (*N*=537)	*p*
Baseline age, mean (SD)	79.2 (5.4)	79.0 (5.2)	79.3 (5.6)	0.42
Retirement age, mean (SD)	64.9 (5.6)	64.8 (5.58)	65.0 (5.55)	0.47
Education (years), mean (SD)	12.9 (3.6)	11.3 (2.9)	14.7 (3.4)	<.001
Mental work demands, mean (SD)	4.8 (2.0)	3.2 (1.3)	6.5 (0.9)	<.001
Composite cognition, mean (SD)	49.8 (10.0)	46.6 (9.9)	52.9 (52.1)	<.001
Female, %	59.1%	54.6%	64.1%	0.001
Ethnicity, %	Caucasian=68.6%; African American=25.6%; Others=5.8%	Caucasian=61.9%; African American=30.1%; Others=7.2%	Caucasian=75.8%; African American=19.9%; Others=4.3%	<.001
Low income, %	25.6%	36.8%	13.5%	<.001

Note. To compare the significance between low and high mental work demands group, t-test was used for continuous variables and Chi-square test was used for categorical variables.

Table 8. The effects of occupational complexity on levels and rates of change in composite cognitive scores

	Model 1: Time from retirement			**Model 2: Time from baseline**		
Fixed effects	estimate	SE	*p*	estimate	SE	*p*
Intercept	52.973	1.143	<.001	49.634	0.378	<.001
Linear time effect (years)*	-0.084	0.128	0.510	0.242	0.135	0.074
Quadratic time effect (years)*	-0.009	0.003	0.010	-0.080	0.013	<.001
Practice effect	0.704	0.198	0.000	-0.039	0.254	0.879
Baseline age	-0.363	0.062	<.001	-0.018	0.054	0.735
Being male	-1.316	0.587	0.025	-1.190	0.599	0.047
Education (years)	0.992	0.104	<.001	1.023	0.105	<.001
Mental work demands	1.279	0.303	<.001	0.742	0.177	<.001
Mental work demands × time*	-0.034	0.015	0.027	-0.031	0.029	0.297
Random effects						
Var (Intercept)	86.535	11.266	<.001	70.377	3.822	<.001
Var (Time*)	0.094	0.037	0.005	0.421	0.103	<.001
Cov (intercept, Time*)	-1.513	0.608	0.013	0.608	0.561	0.278
Residual	13.383	0.977	<.001	10.588	0.740	<.001
AR(1)	0.362	0.047	<.001	0.227	0.051	<.001

* Time represents time from retirement in Model 1 and time from baseline in Model 2.

Table 9. The effects of job descriptions on levels and rates of change in the composite cognitive score using time from retirement

	Levels			Rates of change		
	estimate	SE	*p*	estimate	SE	*p*
Complexity with data	0.481	0.344	0.163	-0.018	0.019	0.345
GED: reasoning	1.285	0.380	0.001	-0.040	0.019	0.039
GED: mathematics	0.748	0.334	0.025	-0.015	0.018	0.416
GED: language	1.292	0.301	<.001	-0.044	0.015	0.005
Specific vocational preparation	0.840	0.298	0.005	-0.023	0.016	0.150
Intelligence	1.480	0.295	<.001	-0.037	0.016	0.019
Verbal aptitude	1.305	0.267	<.001	-0.037	0.014	0.010
Numeric aptitude	1.180	0.383	0.002	-0.016	0.021	0.429
Repetitive processes (-)	0.499	0.243	0.041	-0.010	0.013	0.432
Abstract and creative activities	0.993	0.256	0.000	-0.041	0.014	0.004

Note. Covariates: years of education, gender, baseline age, linear and quadratic time effects (time from retirement), practice effect.

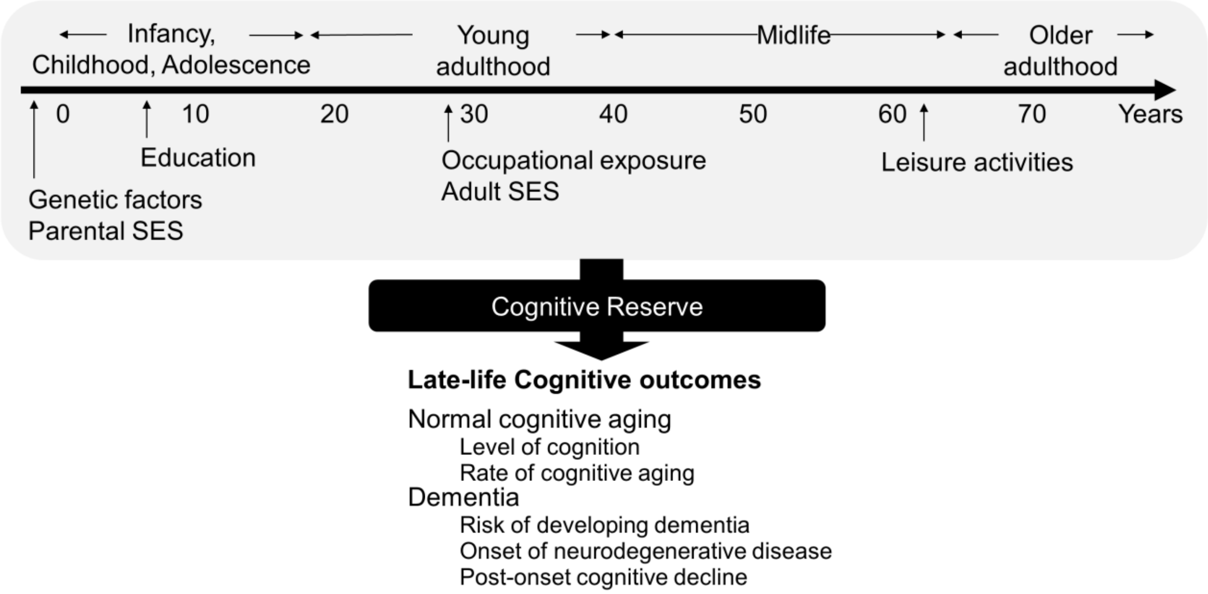


Figure 1. A heuristic model of cognitive reserve that represents temporal relations of major genetic and environmental effects on late-life cognition. Upward arrows indicate the approximate temporal points that the given factor starts to have relatively strong influence on cognitive reserve within each period of life span. Mediating/confounding factors, such as life habits, diet, or vascular risk factors, were not included in the model.

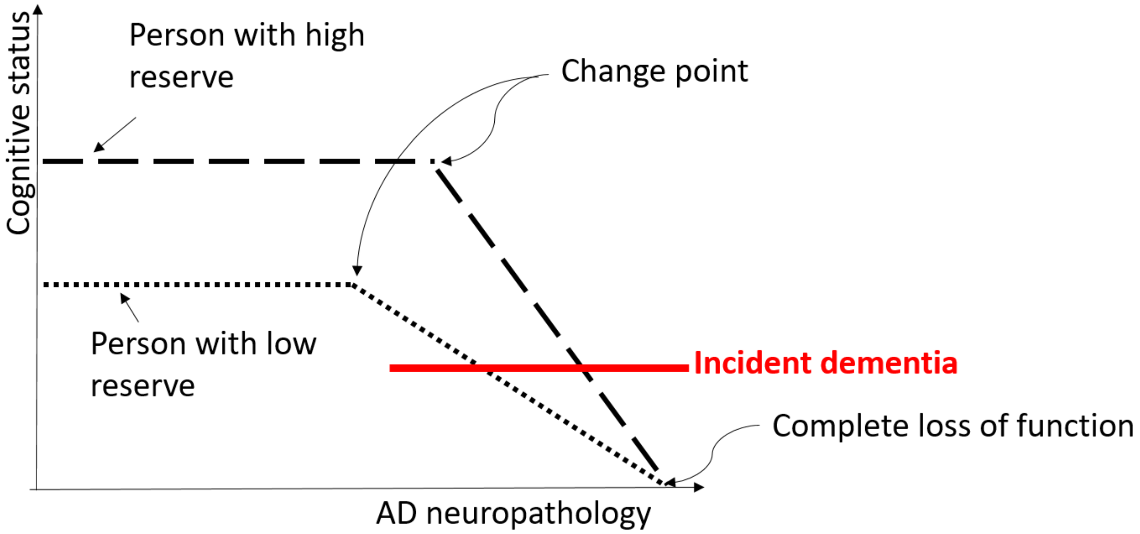


Figure 2. Representation of how cognitive reserve modifies the onset of impairment as well as the rates of post-onset decline. The onset of clinical diagnosis of AD is delayed for individuals with high cognitive reserve and post-onset rates of decline is more rapid among individuals with higher cognitive reserve. Adapted from “Efficiency, Capacity, Compensation, Maintenance, Plasticity: Emerging Concepts in Cognitive Reserve,” by D. Barulli and Y. Stern, (2013, p. 503), *Trends in Cognitive Sciences*, 17(10), p. 503. Copyright 2018 by the Elsevier Inc.

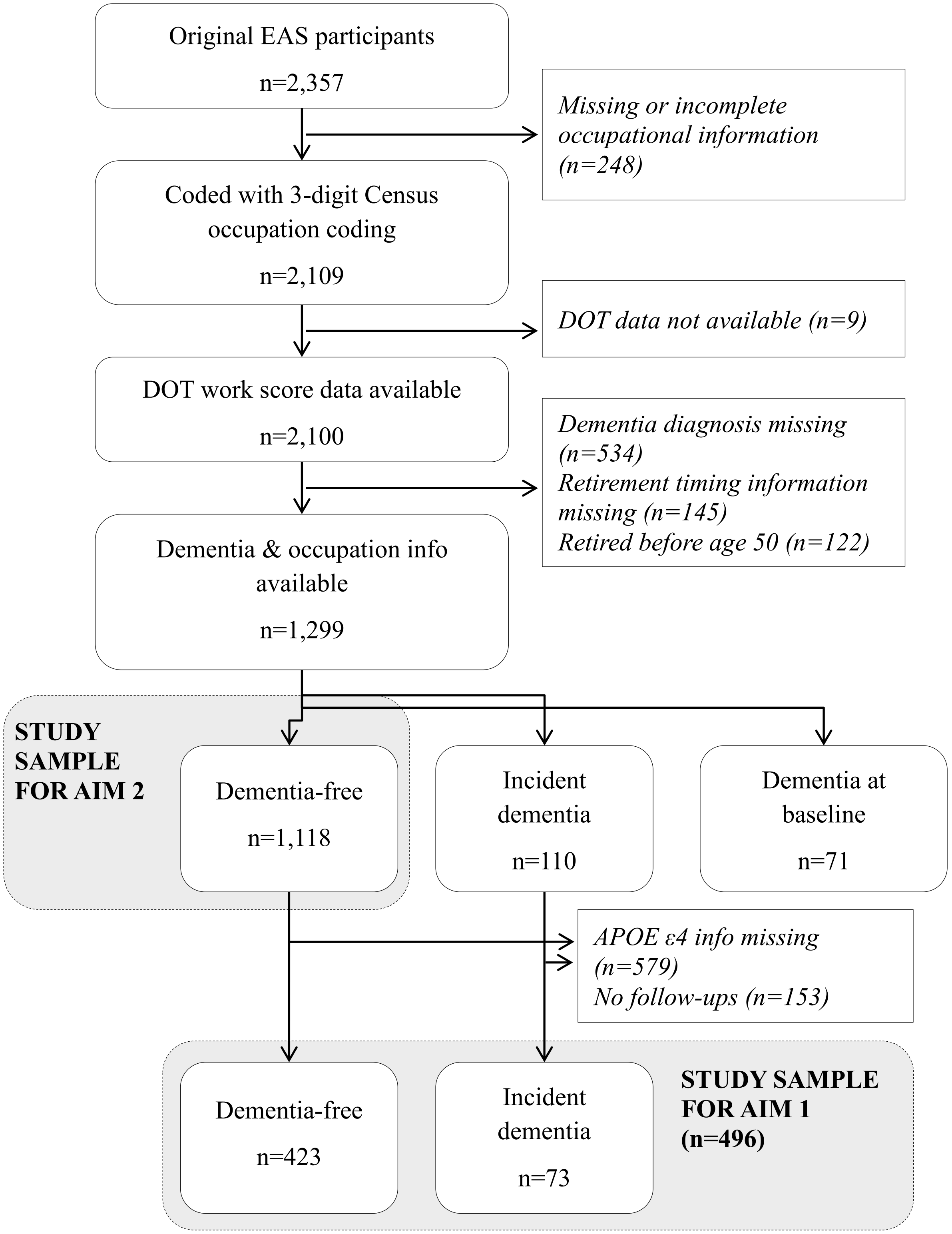


Figure 3. Sample selection for Aim 1 and Aim 2.

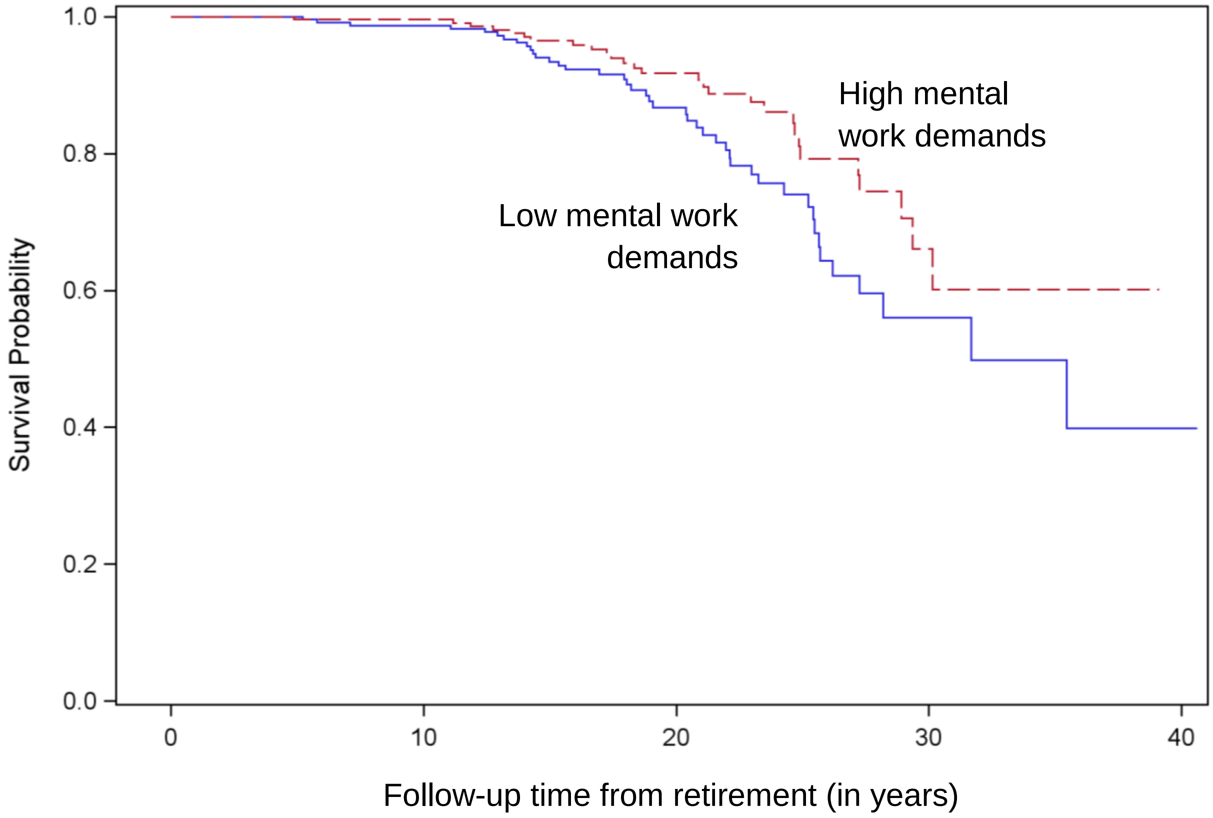


Figure 4. Kaplan-Meir survival curves for dementia in high and low mental work demands groups

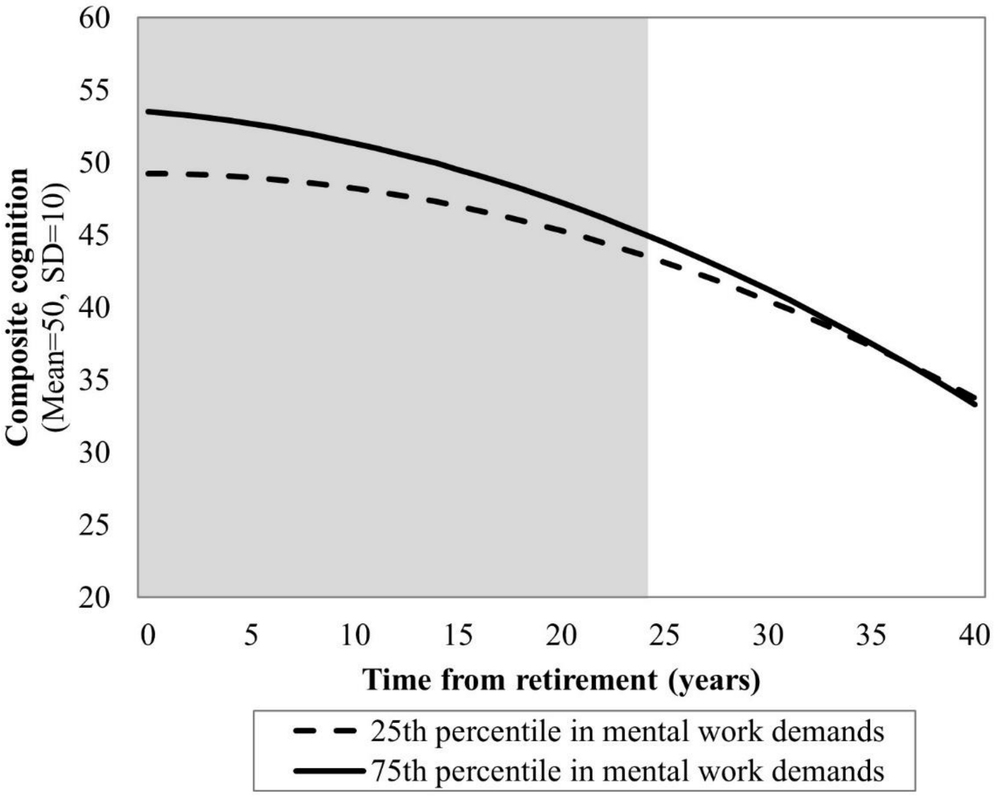


Figure 5. Changes in cognition after retirement between males in 75th percentile of mental work demands and males in 25th percentile. The practice effect, which is fixed across mental work demands, was not included in the plot because each individual had different study entry. The shaded area indicates that the significant effects of mental work demands in levels of cognition lasted 24 years post-retirement.

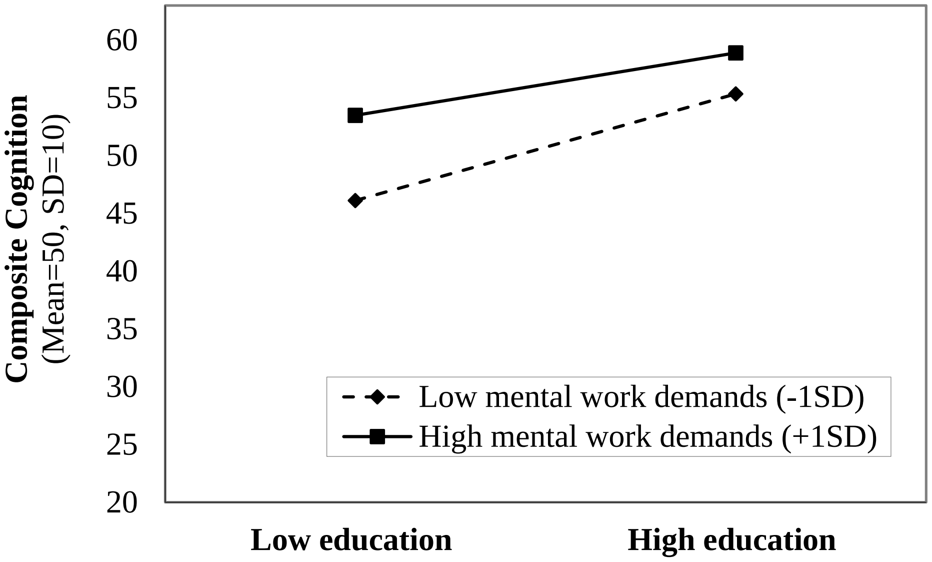
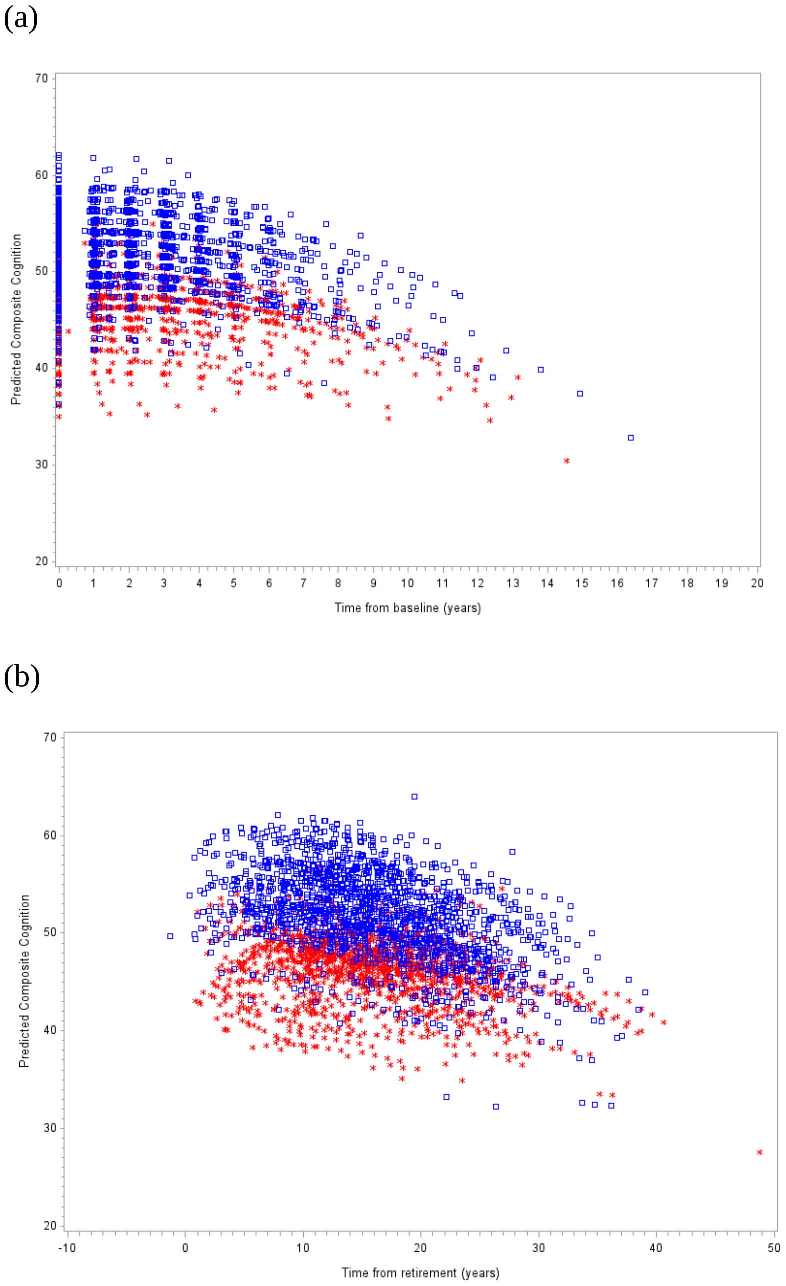


Figure 6. Two-way interaction effect between mental work demands and education on initial level of cognition



* * * : low mental work demands, □ □ □: high mental work demands

Figure 7. Predicted composite cognition as a function of time. (a) Time from baseline model, (b) Time from retirement model.

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Appendix

Appendix 1. Scale of General Education Development (U.S. Department of Labor, 1972)

Level	Reasoning development	Mathematical development	Language development
6	Apply principles of logical or scientific thinking to a wide range of intellectual and practical problems. Deal with nonverbal symbolism (formulas, scientific equations, graphs, musical notes, etc.) in its most difficult phases. Deal with a variety of abstract and concrete variables. Comprehend the most abstruse classes of concepts.	ADVANCED CALCULUS: Work with limits, continuity, real number systems, mean value theorems, and implicit function theorems. MODERN ALGEBRA: Apply fundamental concepts of theories of groups, rings, and fields. Work with differential equations, linear algebra, infinite series, advanced operational methods, and functions of real and complex variables. STATISTICS: Work with mathematical statistics, mathematical probability and application, experimental design, statistical inference, and econometrics.	Same as Level 5.
5	Apply principles of logical or scientific thinking to define problems, collect data, establish facts, and draw valid conclusions. Interpret an extensive variety of technical instructions in mathematical or diagrammatic form. Deal with several abstract and concrete variables.	ALGEBRA: Work with exponents and logarithms, linear equations, quadratic equations, mathematical induction and binomial theorem, and permutations. CALCULUS: Apply concepts of analytic geometry, differentiations, and integration of algebraic functions with applications. STATISTICS: Apply mathematical operations to frequency distributions, reliability and validity of tests, normal	READING: Read literature, book and play reviews, scientific and technical journals, abstracts, financial reports, and legal documents. WRITING: Write novels, plays, editorials, journals, speeches, manuals, critiques, poetry, and songs. SPEAKING: Conversant in the theory, principles, and methods of effective and persuasive speaking, voice and diction, phonetics, and discussion and debate.

		curve, analysis of variance, correlation techniques, chi-square application and sampling theory, and factor analysis.	
4	Apply principles of rational systems to solve practical problems and deal with a variety of concrete variables in situations where only limited standardization exists. Interpret a variety of instructions furnished in written, oral, diagrammatic, or schedule form.	ALGEBRA: Deal with system of real numbers; linear, quadratic, rational, exponential, logarithmic, angle and circular functions, and inverse functions; related algebraic solution of equations and inequalities; limits and continuity and probability and statistical inference. GEOMETRY: Deductive axiomatic geometry, plane and solid, and rectangular coordinates. SHOP MATH: Practical application of fractions, percentages, ratio and proportion, measurement, logarithms, practical algebra, geometric constructions, and essentials of trigonometry.	READING: Read novels, poems, newspapers, periodicals, journals, mauals, dictionaries, thesauruses, and encyclopedias. WRITING: Prepare business letters, expositions, summaries, and reports, using prescribed format and conforming to all rules of punctuation, grammar, diction, and style. SPEAKING: Participate in panel discussions, dramatizations, and debates. Speak extemporaneously on a variety of subjects.
3	Apply commonsense understanding to carry out instructions furnished in written, oral, or diagrammatic form. Deal with problems involving several concrete variables in or form standardized situations.	Compute discount, interest, profit, and loss; commission, markup, and selling price, ratio and proportion; and percentage. Calculate surfaces, volume, weights, and measures. ALGEBRA: Calculate variables and formulas; monomials and polynomials; ratio and proportion variables; and square roots and radicals. GEOMETRY: Calculate plane and solid figures, circumference, area, and	READING: Read a variety of novels, maganizes, atlases, and encyclopedias. Read safety rules, instructions in the use and maintenance of shop tools and equipment, and methods and procedures in mechanical drawing and layout work. WRITING: Write reports and essays with proper format, punctuation, spelling, and grammar, using all parts of speech.

		volume. Understand kinds of angles and properties of pairs of angles.	SPEAKING: Speak before audience with poise, voice control, and confidence, using correct English and well-modulated voice.
2	Apply commonsense understanding to carry out detailed but uninvolved written or oral instructions. Deal with problems involving a few concrete variables in or from standardized situations.	Add, subtract, multiply, and divide all units of measure. Perform the four operations with like common and decimal fractions. Compute ratio, rate, and percent. Draw and interpret bar graphs. Perform arithmetic operations involving all American monetary units.	READING: passive vocabulary of 5,000-6,000 words. Read at rate of 190-215 words per minute. Read adventure stories and comic books, looking up unfamiliar words in dictionary for meaning, spelling, and pronunciation. Read instructions for assembling model cards and airplanes. WRITING: Write compound and complex sentences, usingn proper end punctuation and employing adjectives and adverbs. SPEAKING: Speak clearly and distinctly with appropriate pauses and emphasis, correct pronunciation, variations in word order, using present, perfect, and future tenses.
1	Apply commonsense understanding to carry out simple one- or two-step instructions. Deal with standardized situations with occasional or no variables in or from these situations encountered on the job.	Add and subtract two-digit numbers. Multiply and divide 10's and 100's by 2, 3, 4, 5. Perform the four basic arithmetic operations with coins as part of a dollar. Perform operations with units such as cup, pint, and quart; inch, foot, and yard; ounce and pound.	READING: Recognize meaning of 2,500 (two- or three-syllable) words. Read at rate of 95-120 words per minute. Compare similarities and differences between words and between series of numbers. WRITING: Print simple sentences containing subject, verb, and object, series of numbers, names, and addresses.

	SPEAKING: Speak simple sentences, using normal word order and present and past tenses.

VITA

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EDUCATION

2018	Ph.D. in Human Development and Family Studies The Pennsylvania State University, University Park, PA, USA
2002	M.A. in Psychology Yonsei University, Seoul, Korea
2000	B.A. in Psychology, English Language and Literature Yonsei University, Seoul, Korea

SELECTED RESEARCH AND TEACHING EXPERIENCE

2013-2016	Research Assistant, *Effects of Stress on Cognitive Aging, Physiology, & Emotion*
2013	Teaching Assistant, *Intro to Human Development & Family Studies*, Penn State
2002	Instructor, *Introduction to Psychology,* Yonsei University
2000	Teaching Assistant, *Experimental Methodology in Psychology,* Yonsei University

SELECTED AWARDS

2016-2018	National Institute on Aging T32 Fellowship, Penn State
2013	Hintz Fellowship, Penn State
2001-2002	Scholarship for Excellent Student, Yonsei University

SELECTED PUBLICATIONS

Hyun, J., Sliwinski, M. J., & Smyth, J. M. (2018). Waking up on the wrong side of the bed: The effects of anticipatory stress on working memory. *Journal of Gerontology: Psychological Science*, Advance online publication. doi:10.1093/geronb/gby042.

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