Unraveling Clusters of Influential and Sex-Specific Risk Factors in the Progression to Alzheimer's Disease

By

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting cognition, daily functioning, and quality of life. Women are disproportionately affected by Alzheimer's disease, with two-thirds of patients being female. Additionally, women have different disease trajectories and poorer prognoses upon diagnosis than men (Hebert, Weuve, Scherr, & Evans, 2013). Exact mechanisms for the disproportionate burden in females are not well understood. As there are no disease-modifying treatments for AD, early detection and diagnosis are imperative to maximizing quality of life.

My dissertation study builds on the work of my three written comprehensive examinations. In my first comprehensive examination, "Identity and Perceptions of Quality of Life in Alzheimer's Disease," I utilized qualitative methods to explore the patient and caregiver perspectives on living with AD and optimizing quality of life. My results revealed a process by which 1) changes in activity occur in response to the diagnosis 2) dyads discover new ways in which to mutually adapt and cope and 3) the person with dementia remains meaningfully engaged in their lives with a generally positive perception of quality of life (Manson, Ciro, Williams, & Maliski, 2020). By taking a person-centered approach to care and accounting for individual levels of baseline engagement, healthcare providers will be able to better identify individual changes over time and positively impact the patient quality of life. This written examination was published in the journal, *Applied Nursing Research*.

Consistent with national statistics, a greater proportion of participants in this first comprehensive examination study were female. Intrigued, I dug into the literature to see if there were any explanations for the disproportionate female burden. I read a call to action paper and

discovered there was a large gap in the literature regarding sex and gender differences in AD. Thus, I decided to pursue this line of research for my next comprehensive exam.

In my second comprehensive exam, "Does Sex Play a Role in Verbal Memory Performance Related to Alzheimer's Disease? A Systematic Review," I completed a systematic review of sex differences in verbal memory (VM) performance across the cognitive continuum. The role of VM is particularly interesting as a decline in VM is a hallmark of early AD and is a large factor in the detection and diagnosis of AD. It is well established in the literature that, across the lifespan, healthy women typically score higher than men on assessments of VM. Emerging evidence suggests that women may have a VM domain-specific form of cognitive reserve which may help explain why women are diagnosed later and their trajectory of disease is different than men's. Results of the systematic review revealed that while research on the role of sex on VM in AD is in its infancy, there is an emerging pattern where mild cognitive impairment (MCI) is a critical stage when the impact of sex becomes accentuated (Manson, Dean, Williams, & Maliski, 2019).

In my third comprehensive exam, "The Interplay of Sex and Verbal Memory Performance from Normal Cognition to Alzheimer's Disease: An Intricate Story," I utilized quantitative methods to further investigate the pattern of VM change between men and women across the cognitive continuum. I completed retrospective analyses on two cohorts of participants from the University of Kansas Alzheimer's Disease Center's clinical cohort, which is part of the National Alzheimer's Coordinating Center Uniform Data Set. Results from analyses with each cohort were inconsistent, highlighting the heterogeneity of disease trajectories, the importance of biomarkers to better describe the clinical syndrome, and the need to better understand the various phenotypes leading to AD.

My comprehensive examinations provided the foundational work leading to my dissertation. I learned that disease trajectories are quite heterogeneous and that additional work was needed to begin addressing the gap in the literature regarding sex differences in disease profiles. As such, I took a comprehensive approach to help better define phenotypes of amnestic MCI (aMCI), a transitional stage between normal cognition and AD. Using the Alzheimer's Disease Neuroimaging Initiative[1] (ADNI) database, results from my dissertation study, "Unraveling Clusters of Influential and Sex-Specific Risk Factors in the Progression to Alzheimer's Disease," revealed four subtypes of aMCI-AD, only one of which was predominantly female. Each subtype had a unique profile, highlighting the heterogeneity within the clinical syndrome, as well as the differences in profiles between men and women. Overall, my results demonstrate that the aMCI-AD population has various subtypes and multiple indicators should be considered to better detect the clinical syndrome.

[1]Data in chapter 4 of this dissertation were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI investigators did not contribute to any analysis or writing of this dissertation. A list of the ADNI investigators can be found at: http://adni.loni.usc.edu/about/governance/principal-investigators/.

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Data used in preparation of Chapter 4 of this dissertation were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgment_List.pdf.

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Chapter 1: Identity and Perceptions of Quality of Life in Alzheimer's Disease

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Abstract

Background: With life expectancy on the rise and the baby boomer generation growing older, Alzheimer's disease (AD) will affect more individuals and families than ever before. Therefore, it is imperative that healthcare providers identify the objective and perceived factors which positively and negatively affect the lived experience of progressing through AD. **Aim:** The goal of this exploratory qualitative research is to begin to develop an in-depth description of the perceptions related to life satisfaction in early-to mid-AD from the patient and caregiver perspectives. **Methods:** A convenience sample of four community-dwelling AD patients and caregivers were recruited from a local Alzheimer's Association support group. Semi-structured interviews were conducted together with participants and caregivers. **Results:** The major findings of this study uncovered a process by which 1) changes in activity occur in response to the diagnosis 2) dyads discover new ways in which to mutually adapt and cope and 3) the person with dementia remains meaningfully engaged in their lives with a generally positive perception of quality of life (QoL). **Conclusions:** These preliminary findings are a promising line of research and have implications for Alzheimer's patients, their families, and person-centered care. By accounting for individual levels of baseline engagement and taking each patient's perspective into account, nurses have the ability to identify individual changes over time and positively impact the patient's QoL. Further studies with larger and more diverse samples are needed to expand upon this preliminary framework.

Introduction

With life expectancy on the rise and the baby boomer generation growing older, it is predicted that by 2050, Alzheimer's disease (AD) will affect 13.8 million people in the United States, an increase of nearly 138% from present day ("2019 Alzheimer's disease facts and figures," 2019). Therefore, it is imperative for healthcare providers to identify the objective and perceived factors which will positively and negatively affect the experience of progressing through AD. As with other chronic diseases, a diagnosis of AD impacts self-identity and may be accompanied by feelings of anxiety, depression, and fear of what the future will bring (Gillies & Johnston, 2004).

Self-identity is constructed over the lifespan. Identity is formed, maintained, and altered due to life interactions and circumstances (Beard, 2004). One's identity is constantly evolving, particularly when faced with a chronic disease diagnosis (Adams, Pill, & Jones, 1997). Thus, the sense of self may be called into question and reconstructed when living with AD (Cohen-Mansfield, Golander, & Arnheim, 2000). It is important to understand adaptive strategies to maintain self-identity in early AD in order to facilitate continuity of the self as cognition continues to decline.

Currently the primary goals of clinical intervention and treatment include symptom management, psychosocial support, and maintaining or improving quality of life (QoL) (Ettema et al., 2005; Harrison, Noel-Storr, Demeyere, Reynish, & Quinn, 2016; Machado et al., 2009; Small et al., 1997). Lawton's theoretical model of QoL in AD includes four domains: objective environment, behavioral competence, domain-specific perceived quality of life, and psychological well-being (Lawton, 1997). This study will focus on domain-specific perceived QoL which involves the degree of satisfaction in life, including social functioning, leisure

activities, and self-identity. It is essential that assessment of QoL is a distinct and prominent part of treatment plans and patient care. However, QoL is inherently multidimensional, making objective and subjective indices difficult to assess (Lawton, 1997; Ready & Ott, 2003).

Currently utilized methods of assessing QoL in AD include professional observation, proxy report, and self-report. Professional observation is an indirect method to assess and infer QoL and is usually reserved for more severe and institutionalized patients (Missotten, Dupuis, & Adam, 2016; Mossello & Ballini, 2012). Historically, proxy report has been used because of patient changes in cognitive abilities, including attention, memory and language skills, and insight. Such changes may present obstacles to an accurate representation of objective QoL (Horning, Melrose, & Sultzer, 2014; Howland et al., 2017). However, more recent studies suggest that individuals with mild to moderate AD are able to reliably self-report well-being and subjective QoL (Bruvik, Ulstein, Ranhoff, & Engedal, 2012; Frank & Forbes, 2017; Torisson, Stavenow, Minthon, & Londos, 2016).

Because there is no gold standard, proxy assessment may be used alone or in addition to self-report assessment. It is important to note that, to date, the literature shows inconsistencies between proxy and self-reported subjective QoL in people with AD (Conde-Sala, 2009; Hongisto, 2015; Zucchella, 2015). One explanation for such discrepancy is that both professional observation and proxy assessment disregard the patient's perspective, an essential element to accurately capturing subjective QoL (Brod, Stewart, Sands, & Walton, 1999; Whitehouse, 1999). Additionally, professional observation and proxy assessment are subject to the observer's biases. Thus, although insight and cognitive function may change throughout the progression of AD, self-evaluation of QoL provides the best understanding of the subjective experience of life with the disease. While there are many self-report and informant-report rating scales assessing QoL in

AD patients, qualitative data on meaningful activities which contribute to a positive QoL are lacking.

It is well established in the normal aging literature that remaining engaged in meaningful activities leads to a more positive QoL and sense of self-identity (Eakman, Carlson, & Clark, 2010; Kaufman, 1986). Atchley's continuity theory of aging and other adult developmental perspectives propose that maintaining participation in daily activities brings purpose and a sense of life satisfaction (Atchley, 1989; Baltes & Baltes, 1990; Yerxa, 1998). Life satisfaction is a subjective evaluation of QoL and is a key indicator of well-being (Jan & Masood, 2008). It is possible that there is a gap in the literature regarding self-reported, subjective data on meaningful activities in AD because healthcare providers and caregivers hold implicit biases that person(s) with dementia (PwD) cannot accurately recall, assess, and discuss meaningful activities and subjective QoL. However, it is important to note that the literature suggests that in early AD, patients can accurately self-report subjective QoL (Brod et al.,1999; Feinburg & Whitlatch, 2001; Logsdon, Gibbons, McCurry, & Teri, 1999). Further, there may be fewer opportunities to engage as the severity of the disease progresses and mental and physical functions decline.

One way to obtain a deeper understanding of the individual experience of QoL in AD is via semi-structured interviews with open-ended questions. By eliciting specific narratives about the types of activities that lead to the perception of positive daily living, nurses and caregivers will gain an understanding of the experience of living with AD, which is difficult to uncover with quantitative methods. Additionally, answers to structured questions may reveal more specific and individual ways in which to employ coping strategies while also uncovering individual differences regarding importance and prioritization of activities. This exploratory study aims to provide a preliminary and foundational understanding of the experiences and

perceptions of people living with early-to mid-AD and their caregivers related to life satisfaction and QoL.

Methods

A qualitative descriptive study design as Sandelowski (2000) has described was used to characterize and better understand the experiences and perceptions of QoL in people with early-to mid-stage AD. This qualitative method is optimal as it produces findings close to the data and offers a comprehensive summary of patient perceptions through development of codes, descriptive categories, and themes (Sandelowski, 2000, 2010). This study was approved by the local Institutional Review Board. Because the intended participants involved a vulnerable population, informed consent was obtained from their legally authorized representative (LAR); in all cases, this was a spouse. Assent was obtained from the PwD. Consent was also obtained from the LAR to use their data from the interviews.

Participants

Our sample was recruited from a local Alzheimer's Association early-stage support group. Participants were community dwelling and lived in a metropolitan area. To be eligible, participants had to meet the following criteria: (a) age 55 years or older; (b) at least one subjective memory complaint; (c) Mini Mental Status Exam (MMSE) $\geq$ 10; (d) functional hearing; (e) live in a community setting with a caregiver that could provide study consent. Participants were excluded if they had a clinical diagnosis of severe Alzheimer's dementia or a neurological disorder other than Alzheimer's dementia (i.e. stroke, Parkinson's disease). All PwD were Caucasian Non-Hispanic, 55 – 80 years of age, and had a mean MMSE score of 22.

Procedures

Once eligibility was confirmed and informed consent obtained from the patient and their caregiver, semi-structured interviews with open ended questions were conducted with the participant and their primary caregiver. The interview consisted of five questions to elicit narratives (see Table 1). While there was a set of structured questions, thoughts and comments were expanded upon or explained as needed. Caregivers elaborated on the participant's answers as they saw fit. A recording device was used to audio record the interviews which typically lasted 25 to 40 minutes. A total of four dyads were included: three female PwD/male caregiver dyads and one male PwD/female caregiver dyad.

Data Analysis

Audio recordings from the semi-structured interviews were transcribed verbatim. Analysis began with line-by-line coding of transcriptions. During the coding process, the team, which included two qualitative experts, read the transcriptions repeatedly to gain an impartial and broad understanding of the data. Initial codes were provisional, comparative, and grounded in the data (Artinian, 1988). Once codes were established by the team, the authors met to discuss initial codes and identify preliminary emergent descriptive categories (Sandelowski & Barroso, 2003). Authors then revisited the data to further describe and develop properties of categories and establish themes (Hill, Thompson, & Williams, 1997). From there, major themes and sub-themes were established and relationships among themes emerged. Authors achieved agreement on final major themes and relationships collaboratively, contributing to credibility of the data. This iterative process facilitated unbiased description of the data. Analysis notes and memos were maintained throughout the study (Miles, Huberman, & Saldaäna, 2014).

Results

The analysis uncovered an overarching evolution of self-identity. Components of this process included three major themes influenced by three transitional factors.

Major Themes Changes in Activity

Participants described changes in activity including social, physical, and daily activities, as well as lifestyle in response to the diagnosis of AD. Underlying the participant narratives was a sentiment of a loss of or struggle with identity. Not only did the diagnosis and memory problems affect them in the immediate, but also, it threatened their life trajectory and plans for the future.

Participant 1: I'd been doing everything that I thought I could do. I could drive, I could do this and I could do that and then all of a sudden it's not… I wish that I didn't have to be so needy. And the really, really, really, I don't like it. It's, I need to be me.

Caregiver 1: She really missed her business. Not so much because of the business. It wasn't like a health club, it was more like a sisterhood . . . we meet more people for her to interact with and that kind of helps offset the loss to the sisterhood.

Participant 2: I want to be able to remember those things (appointments) so I don't interrupt their workload and things like that. I don't want to be causing problems.

Participant 3: Well, I can tell a difference. I think I watch more TV now than I used to.

Mutual Adaptation

As self-identity was brought into question and/or threatened after the diagnosis, mutual adaptation aided in redefining and regaining a sense of purpose and identity. Specifically, this group demonstrated particular resilience when overcoming their frustration with an externally changing world. They refocused their energy on what they could rather than could not do. While participants described feelings of frustration with their memory and the disease, they were only temporary and eventually passed. Instead of giving up, dyads sought help from others while

learning to understand and accept the new state of 'normal.' Modifying activities and lifestyle allowed the PwD to have continuity of life from before the diagnosis.

Caregiver 1: She got a lot of personal satisfaction from helping people get back, physically recovering from surgeries, recovering from illnesses. Helping people get back socially to a degree after they had personal problems with their family problems. And we really needed to work on filling that with other activities and that's where we combined the two things.

Participant 2: It's temporary (frustration). It is because most of the time, I, you know, I feel pretty normal, you know. Like I don't sit around and think about the fact that I have this disease.

Participant 4: I think things the first year were frustrating to me and that took me a while to . . . it was just frustrating maybe is the best word I can think of right now . . . and it just took me a while to you know, say you know, understand that what it is, is what it is.

Outcomes: Remaining Engaged

Because of these adaptive changes and coping strategies, participants were able to remain actively and meaningfully engaged in their lives and communities. Caregivers purposefully capitalized on continuing the social, physical, and daily activities that their spouse had always enjoyed. Maintaining meaningful social relationships was particularly important in this group. Continued engagement helped facilitate reconciliation and restoration of sense of purpose, control, and independence. Recognizing and accepting limitations facilitated more effective modifications.

Caregiver 2: There's really no difference in our living our lives now than we did two years ago as far as what we're doing. We just get through it a little differently.

Participant 3: So, you know, we have a wonderful church and so that feeds you. All the people that you know that you give to, they will eventually give you back.

Participant 4: And, and it's still, you know, every time when I get into the car I don't drive very far. But yet I enjoy being able to do it (driving). But since I just go mainly places that are well known, I just make sure I'm doing it the way a good boy should.

Factors that Support Transition

Maintaining faith and hope facilitated the ability to push forward and overcome feelings of frustration, sadness, and anger. Additionally, the Alzheimer's Association support group gave participants education, support, and a sense of community while facilitating the ability to take control and retain meaningful activities in their lives. Finally, support from others appeared to facilitate adaptation to a new normal and provide meaning in life. Whether from family, close friends, or more distal networks, participants derived a sense of reciprocity, aiding in the preservation of social identity.

P2: I'm surrounded with great friends and family . . . I'm going to mess up every now and then but all the people who I deal with like that are, are accommodating . . . everybody knows what's going on and they're very supportive.

Participant 3: I just want to continue to try and stay positive and not give up…overall, I think just try to do my best every day and remember that we're going to find a cure for this.

Interviewer: So the support group has been a good coping mechanism?

Participant 4: Oh definitely. Like, just you know, being in a room with 20+ people that are in the same situation. You know, some, and with 20 people with Alzheimer's or dementia or mild cognitive impairment or whatever you want to call the thing. You know is, uh, you are all at different stages but yet you know that they're all, all 20 of us are in the same, have the same thing, whatever it is.

The interaction of processes facilitating reconciled identity and subsequent positive perceptions of QoL is depicted in Figure 1. Initially, changes threaten identity, causing anxiety and feelings of not being 'me.' To cope, mutual adaptation occurs, facilitated by transitional factors to increase effectiveness of adaptations and the will to push forward. Finally, outcomes are more positive due to the effective coping mechanisms and remaining engaged, reconciling and restoring one's sense of identity and QoL.

Discussion

We explored the patient perspective of meaningful activities associated with subjective QoL. The goal of this research was to begin to develop an in-depth description to better understand the experiences and perceptions related to life satisfaction in early-to mid-AD. The major findings of this study uncovered a process by which changes in activity occur in response to the diagnosis, dyads discover new ways in which to mutually adapt and cope, and ultimately, the PwD is able to remain meaningfully engaged in their lives with a generally positive perception of QoL.

Our findings are consistent with the literature on changes in identity in early AD (Johannessen, Engedal, Haugen, Dourado, & Thorsen, 2018). Initially, participants described a threat to identity due to the diagnosis and life changes that necessarily had to be made. Subsequently, developing adaptive strategies allowed the PwD to negotiate their identity. Ultimately, a sense of reconciliation by integration of a 'new' identity occurred. As participants were able to remain actively engaged in their lives, they were able to create continuity of the self.

These findings have broad implications for Alzheimer's patients, their families, and person- centered care in nursing. Qualitative description allows healthcare professionals to take into consideration the individuality and personal values of each patient and caregiver. Upon

diagnosis, it is imperative to gather a baseline description and understanding of activities that are most meaningful to the patient, how those activities may feed into their identity, and current levels of engagement.

At regular clinic visits, nurses have the ability to identify individual changes over time, such as social disengagement or lack of effective adaptive strategies. Nurses may be able to identify reprioritization of meaningful activities and can provide supportive resources for the patient and their caregiver. Additionally, as part of the care plan, healthcare providers should proactively encourage the transitional factors we found to have a significant effect on perception of QoL. Working with multidisciplinary teams, nurses can offer access to educational resources, support groups, and encourage building strong networks of social support.

We have begun to develop a descriptive framework of mechanisms to maintain positive subjective QoL in early-to mid-stage AD. While saturation was not reached, the results of this study provide foundational themes for further, in-depth exploration. The individual voice and perspective should be listened to and have an impact on their care. Supporting reconciliation and continuity of identity over the course of AD may improve perceptions of QoL, a primary outcome of treatment.

Limitations

We recruited a small, convenience sample from the local Alzheimer's Association made up of white, middle to high income dyads with self-reported good to very good health. It is possible that our participants may be more proactive about adaptations and strategizing than dyads who do not participate in support groups. Our participants may have a higher baseline level of social engagement and support which facilitated overcoming sadness, frustration, and fear, and ultimately aided in identity reconciliation.

Willingness to be interviewed may also be indicative of a higher baseline QoL and more successful adaptation to changes related to an Alzheimer's diagnosis. Additionally, we used a qualitative descriptive method. While this type of study design can establish initial themes, future work is necessary to develop theories and implement interventions to address perceptions of QoL and self-identity in early-to mid-AD for patients and caregivers.

Conclusions

We have provided knowledge about how dyads can utilize meaningful activities and coping strategies to remain actively engaged in life. Future research should aim to further develop this model into a theory in more diverse groups, including race, ethnicity, and other related dementias. Additionally, though our sample only included one female caregiver/male PwD dyad, we found striking differences in the male versus female caregiver dynamic. Differences in gender dyads may provide another rich area for further description.

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Table 1.

Patient Interview Guide

1. To start, please tell me about the activities that make you happy.
2. Would you please talk about how doing these activities that bring joy to your life has changed since your diagnosis?
3. Now I would like to hear about your relationships with others. What differences have you noticed since your diagnosis, if any, with family members? With friends? How has this been for you?
4. Close your eyes and imagine that you are able to do the things you like to do without any problems. What problems or obstacles would have to be removed for you to perform them the way you desire?
5. Is there anything we haven't covered that you feel would be important for us to know?

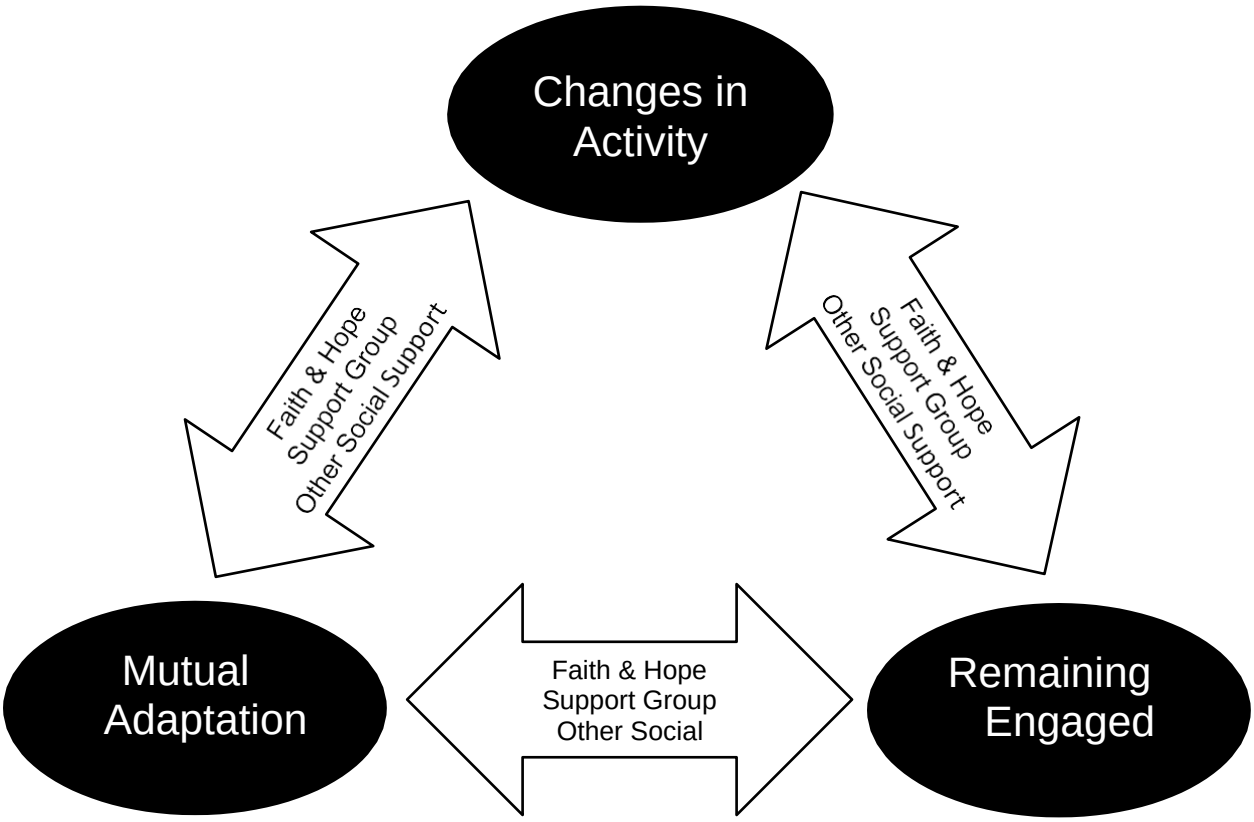

Figure 1. The interaction of processes facilitating reconciled identity and positive QoL.

Chapter 2: Does Sex Play a Role in Verbal Memory Performance Related to Alzheimer's Disease? A Systematic Review

Manson, A., Dean, E. E., Williams, K. N., & Maliski, S. L. (2019). *Does sex play a role in verbal memory performance related to Alzheimer's disease? A systematic review*. Manuscript submitted for publication.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is the most common type of dementia (Reitz, Brayne, & Mayeux, 2011). Women are disproportionately affected by AD, making up nearly two-thirds of patients in the United States (Hebert, Weuve, Scherr, & Evans, 2013). In addition, females are typically diagnosed at later stages, have faster rates of cognitive and functional decline after diagnosis, display more advanced neuropathology, and have a poorer prognosis (Gao, Hendrie, Hall, & Hui, 1998; Tschanz et al., 2011). Though women typically live longer than men, the increased incidence of women with AD cannot be attributed to the greater longevity (Viña & Lloret, 2010). Women have about a 12% lifetime risk of developing AD whereas men only have about a 6% risk (Seshadri et al., 1997). Exact mechanisms for the disproportionate burden in females are not well understood. However, the current literature suggests there may be unique biological underpinnings leading to AD neuropathology in women (Andrew & Tierney, 2018; Mosconi et al., 2018; Viña & Lloret, 2010). The role verbal memory (VM) plays in AD is of particular interest, as a decline in verbal memory is a hallmark of early AD. VM assessment is used to detect and diagnose AD, and women typically score higher on such assessments (McKhann et al., 1984). Cognitive reserve theory may help explain the sex differences in VM performance and differences in AD prognosis.

Cognitive Reserve Theory

Across the lifespan, healthy women typically score higher than men on assessments of VM (Aartsen, Martin, & Zimprich, 2004). Emerging evidence in the literature suggests that this advantage in VM is a form of cognitive reserve in women, which may help explain why women are diagnosed later and their trajectory of AD is different (Beinhoff, Tumani, Brettschneider,

Bittner, & Riepe, 2008; Sundermann et al., 2017; Sundermann, Maki, et al., 2016). Cognitive reserve theory suggests that those with higher levels of education, higher IQ, and other advantageous cognitive variables have a fallback capacity which allows maintained cognitive functioning despite neuropathology. Relative to AD, the theory posits that persons with higher reserve have more brain pathology upon diagnosis than those with lower reserve. However, once a certain neuropathological threshold depletes the compensatory networks, those with higher cognitive reserve demonstrate a more rapid cognitive decline due to the severe neuropathology (Stern, 2002; Sundermann, Maki, et al., 2016). Due to the lifelong female advantage in VM and potential domain-specific cognitive reserve, it is important to understand the effect of sex on VM performance.

Verbal Memory

As noted previously, a decline in VM performance is a key indicator of AD and can be measured in multiple ways. Assessments of VM are typically part of a larger, comprehensive neuropsychological battery, such as the Wechsler Memory Scale (Wechsler, 1997). Two common types of VM assessments include word list learning and recall and story learning and recall. Examples of word list learning and recall tests include the Rey Auditory Verbal Learning Test (RAVLT) and the Word List Memory and Recall tests. These tasks require individuals to recite a list of unrelated words which they have been verbally told. Similarly, assessments of story learning and recall, such as the Logical Memory test, require participants to recall details of a short story which they have been verbally told. Both types of assessments require trials of verbal learning (also referred to as immediate recall) and memory (delayed recall). See Table 1 for more details on these assessments.

Different areas of the brain are involved in verbal memory, including the prefrontal cortex and the medial temporal lobe (MTL) (Squire, Stark, & Clark, 2004). Immediate recall may more strongly reflect processes of working memory while delayed recall requires long term storing of information (Baddeley, 2003; Wolk & Dickerson, 2011). Proper encoding of information, facilitated by the prefrontal cortex and parietal regions, is necessary to convert information in the working memory to long term memories in the MTL (Champod & Petrides, 2007; Wolk & Dickerson, 2011). In particular, the entorhinal cortex and hippocampus play an important role in memory consolidation and show the earliest neuropathological changes in AD (Braak & Braak, 1991). The inability to consolidate memories may be reflected as poorer delayed recall (Welsh, Butters, Hughes, Mohs, & Heyman, 1991). These processes are important in understanding the VM changes associated with AD.

Stages of Cognitive Change and the Impact on VM

The evolution from normal cognition (NC) to AD is a progressive process which occurs over time. Mild cognitive impairment (MCI) is an intermediate stage between NC and severe cognitive decline associated with dementia (Petersen, 2004). Identifying the MCI stage is important as clinical manifestations (e.g. changes in VM) are not yet advanced and it may be an opportune window of time to slow progression of cognitive decline and prevent advancement to dementia.

Amnestic MCI (aMCI) is a preclinical stage of AD and indicates predominant impairment in the memory domain. In aMCI, other cognitive domains, such as executive function and attention, remain intact and activities of daily living are generally unaffected; however, individuals report subjective memory complaints (Dubois et al., 2007). While MCI is predictive of conversion to clinically diagnosable dementia, aMCI is specifically predictive of

conversion to AD dementia (Dubois et al., 2007; Grundman et al., 2004). VM is important to track over time, especially during MCI, as a decline in VM performance is an early sign of AD. In particular, poor delayed recall performance as compared to immediate recall performance, is more indicative of conversion from MCI to AD (Perri, Serra, Carlesimo, & Caltagirone, 2007).

Biomarkers of AD

Biomarkers are emerging as important indicators for predicting onset and progression of AD. Biomarkers are substances or indictors of a biological state and may exist years before the onset of clinical symptoms. There are various types of biomarkers associated with AD, including genetic, neurodegenerative, and metabolic markers. However, the two hallmark biomarkers of AD include intracellular neurofibrillary tangles and extracellular amyloid-β (Aβ) plaques (Jack et al., 2013; Yankner, 1996). See Table 2 for more information on AD-related biomarkers and how they are measured.

As a decline in VM performance is a preliminary clinical manifestation of early AD, it is important to understand the temporal evolution of biomarkers associated with VM performance. Unfortunately, the process of biomarker-related changes is not linear and there is considerable heterogeneity in progression among individuals. The accumulation of cortical Aβ plaques is thought to be an initial biomarker of AD and plays an important role in the cognitive dysfunction which manifests later in the disease (Jack et al., 2010). Some suggest that metabolic markers, such as temporal lobe glucose metabolism rate (TLGluMR), may reflect pathologic changes that occur later on in the disease and are more tightly associated with cognitive changes (Sundermann et al., 2017). Currently, little is known about the relationship between biomarkers, sex, and the progression of AD.

Multi-Center Data Sets on AD

National databases and registries are a useful method of obtaining information on large numbers of people and across populations. Multi-center data sets and registries are becoming more common for diseases such as AD and provide an easy way of standardizing methods across data collection and clinical trials. As data from various AD data sets are freely available to researchers, national registries and databases provide a valuable tool for better understanding the trajectory of disease progression. In particular, these data sets provide a tool to examine and better understand sex differences across the AD spectrum. See Table 3 for information on two AD databases within the United States and one AD registry in Austria.

Current Study

Researchers have begun to investigate the role of sex on VM performance in the progression from NC to AD. Only a handful of studies have included biomarkers as a tool to better understand differences in AD presentation and progression between men and women. Understanding the influence of sex on biomarkers, clinical symptoms, and progression of AD is critical for preventive strategies and improved outcomes for women. This study aims to systematically review the current state of the literature regarding the role of sex on VM performance in AD.

Materials and Methods

Search Strategy and Study Inclusion

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & The, 2009). The electronic search was conducted in January 2019 and included CINAHL complete, MEDLINE, and PsycINFO with no filters in the search findings. The following search strategy was used: (“sex”

OR “gender”) AND “verbal memory” AND “Alzheimer’s disease.” This search returned 213 articles, including duplicates, and included articled published between 1986 and 2019. Eligibility criteria included: (i) the abstract reported in the English language (ii) the study used one or more measurements of VM performance (iii) non-animal, human subjects.

Study Selection

Initially, titles and abstracts were screened by the lead author. Articles relevant to the topic of review were selected and the full-texts were reviewed. Two more articles were identified through a bibliographic search. Studies including human participants with neurological disorders other than MCI or Alzheimer’s dementia were excluded (i.e. stroke, Parkinson’s disease, etc.). Articles were independently reviewed by the lead and secondary authors to make sure all articles met inclusion criteria. There was no disagreement between authors. See Figure 1 for a summary of the selection process.

Results

Description of Studies

Of the 215 articles returned from our search, a total of eight studies were included, all of which were cross-sectional. Participant age ranged from 61-91. Sample sizes study ranged from 59 (McPherson, Back, Buckwalter, & Cummings, 1999) to 1,583 (Sundermann, Tran, Maki, & Bondi, 2018) and included a total of 6,372 participants. Two studies only included participants with AD (McPherson et al., 1999; Pusswald et al., 2015), while the other studies compared between and among NC, MCI, and AD groups. Exclusionary criteria varied, though most studies excluded other neurological disorders. Commonly reported covariates included age and education. Five of the eight articles used the Rey Auditory Verbal Test (RAVLT) to assess VM. See Table 1 for more details on each VM assessment and Table 4 for more details on each

individual study. Three studies compared sex using only assessments of VM, while the other five studies included biomarkers in the analyses. We have divided the results section based on these differences to better compare articles.

Assessment of VM Only

Only participants with AD

In the two studies with only AD participants, results indicated that women scored lower than men on assessments of VM. McPherson et al. (1999) found that women scored lower than men on the immediate recall of the second story and on the delayed recall of the Logical Memory test. Similarly, Pusswald et al. (2015) found that women scored lower than men on assessments of verbal learning (using the Word List memory test) and memory performance (using the Word List Recall test). These differences were seen across all severity and age-stratified subgroups.

NC compared to AD

Chapman et al. (2011) used the Logical Memory subtest to examine the impact of sex on VM performance in NC and AD. In NC, women scored higher than men on immediate and delayed recall while the effect reversed in AD: women scored lower than men on immediate and delayed recall. Additionally, discriminant analyses showed 100% accuracy in classifying women as AD or control and 88% accuracy in classifying men with AD. Thus, the Logical Memory test was better at detecting AD in women than men.

Assessment of VM Including AD Biomarkers: Moderating Effects of Sex

When comparing VM performance between and across diagnostic groups (NC, MCI, AD), interactions between sex and AD-related biomarkers were typically driven by the MCI

group. Across studies, NC women typically scored higher than men, regardless of stratification by biomarkers. And in AD, women typically outscored men on immediate but not delayed recall.

Caldwell, Berg, Cummings, and Banks (2017) compared between two diagnostic groups (NC, early MCI) to investigate whether sex moderated the effect of cortical Aβ burden on 1) VM performance and 2) on hippocampal volume (HV). Overall, their findings demonstrated that women were impacted differently by Aβ burden than men. In NC, women outscored men on verbal learning and memory, regardless of Aβ burden. However, early MCI women with high Aβ burden scored lower than women with low Aβ burden. Regardless of diagnostic group, VM performance tended to be poorer in men with high Aβ burden than in men with low Aβ burden.

Similarly, Sundermann et al. (2017) examined the interactive effect of sex and cortical Aβ burden on VM performance; however, they assessed across three diagnostic groups (NC, aMCI, AD) and found slightly different outcomes. Results were driven by the aMCI group, but only on delayed recall performance. Specifically, women with low to moderate Aβ burden outscored men with low to moderate Aβ burden; however, this association disappeared at high levels of Aβ burden. In NC and AD groups, regardless of Aβ burden, women outscored men on immediate (NC, AD) and delayed recall (NC only).

Instead of cortical Aβ burden, Sundermann, Maki, et al. (2016) was interested in the interactive effect of sex and TLGluMR on VM. Again, comparing across all three diagnostic groups, their results were almost identical to those of Sundermann et al. (2017). In aMCI, women with medium to high TLGluMR scored higher than men with medium to high TLGluMR on both immediate and delayed recall. This female advantage disappeared at lower levels of TLGluMR where men and women scored the same. In NC and AD groups, women outscored men on immediate (NC, AD) and delayed recall (NC only), regardless of TLGluMR.

In another similar design, Sundermann, Biegon, et al. (2016) compared across all three diagnostic groups (NC, aMCI, AD), but using hippocampal volume/intracranial volume ratio (HpVR) as a biomarker. Consistent with the pattern of other results (Sundermann et al., 2017; Sundermann, Maki, et al., 2016), women with larger HpVR outscored men on both immediate and delayed recall performance. However, this association disappeared in participants with smaller HpVR. In NC and AD groups, women outscored men on immediate recall, regardless of HpVR. On delayed recall, NC women outscored NC men; however, no gender differences were seen on delayed recall performance in AD.

Similar to the studies discussed thus far, Sundermann et al. (2018) examined the role of sex on VM performance across the AD continuum (NC, MCI, AD). However, this study added a unique analysis by attempting to determine a temporal relationship of interactive effects of APOE-ε4 status and sex based on three biomarkers (cortical Aβ burden, hippocampal volume, brain glucose metabolism), and one clinical outcome (immediate recall performance). The study did not find any interactive effects of APOE-ε4 status and sex on immediate recall. However, as seen in the other studies, women maintained their VM advantage, outscoring men across all groups. In MCI there was an effect of APOE-ε4 status but not gender: non-carriers always outscored carriers. Additionally, being an APOE-ε4 carrier was associated with higher cortical burden, smaller HpVR, and lower brain glucose metabolism. Thus, in MCI, APOE-ε4 women still maintained their VM advantage. In NC and AD, there were no effects of APOE-ε4 status.

Discussion

While research regarding the role of sex on VM in AD is in its infancy, the results of this review establish an emerging pattern. Consistent with previous literature, in NC, women display an advantage and consistently score higher than men on assessments of VM (Kramer, Delis, &

Daniel, 1988). However, compared to men, the trajectory for women's VM performance is different. aMCI appears to be a critical time when the impact of sex becomes accentuated. Specifically, there is a threshold in aMCI where women's VM declines significantly. Subsequently, in AD, women's VM performance becomes similar to men's, with delayed recall showing a steeper decline than immediate recall.

Even when assessing different biomarkers for interactive effects of sex on VM, MCI still proved to be a crucial period when women's performance begins to significantly change. At low to medium levels of neurodegenerative and metabolic change, women score higher than men on assessments of VM. However, at higher levels of change, the female advantage disappears. Additionally, genetic risk (APOE-ε4) appears to affect men and women differently. In NC, females who are APOE-ε4 carriers do not demonstrate a decline in VM performance as do APOE-ε4 male carriers. And in MCI, despite manifestations of structural and functional problems, females who are APOE-ε4 carriers still outperform males who are APOE-ε4 carriers.

These results support the cognitive reserve theory such that women have a greater neural network to compensate for neurodegenerative damage. However, once their cognitive reserve has been depleted, women display a more rapid rate of decline because neurodegeneration has become so severe. Clinical manifestations of VM impairment are only assessed through cognitive testing and such assessments are not sex-adjusted. Thus, it is plausible that aMCI is only detected when women are at more advanced stages of pathology. As such, women may spend a shorter amount of time in the aMCI stage and convert more quickly to AD than men. Together, these factors could help explain why women are diagnosed at later stages and have a steeper decline once diagnosed.

The present study has important implications for AD research; however, we also acknowledge our limitations. While the search terms were carefully picked to be broad enough to scan and describe the literature but also specific to sex differences and VM, these results are based on eight articles. Additionally, we do not know what role sex plays in VM change across the different stages of AD as severity within AD was not defined in these articles. Finally, the role of biomarkers and its interaction with sex is only beginning to be implemented in AD research. Nevertheless, the evidence reviewed here demonstrates a consistent pattern and supports a direction for further study.

Conclusion

One of the suggested areas of investigation from the Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease is the effect of sex and gender differences on the clinical detection, diagnosis, management, and treatment of AD. This review begins to systematically address the effect of sex on clinical detection and diagnosis, a small part of the gap in the literature. By understanding the differences in risk factors, symptoms, and disease trajectory, the research community is better equipped to design clinical trials and develop new treatments, interventions, and precision medicine. In addition, healthcare providers may need to identify other ways to screen women for MCI to provide the most robust early interventions and slow disease progression.

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Table 1.
Selected Assessments of VM

Assessment	Description
Logical Memory (LM) test	In the LM, an examiner reads a short story (Story A) out loud. The participant is then immediately asked to spontaneously reproduce as many details of the story as possible. This process is repeated twice with another short story (Story B). Each story is comprised of a few sentences. After a delay of approximately 25 minutes filled with other, unrelated cognitive tests, the participant is asked to recall as many details from each story as possible (Wechsler, 1997). The raw score for each story, immediate and delayed recall, ranges from 0-25.
Rey Auditory Verbal Learning Test (RAVLT)	During the RAVLT (Schmidt, 1996), the participant is read a list of 15 unrelated words and is asked to freely recall aloud as many words as possible. This process is repeated for a total of five verbal learning trials. There is a possible raw immediate recall score of 0-75. Next, an interference list of 15 unrelated words is read aloud and the participant is asked to freely recall aloud as many words as possible. The first list is read again, and the participant is asked to freely recall aloud as many words as possible. After a delay of approximately 30 minutes filled with other non-verbal assessments, the participant is asked again to freely recall aloud as many words as possible only from the first list. There is a possible delayed recall score 0-15.
Word List Memory and Recall (WL, WLR) tests	During the WL (Morris et al., 1989), the participant is asked to read each of 10 words presented at a frequency of one word every two seconds. Then the participant is immediately asked to recall as many words as possible. This process is repeated three times for a possible raw score of 0-30. The Word List Recall (WLR) occurs after a delay of 5-10 minutes. The participant is asked to freely recall as many words as possible from the WL, yielding a possible raw score of 0-10.

Note. LM = Logical Memory test; RAVLT = Rey Auditory Verbal Learning Test; WL = Word List Memory test; WLR = Word List Recall test.

Table 2.
Selected Biomarkers of AD

Biomarker	Description
Apolipoprotein E-ε4 (APOE-ε4)	The APOE4-ε4 allele is one of three apolipoprotein E variants and is the most common genetic risk factor associated with AD. APOE4-ε4 is associated with cortical Aβ plaque deposition; however, there is conflicting literature as to whether there is an association among APOE4-ε4 and other biological and clinical markers of AD (Lupton et al., 2016). Sundermann et al. (2018) suggests that such inconsistencies may be due a moderating role of sex on the association between APOE4-ε4 and AD.
Amyloid-β (Aβ) plaques	Cortical Aβ plaques are amino acid peptides derived from the amyloid precursor protein (APP). Aβ dysregulation induces neuronal apoptosis and causes wide spread plaque deposition to accumulate over time (Murphy & LeVine, 2010). An imaging technique frequently used to assess cortical Aβ burden is florbetapir PET (Rowe & Villemagne, 2011; Sundermann et al., 2017). Another mechanism used to measure Aβ burden is cerebrospinal fluid; however, this technique is inherently more invasive.
Hippocampal Volume (HV)	HV is a measure of neurodegeneration and can be assessed using structural magnetic resonance imaging (MRI) and high-dimensional brain mapping tools (Christensen, Joshi, & Miller, 1997). Longitudinal studies have documented that greater HV loss is associated with MCI AD (van de Pol et al., 2006).
Temporal lobe glucose metabolism rate (TLGluMR)	In AD, metabolic impairment is initially visualized in the parietal and temporal lobes (Jacobs, Van Boxtel, Jolles, Verhey, & Uylings, 2012; Mosconi et al., 2006). In addition to HV, temporal metabolic functioning is important in understanding level of VM function. Specifically, temporal hypometabolism is associated with poorer VM performance (Nishi et al., 2010). Temporal lobe glucose metabolism rate (TLGluMR) can be measured with [F]-

	fluorodeoxyglucose-PET (FDG-PET) scans (Petersen et al., 1999).

Note. Aβ = amyloid-β; AD = Alzheimer's disease; APOE4-ε4 = Apolipoprotein E-ε4; APP = amyloid precursor protein; FDG-PET = [F]- fluorodeoxyglucose-positron emission tomography; HV = hippocampal volume; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET = positron emission tomography; TLGluMR = temporal lobe glucose metabolism rate; VM = verbal memory.

Table 3.
National Registries and Databases

Registry/Database	Description
National Alzheimer's Coordinating Center (NACC) – Alzheimer's Disease Centers	Established under the NACC, Alzheimer's Disease Centers (ADCs) are located at major medical institutions across the United States and funded by the National Institute on Aging (NIA). Data are collected on participants with NC, MCI, and Alzheimer's disease and related disorders. All ADC databases include standardized clinical and neuropathological data sets.
Alzheimer's Disease Neuroimaging Initiative (ADNI) database	Initiated in 2004, the ADNI is an ongoing longitudinal, multi-center study which collects data on clinical, imaging, genetic, and biochemical biomarkers of AD in people with NC, MCI, and AD. The ADNI currently has 4 cohorts (ADNI-1, ADNI-2, ADNI-3, ADNI-GO) and makes their data publicly available to researchers across the world.
Prospective Dementia Registry (PRODEM) Austria	The PRODEM Austria was initiated in 2008 and is an ongoing longitudinal, multi-center cohort study funded by the Austrian Alzheimer's Society. The database includes clinical, biological, and social markers of dementia.

Note. AD = Alzheimer's disease; ADC = Alzheimer's Disease Center; ADNI = Alzheimer's Disease Neuroimaging Initiative; MCI = mild cognitive impairment; NACC = National Alzheimer's Coordinating Center; NC = normal cognition; NIA = National Institute on Aging; PRODEM = Prospective Dementia Registry.

Table 1.
Summary of Studies

Reference & Publication Year	Participants	Registry	Assessment of VM	Biomarkers	Conclusion
Caldwell *et al.* 2017	NC = 285 Early MCI = 457	ADNI2 ADNI-GO	RAVLT	[1] Cortical Aβ burden [2] HV	In NC, women outscored men regardless of cortical Aβ burden. In early MCI, women with high cortical Aβ burden scored lower than women with low cortical Aβ burden. In men, regardless of diagnostic group, those with high cortical Aβ scored lower than those with low cortical Aβ burden.
Chapman *et al.* 2011	NC = 42 AD = 42	ADC at Strong Memorial Hospital	LM from WMS-III	-	For analyses, immediate recall scores for Story A and Story B were averaged to yield a mean immediate recall score. In NC, women scored higher than men. In AD, women scored lower than men. Discriminant analyses showed 100% accuracy in classifying women as AD or control and 88% accuracy in classifying men with AD. Thus, the LM was better at detecting AD in women than men.

McPherson *et al.* 1999	AD = 59	ADC at UCLA	LM from WMS-R	-	Women scored lower than men on delayed recall and on the second story of immediate recall.
Pusswald *et al.* 2015	AD = 286	CERAD-Plus	WL, WLR	-	Categorizing disease severity based on a global measure of cognitive function (MMSE), women with mild and moderate AD scored lower than men with mild and moderate AD.
Sundermann, Biegon, *et al.* 2016	NC = 379 aMCI = 694 AD = 235	ADNI1 ADNI2 ADNI-GO	RAVLT	[1] HV	In NC, women scored higher than men, regardless of HpVR. In aMCI, women with larger HpVR significantly scored higher than men. Women with smaller HpVR (more hippocampal atrophy) lost their advantage. In AD, women outscored men on immediate recall only.
Sundermann, Maki, *et al.* 2016	NC = 390 aMCI = 672 AD = 254	ADNI1 ADNI-GO	RAVLT	[1] Brain glucose metabolism	In NC, women scored higher than men, irrespective of TLGluMR. In aMCI, women scored higher than men on immediate and delayed recall; effects which were strongest in women with medium to high

					TLGluMR. In AD, irrespective of TLGluMR level, women scored higher than men on immediate recall. However, women lost this advantage on delayed recall.
Sundermann *et al.* 2017	NC = 304 aMCI = 515 AD = 175	ADNI2 ADNI-GO	RAVLT	[1] Cortical Aβ burden	In NC, women scored higher than men, independent of levels of Aβ burden. In aMCI, women scored higher than men on delayed recall at low and moderate levels of cortical Aβ burden. This female advantage disappeared at high levels of cortical Aβ burden. In AD, women scored higher than men on immediate recall.
Sundermann *et al.* 2018	NC = 702 MCI = 576 AD = 305	ADNI	RAVLT *Immediate recall only	[1] Cortical Aβ burden [2] HV [3] Brain glucose metabolism	Overall, women scored higher than men. Specifically, the NC and AD groups showed the same pattern where there was no interaction of APOE-ε4 status and gender on VM performance. However, women scored higher than men, regardless of APOE-ε4 status.

							In MCI, there was no interaction of APOE-ε4 status and gender. However, APOE-ε4 carriers scored higher than non-carriers and women scored higher than men. Only Caucasians were included to minimize potential population stratification bias in interpreting genetic data.

Note. Aβ = amyloid-β; AD = Alzheimer's disease; ADC = Alzheimer's Disease Center; ADNI = Alzheimer's Disease Neuroimaging Initiative (includes cohorts 1, 2, GO); aMCI = amnestic mild cognitive impairment; APOE-ε4 = apolipoprotein E-ε4; CERAD- Plus = Consortium to Establish a Registry for Alzheimer's disease neuropsychological battery; HV = hippocampal volume; LM = Logical Memory subtest; MCI = mild cognitive impairment; MMSE = Mini Mental Status Exam; NC = normal cognition; RAVLT = Rey Auditory Verbal Learning Test; VM = verbal memory; WL = Word List memory test; WLR = Word List Recall; WMS = Wechsler Memory Test (versions R, III).

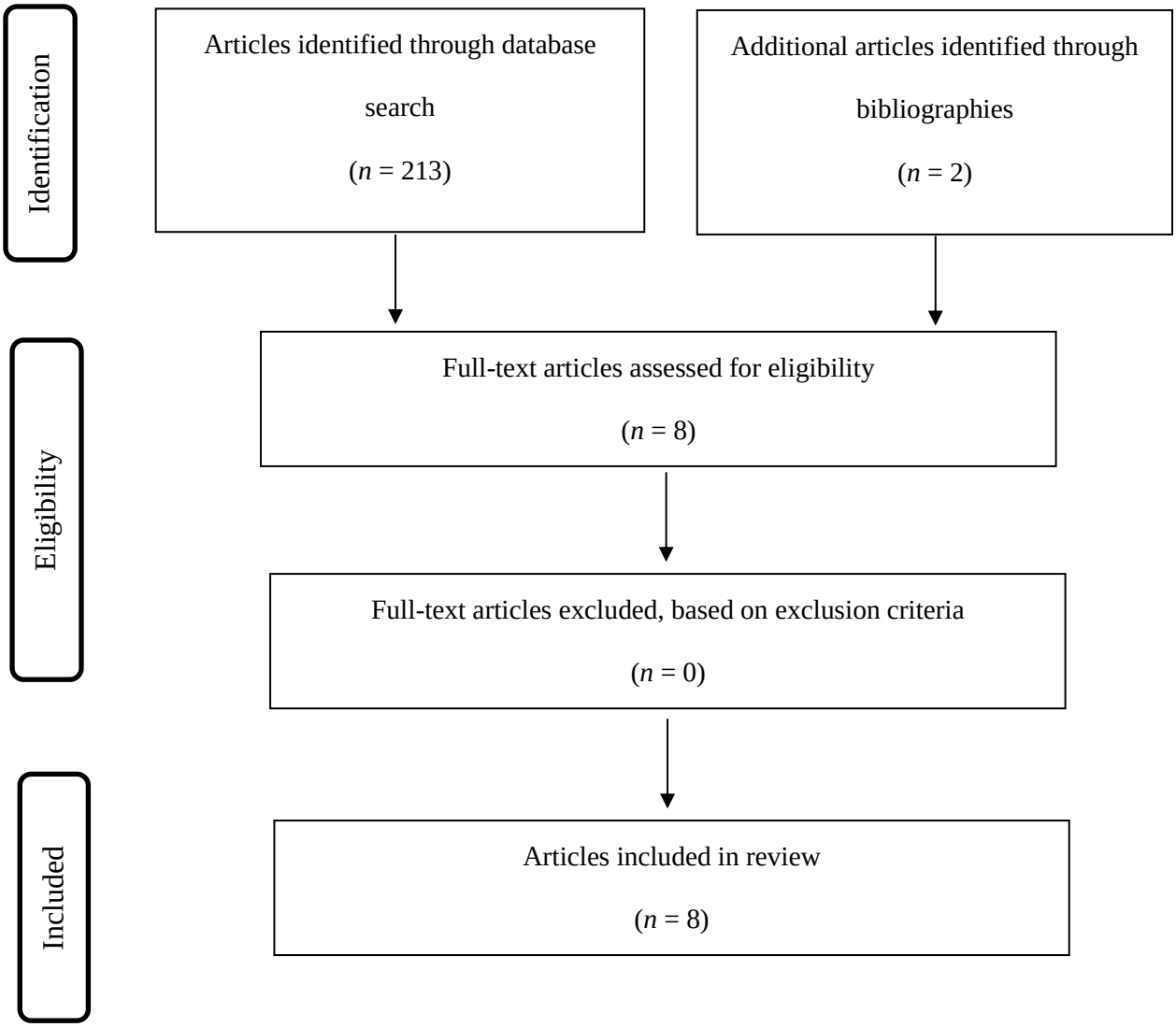

Figure 1. Literature search and article selection flow diagram.

Chapter 3: The Interplay of Sex and Verbal Memory Performance from Normal Cognition to Alzheimer's Disease: An Intricate Story

Manson, A., Dean, E. E., Williams, K. N., & Maliski, S. L. (2019). *The interplay of sex and verbal memory performance from normal cognition to Alzheimer's disease: An intricate story.* Unpublished manuscript.

Introduction

Women are disproportionately affected by Alzheimer's disease (AD), with two-thirds to one-third of patients being female (Hebert, Weuve, Scherr, & Evans, 2013). AD is an irreversible, progressive neurodegenerative disorder causing detrimental impairment in cognition. Researchers and clinicians recognize that the onset of symptomology and disease progression are heterogeneous (Ferreira, Wahlund, & Westman, 2018). Sex may be an important variable influencing incongruencies (Seshadri et al., 1997). Across the lifespan, women have about a 12% lifetime risk of developing AD whereas men only have about a 6% risk. This increased risk is not due to the greater longevity of women (Seshadri et al., 1997). Though the reasons for such disparity are not fully understood, the literature suggests that unique biological mechanisms affecting AD pathology may be at play (Andrew & Tierney, 2018; Mosconi et al., 2018; Viña & Lloret, 2010). Understanding sex-specific risk factors and disease progression are important for early diagnosis and the use of precision medicine (i.e., individualized treatment) to enhance outcomes and quality of life (QOL) in AD.

The literature regarding understanding the role sex plays in the development and trajectory of AD is in its infancy. In particular, few studies have examined the sex differences associated with verbal memory (VM) in AD. VM is a critical factor when screening for and diagnosing AD because a decline in VM is indicative of preclinical AD (Albert, Moss, Tanzi, & Jones, 2001; Bondi et al., 1994; McKhann et al., 1984). VM is typically assessed by word list recall (e.g., Rey Auditory Verbal Learning Test) or story recall (e.g., Logical Memory test) and includes two components: immediate recall and delayed recall.

Across the lifespan and consistently reported within the literature, women with normal cognition (NC) perform better than men with NC on both immediate and delayed recall (Aartsen,

Martin, & Zimprich, 2004; Herlitz, Nilsson, & Bäckman, 1997; Kramer, Yaffe, Lengenfelder, & Delis, 2003). However, the pattern of change in VM between men and women may be different across the continuum of normal to pathologic cognition (Manson, Dean, Williams, & Maliski, 2019). Two studies assessing VM performance within AD found that women scored lower than men on delayed recall for both word list recall and story recall (Chapman et al., 2011; McPherson, Back, Buckwalter, & Cummings, 1999; Pusswald et al., 2015). On the other hand, other studies have found that in AD, men and women's performance does not differ on delayed recall (Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). Clearly, there are mixed findings regarding the interplay of sex and VM in AD.

VM function relies on structures within the medial temporal lobe (MTL), in particular, the entorhinal cortex and hippocampus (Squire, Stark, & Clark, 2004). In AD, the MTL is the brain region where neurodegeneration is first apparent (Braak & Braak, 1991). Biomarkers are substances or indicators of a biological state and may exist years before the onset of clinical symptoms. In AD, biomarkers may provide an in vivo measure of neural dysfunction (de Leon et al., 2001). AD biomarkers of neurodegeneration, some of which measure degeneration within the MTL, include but are not limited to increased cortical Aβ burden, a decrease in hippocampal volume, and a reduction in temporal lobe glucose metabolism rate. One of the genetic biomarkers for AD is the apolipoprotein E (APOE) ε4 allele. The APOE-ε4 genotype is associated with accelerated cognitive decline and other biomarkers of neurodegeneration in AD (Khan et al., 2017). Carriers of the APOE4-ε4 allele are at the highest genetic risk of developing AD (Riedel, Thompson, & Brinton, 2016).

In the progression from NC to AD, there is significant heterogeneity in symptomology and disease trajectory (Petersen et al., 2001; Sachdev et al., 2012). Mild cognitive impairment

(MCI) is an intermediate stage of cognition, including amnestic MCI (aMCI) and non-amnestic MCI (naMCI; Albert et al., 2011). While subtypes of MCI have been identified, they have not been characterized beyond domain of cognitive impairment (e.g., memory, executive function, language) and number of domains affected (single versus multiple). For example, in aMCI, there is a primary deficit in the memory domain which may or may not be accompanied by a secondary deficit in another cognitive domain. While MCI is a heterogenous stage of cognition, it is important to study the effects of sex and VM differences during this stage to better understand the trajectory of cognitive decline in AD.

Though only a handful of studies within the last three years have looked at the relationship between VM, sex, and biomarkers of AD, preliminary results suggest that biomarkers may help advance our understanding of sex-specific associations between neurodegeneration and VM performance (Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016; Sundermann, Tran, Maki, & Bondi, 2018). Though the results are somewhat mixed regarding the role of biomarkers, when comparing across the continuum of disease (NC, MCI, AD), MCI appears to be a critical time when women lose their VM advantage. One theory, cognitive reserve theory, posits that individuals with certain traits such as higher education, IQ, an enriched environment, and other favorable traits, have compensatory neural networks which can moderate deleterious changes in the brain (Stern, 2012). Those with higher cognitive reserve may be able to maintain cognitive functioning despite progressive neuropathologic deterioration. However, in relation to AD, there is a threshold when these compensatory networks can no longer mitigate neurodegeneration and a steep decline in cognition ensues (Sundermann et al., 2017).

Preliminary evidence using biomarkers to help delineate sex-specific patterns of VM suggests that women may have a higher cognitive reserve, allowing them to appear cognitively healthy despite the development of AD-related neuropathology. The critical period when women's neural networks become too depleted to compensate for significant neurodegeneration may occur during MCI (Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). However, it is not clear whether women with MCI maintain an advantage on both immediate and delayed recall and sex-specific trajectories may be dependent upon degree of neurodegeneration (Caldwell, Berg, Cummings, & Banks, 2017; Sundermann, Biegon, et al., 2016). Regarding genetic risk, results consistently show that APOE-ε4 non-carriers perform better than carriers (Sundermann et al., 2017; Sundermann, Maki, et al., 2016). Few studies have 1) compared VM performance across the continuum of cognition (NC, MCI, AD) and 2) included at least one biomarker of AD as a measure of neurodegeneration or genetic risk. Therefore, additional research is warranted to better understand the sex-specific trajectories of AD-related changes in VM.

In this study, we sought to further investigate the pattern in VM change between men and women across NC, MCI, and mild AD groups. Specifically, we were interested in comparing the differential impact of diagnostic group on VM between men and women while including APOE-ε4 genotype as a biomarker of AD. In order to address our research aim, we performed two studies. Study 1 included a clinical cohort from the Uniform Data Set (UDS) version 2 (described below) using the immediate and delayed recall from the Logical Memory test. Study 2 included another clinical cohort from the UDS version 3 using the immediate and delayed recall from the Craft Story 21 test. For both studies, we hypothesized that sex would have an interactive effect across diagnostic groups such that 1) NC women would outperform NC men on

immediate and delayed recall 2) MCI women would outperform MCI men on immediate and delayed recall and 3) AD women and men would perform equally on both immediate and delayed recall. Regarding genotype, we hypothesized that non-carriers would outperform carriers across all groups.

Methods

Sample and Procedure

Cross-sectional data were extracted from the University of Kansas Alzheimer's Disease Center (KU ADC) which is part of the National Alzheimer's Coordinating Center's (NACC) UDS. Detailed information about NACC can be found at https://www.alz.washington.edu/WEB/researcher_home.html. The NACC was established in 1999 by the National Institute on Aging (NIA) as a national database including longitudinal data on cognitively normal subjects as well as those with MCI and AD and related disorders. The UDS includes data on sociodemographics, family history, dementia history, neurological exam findings, functional status, neuropsychological test results, clinical diagnosis, imaging, and APOE genotype.

The KU ADC was funded in 2011 and enrolled their first participant in June 2012. Participants are recruited from community organizations, volunteers wishing to contribute to dementia research, clinical referrals, and self-referrals from patients and family members. As part of the clinical cohort, all participants receive standard clinical and cognitive evaluations on an annual basis.

Uniform Data Set (UDS)

Currently, there are three versions of the UDS. In version 2, various neuropsychological assessments were unavailable to non-ADC affiliated community researchers who did not own

individual licensing agreements and other tests lacked sensitivity to detect very early cognitive decline. Thus, the UDS version 3 implemented a battery of nonproprietary and more sensitive neuropsychological assessments. In version 3, the Craft Story 21 test replaced the Logical Memory test as a measure of VM and the Montreal Cognitive Assessment (MoCA) replaced the Mini Mental Status Exam (MMSE) as a global measure of cognitive impairment (Monsell et al., 2016).

A crosswalk study was completed before the new neuropsychological tests were implemented in order to confirm that the new assessments sufficiently correlated with the old assessments. The Logical Memory and Craft Story 21 had an immediate recall Spearman's correlation of $\rho = .73$ and a delayed recall Spearman's correlation of $\rho = .77$. The MMSE and MoCA had a Spearman's correlation of $\rho = .77$ (Monsell et al., 2016). Due to the change in VM assessments and statistically different group means for immediate ($p < .0001$) and delayed recall ($p < .0001$), we separately analyzed participant data from the two UDS versions.

In all versions of the UDS, part of the clinical evaluation includes the Clinical Dementia Rating (CDR). The CDR rates dementia severity and includes assessment of memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. A CDR score of 0 indicates normal cognitive functioning, 0.5 indicates MCI, 0.5 or 1 indicates mild AD, 2 indicates moderate AD, and 3 indicates severe AD (Morris, 1993).

NC, MCI, and AD diagnoses were made at a consensus conference after the examination of all available information. Specifically, study clinicians trained in dementia assessment conducted a standard clinical evaluation, including the CDR, and a trained psychometrician administered a comprehensive cognitive testing battery (Morris, 1993). Based on the clinical and psychometric test results reviewed by clinicians, a clinical neuropsychologist, and raters, a final

consensus diagnosis was made. An AD dementia diagnosis was determined using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA) (McKhann et al., 1984). Etiology of disease was determined following the National Institute on Aging-Alzheimer's Association workgroup diagnostic guidelines for AD which include the category for "mild cognitive impairment due to Alzheimer's diseases" (Albert et al., 2011).

Inclusion Criteria

Participants with NC, MCI, and AD were included. The UDS includes participants with various etiologies and types of dementia. For the MCI and AD groups, since a decline in VM is specifically associated with future development of AD, only participants with an etiology of the Alzheimer's type were included in our analyses. Further, participants can have a diagnosis of AD in addition to another comorbid type of dementia. We only included participants with AD as the primary contributing cause of observed cognitive impairment in our analyses. Participants with a CDR of up to 1, indicating mild AD, were included. Finally, participants who were classified as cognitively impaired but not MCI were excluded. Figure 1 shows flowcharts of the analytic samples for Studies 1 and 2. Research using the UDS data was approved by the University of Kansas Medical Center Human Subjects Committee and informed consent was obtained for all participants and/or their legally authorized representative.

Dependent Variables

Logical Memory test

Study 1 used the Logical Memory test as an assessment of VM. In this test, an examiner reads a short story out loud. To measure immediate recall, the participant is immediately asked to spontaneously reproduce as many details of the story as possible. The story is comprised of a few

sentences. A delay of approximately 25 minutes is filled with other, unrelated cognitive tests. After this delay interval, delayed recall is assessed by asking the participant to recall as many details from the story as possible (Wechsler, 1997). The scores for immediate and delayed recall range from 0-25 each.

Craft Story 21 test

Study 2 used the Craft Story 21 test which follows the same format as the Logical Memory test. The Craft Story was developed by Craft et al. (1996) and includes multiple forms of story recall to study the impact of insulin on cognition in mild AD. The UDS Clinical Task Force and Neuropsychology Work Group concluded that the Craft Story 21 content was most relevant to a diverse population and thus was chosen for the UDS version 3 assessment of VM (Weintraub et al., 2018).

Independent Variables

Sex was defined by participant self-report of male or female. Diagnoses of NC, MCI, and AD were determined at the consensus conference discussed previously. APOE-ε4 genotype was confirmed by a blood test. Participants were categorized as carriers (possesses at least one ε4 allele) or non-carriers (does not possess any ε4 alleles).

Covariates

Models were adjusted for participant age and level of education as previous research has shown these sociodemographic characteristics may be potentially confounding variables (Sundermann et al., 2017; Sundermann, Maki, et al., 2016). Both variables were assessed as continuous.

Statistical Analysis

Baseline visit data were used in our analyses. For Study 1, we examined differences between sexes in demographic variables (age and education), APOE-ε4 carrier status, MMSE scores, and outcome variables (immediate and delayed recall) using independent t-tests for continuous variables and X^2 for categorical variables. In the overall sample, separate multiple linear regressions were run for both immediate and delayed recall. Predictor variables in each model included sex, diagnosis, and a sex by diagnosis interaction, covarying for age and education. APOE-ε4 genotype was inserted as a predictor variable; however, it was not significant in any models and thus was taken out in subsequent models. Secondary analyses examined the independent association of sex with immediate and delayed recall performance within diagnostic groups (NC, MCI, AD). This resulted in a total of eight regression models. For Study 2, we used the same approach with two exceptions: 1) we used the MoCA instead of MMSE based on revisions to UDS version 3 and 2) APOE-ε4 was not included as a predictor variable because less than 15% of participants had genotyping data available.

Results

Study 1, UDS version 2

A total of 425 participants were included in our overall analyses including participants with NC (CDR = 0; *n* = 258), MCI (CDR = 0.5, *n* = 56), and AD (CDR = 0.5 or 1, *n* = 111). The age range was 53 – 93 years of age and included 60% females and 40% males. The sample was 92.7% white (*n* = 394), 6.8% Black or African American (*n* = 29), and 0.5% Asian (*n* = 2). The sample had an average of 16.2 years of education. In the overall sample and within diagnostic groups, women were statistically younger ($t = 3.25$, $p < .002$) and less educated ($t = 3.72$, $p < .001$). In the overall sample, women scored significantly higher on the MMSE than men (t = -

2.94, $p < .004$); however, this pattern did not hold true when broken down by diagnosis (see Table 1). In the overall sample, women scored significantly higher than men on immediate ($t = -4.09$, $p < .0001$) and delayed recall ($t = -4.78$, $p < .0001$). In the overall sample, APOE non-carriers scored significantly higher than carriers on immediate ($t = 4.77$, $p < .0001$) and delayed recall ($t = 4.98$, $p < .0001$).

The overall regression models were significant for immediate and delayed recall ($p < .0001$) with a non-significant trend for the sex by diagnosis interaction for immediate recall (b [unstandardized coefficient] = 18.04, $SE = 1.91$, $p = .12$ for women vs $b = 16.74$, $SE = 2.36$, $p = .12$ for men) but not delayed recall ($p = .36$). Stratifying by diagnosis (NC, MCI, AD), sex was a significant predictor of immediate recall in NC where women scored higher than men ($b = 17.27$, $SE = 2.43$, $p < .002$ for women vs $b = 15.90$, $SE = 2.86$, $p < .002$ for men). However, sex did not significantly predict immediate recall in MCI ($p = .93$) nor in AD ($p = .28$) (see Figure 2). In diagnosis-stratified analyses for delayed recall, sex was a significant predictor in NC, where women scored higher than men ($b = 16.30$, $SE = 2.68$, $p < .002$ for women vs $b = 14.79$, $SE = 3.15$, $p < .002$ for men). However, sex did not significantly predict delayed recall in MCI ($p = .73$) nor in AD ($p = .43$) (see Figure 3).

Study 2, UDS version 3

A total of 344 participants were included in our overall analyses including participants with NC (CDR = 0, $n = 268$), MCI (CDR = 0.5, $n = 22$), and AD (CDR = 0.5 or 1, $n = 54$). The age range was 55 – 89 years of age and included 69% females and 31% males. The sample was 92.7% white ($n = 319$), 5.52% Black or African American ($n = 19$), 0.58% Asian ($n = 2$), 0.58% Asian ($n = 2$), and 0.58% ($n = 2$) missing. The sample had an average of 16.4 years of education. In the overall sample and within diagnostic groups, men and women did not statistically differ in

age nor years of education (see Table 2). In the overall sample (t = -2.25, p < .04) and in the NC group (t = -2.88, p < .005), women scored significantly higher on the MoCA than men; however, men and women scored equally in MCI and AD (see Table 2). In the overall sample, men and women scored equally on immediate (t = -0.41, p = .68) and delayed recall (t = -0.62, p = .53).

The overall regression models were significant for immediate and delayed recall (p < .0001) with a non-significant trend for the sex by diagnosis interaction for immediate recall (b = 27.78, SE = 2.45, p = .10 for women vs b = 27.83, SE = 2.93, p = .10 for men) and delayed recall (b = 27.01, SE = 2.69, p = .14 for women vs b = 26.80, SE = 3.21, p = .14 for men). Stratifying by diagnosis for immediate recall, sex was not a significant predictor in NC (p = .96) nor in AD (p = .93). However, in MCI there was a non-significant trend where men scored higher than women (b = 10.50, SE = 2.43, p = .10 for women vs b = 13.55, SE = 2.95, p = .10 for men) (see Figure 4). Stratifying by diagnosis for delayed recall, sex was not a significant predictor in NC (p = .58), MCI (p = .28) nor AD (p = .49) (see Figure 5).

Discussion

To the best of our knowledge, this is the first study to investigate the effect of sex on VM across diagnostic groups in a local Alzheimer's Disease Center's UDS clinical cohort. In Study 1, our hypotheses were partially supported. In NC, women displayed a VM advantage on both immediate and delayed recall. In AD, women lost their advantage and scored equal to men on both immediate and delayed recall. Across all groups, APOE-ε4 non-carriers scored higher than carriers on both immediate and delayed recall. Counter to our hypothesis, in MCI, women performed equal to men on both immediate and delayed recall.

There was a trend toward a sex by diagnosis interaction for immediate recall. Stratifying by diagnosis significantly lowered the group sample sizes, particularly in the MCI group (35

males and 21 females). Previous studies which found a female VM advantage in MCI included >200 male and female participants each (Caldwell et al., 2017; Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). Our small, stratified group sizes may not be adequate to reliably detect a true difference. Further, while MCI is predictive of conversion to clinically diagnosable dementia, aMCI is specifically predictive of conversion to AD dementia (Grundman et al., 2004). Due to extremely small sample sizes, we were not able to stratify MCI into amnestic and non-amnestic subtypes. Therefore, these results may reflect a more heterogeneous sample.

In Study 2, our hypotheses were not supported. For immediate recall, there was a trend toward a sex by diagnosis interaction driven by the MCI group where men scored higher than women. For delayed recall, there was an overall trend toward a sex by diagnosis interaction. However, in stratified analyses, sex was not a significant predictor in any diagnostic group. As the VM advantage in healthy women is well established within the literature, it is noteworthy that in this sample, women did not score higher than men in NC on either immediate or delayed recall (Aartsen et al., 2004; Herlitz et al., 1997; Kramer et al., 2003). Perhaps this finding may reflect inconsistent differences in the cognitive abilities of our NC group as women in both the overall sample and NC scored higher on the MoCA, a global measure of cognition.

Specifically, the MoCA has a total of 30 points with a cutoff score of ≥ 26 points indicating NC. While not enough to diagnose MCI, scores < 26 are indicative of cognitive impairment (Nasreddine et al., 2005). In the Study 2 cohort, NC men had an average score of 25.5 and NC women had an average score of 26.3. Based on normative data, participants within this NC sample scored at the lowest end and slightly below the set cutoff point (Nasreddine et al., 2005). These low MoCA scores may give insight as to why 1) women in the NC group did

not display a VM advantage and 2) there was a non-significant trend toward an interaction in MCI where women scored lower than men on immediate recall.

In previous studies showing a female VM advantage in MCI, the Rey Auditory Verbal Learning Test (RAVLT) was used to assess VM (Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). The RAVLT is a word list memory test while the Logical Memory and Craft Story 21 are story recall tests. Studies on sex differences in VM performance in healthy adults suggest that women employ different cognitive strategies than men. In particular, women cluster items to be remembered by semantic and phonological categories (Koren, Kofman, & Berger, 2005; Weiss et al., 2006). Thus, it is possible that word list and story recall tests elicit different types of cognitive strategies in men and women, particularly with AD-related cognitive decline. However, this would not explain the discrepancy in results between Study 1 (Logical Memory) and Study 2 (Craft Story).

It is also important to note procedural differences which may help explain our findings. Specifically, story recall assessments of VM typically involve presenting two unrelated stories, one after another. The NACC protocol only presents one story. Chapman et al. (2011) used the Logical Memory (with two stories) to assess VM and found that women scored significantly higher in NC but significantly lower in AD on both immediate and delayed recall. Additionally, the RAVLT includes five learning (immediate recall) trials. Consistently, four studies using the RAVLT have found a female advantage in MCI groups (Chapman et al., 2011; Sundermann et al., 2017; Sundermann, Biegon, et al., 2016; Sundermann, Maki, et al., 2016). Compared to multiple trials, a singular presentation of verbal information does not elicit the same proactive interference and may not be as taxing on memory systems. The amount of information needing to be encoded, consolidated, stored, and retrieved for multiple trials is quite different than one.

These differences and our results highlight the larger discussion of 1) the lack of standardization in the number of neuropsychological assessments and inconsistencies in domain-specific tests used in MCI and 2) not subdividing MCI groups based on probable etiology (i.e., AD, cerebrovascular disease, Parkinson's disease) (Diaz-Mardomingo, Garcia-Herranz, Rodriguez-Fernandez, Venero, & Peraita, 2017; Pusswald et al., 2013). Such discrepancies may be an indicator of why there is substantial heterogeneity regarding patterns of cognitive decline and the effect of sex in MCI.

Because there are not any definitive clinical tests to confirm MCI or AD, identifying variables relating to risk of cognitive decline is imperative. However, cognitive profiles and trajectories of disease between men and women may be quite heterogeneous. Our studies uncovered inconsistent results regarding the role of sex in VM performance across diagnostic groups. As previous preliminary work suggests that the effect of sex in VM may depend on magnitude of neurodegeneration within MCI and AD, future studies should aim to include such biomarker variables.

This is the first study to use local NACC UDS data to study the effect of sex on VM across the continuum of cognition from NC to AD. Our study provides further evidence for the critical need to standardize methods in the neuropsychological assessment of MCI and AD. Further, since we only included MCI and dementia participants with AD etiology, we have added to the literature regarding disease and sex-specific patterns of cognitive decline. This information is paramount to our understanding of sex differences in neurodegeneration and clinical presentation. Additionally, this information provides a preliminary understanding of the effect of using different methods for early detection of cognitive decline. Overall, the scientific and

clinical communities need to take careful consideration of the methods used and the interplay of sex differences in screening and diagnosing AD.

Limitations

We were unable to divide our MCI group into amnestic and non-amnestic MCI subtypes due to sample size. As aMCI is most indicative of future development of AD, results from subtype analyses may uncover different patterns of change between males and females. Further, we only included mild AD (CDR=1). The trajectory of deterioration for men and women may be different in moderate and severe stages of AD. Finally, we did not include biomarkers of neurodegeneration (e.g., hippocampal volume, temporal lobe glucose metabolism) in our models. However, our study adds to the preliminary body of knowledge regarding sex-specific patterns of cognitive change in the progression to AD and highlights the need for additional research to investigate our hypotheses.

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Table 1.
Study 1 Sample Characteristics.

	Total Sample *N* = 425		Diagnosis = NC *n* = 258		Diagnosis = MCI *n* = 56		Diagnosis = AD *n* = 111	
	Male *n* = 171	Female *n* = 254	Male *n* = 80	Female *n* = 178	Male *n* = 35	Female *n* = 21	Male *n* = 56	Female *n* = 55
Age	74.02* (7.09)	71.71* (7.23)	73.35* (6.27)	70.88* (6.53)	74.00* (7.14)	73.33* (7.64)	74.98* (8.13)	73.80* (8.71)
Education (years)	16.88* (3.18)	15.79* (2.82)	17.29* (2.92)	16.20* (2.85)	16.49* (3.42)	15.67* (2.48)	16.55* (3.35)	14.53* (2.52)
Total MMSE score	26.65* (3.91)	27.71* (3.47)	28.95 (1.30)	29.27 (1.06)	27.51 (1.98)	26.86 (2.87)	22.82 (4.39)	23.00 (4.35)

Note. *indicates statistical significance. AD = Alzheimer's disease; MCI = mild cognitive impairment; MMSE = Mini Mental Status Exam; NC = normal cognition, UDS = Uniform Data Set.

Table 2.
Study 2 Sample Characteristics.

	Total Sample *N* = 344		Diagnosis = NC *n* = 268		Diagnosis = MCI *n* = 22		Diagnosis = AD *n* = 54	
	Male *n* = 107	Female *n* = 237	Male *n* = 79	Female *n* = 189	Male *n* = 10	Female *n* = 12	Male *n* = 18	Female *n* = 36
Age	71.78 (5.92)	70.84 (5.58)	71.53 (5.28)	70.39 (5.11)	76.20 (5.47)	73.83 (5.10)	70.39 (7.81)	72.17 (7.46)
Education (years)	16.60 (2.68)	16.29 (5.94)	16.65 (2.60)	16.23 (2.36)	16.60 (3.69)	14.25 (2.60)	16.39 (2.52)	17.31 (14.27)
Total MoCA raw score	23.26 (5.22)	24.74* (6.46)	25.53 (2.27)	26.38* (2.18)	19.90 (4.82)	20.17 (3.19)	15.17 (5.83)	17.64 (13.38)

Note. *indicates statistical significance. AD = Alzheimer's disease; MCI = mild cognitive impairment; MMSE = Mini Mental Status Exam; NC = normal cognition, UDS = Uniform Data Set.

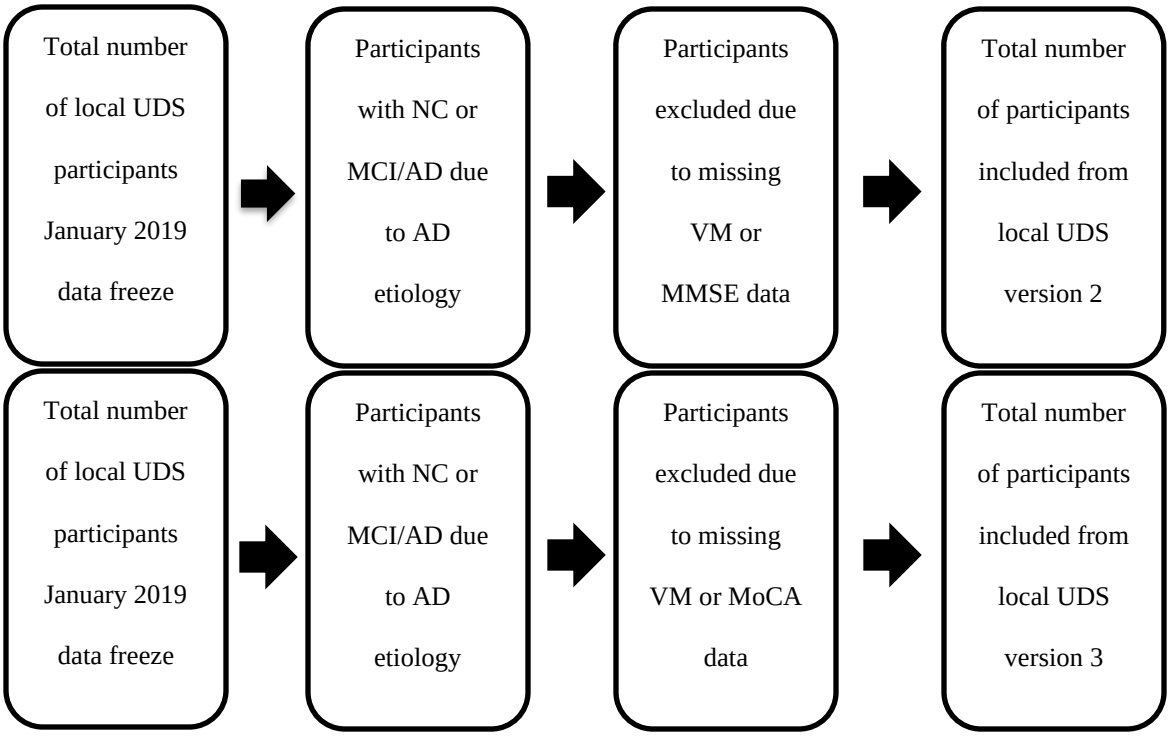

Figure 1. Sample size flow charts for Studies 1 and 2, respectively. AD = Alzheimer's disease; MCI = mild cognitive impairment; MMSE = Mini Mental Status Exam; NC = normal cognition; UDS = Uniform Data Set; VM = verbal memory.

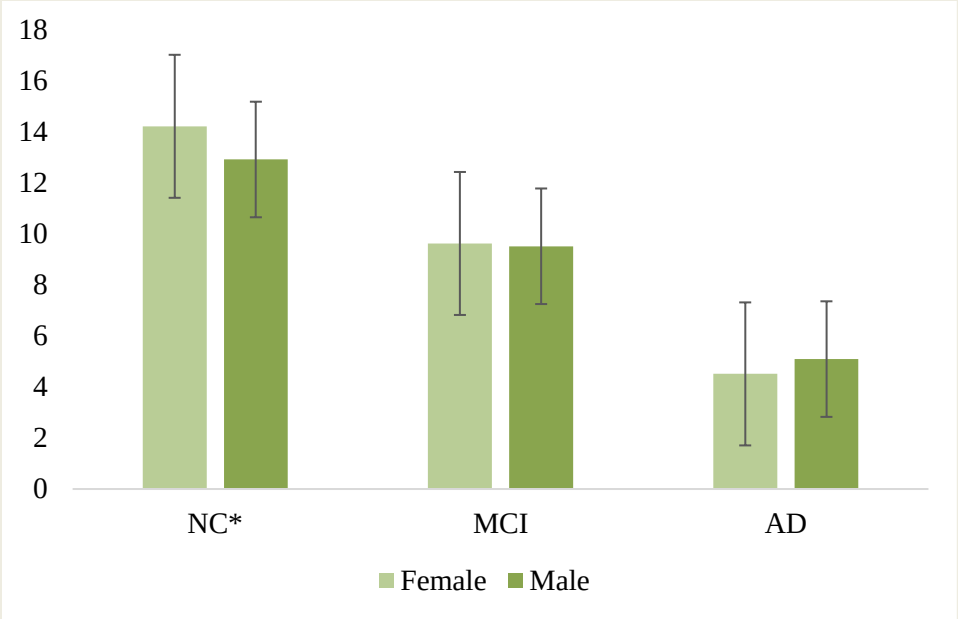

Figure 2. Bar graph displaying the effect of sex on immediate recall score of the Logical Memory test in Study 1. * indicates statistical significance. AD = Alzheimer's disease; MCI = mild cognitive impairment; NC = normal cognition.

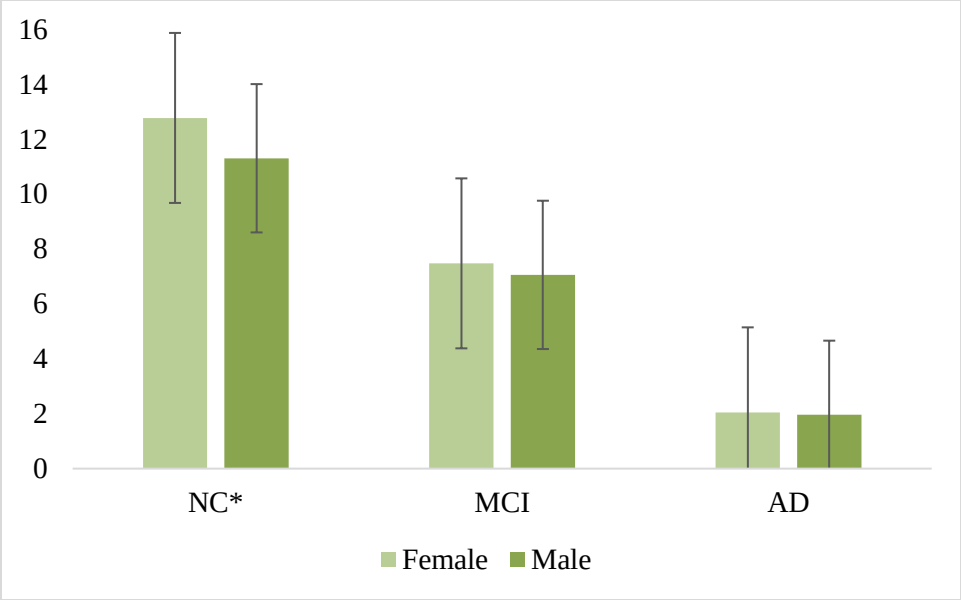

Figure 3. Bar graph displaying the effect of sex on delayed recall score of the Logical Memory test in Study 1. * indicates statistical significance. AD = Alzheimer's disease; MCI = mild cognitive impairment; NC = normal cognition.

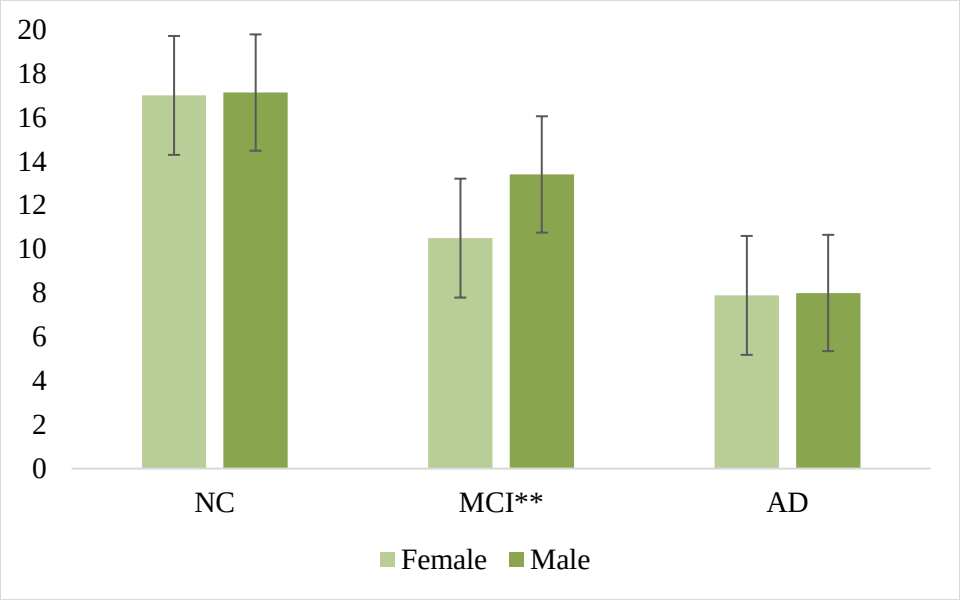

Figure 4. Bar graph displaying the effect of sex on immediate recall score of the Craft Story 21 test in Study 2. ** indicates a trend toward statistical significance. AD = Alzheimer's disease; MCI = mild cognitive impairment; NC = normal cognition.

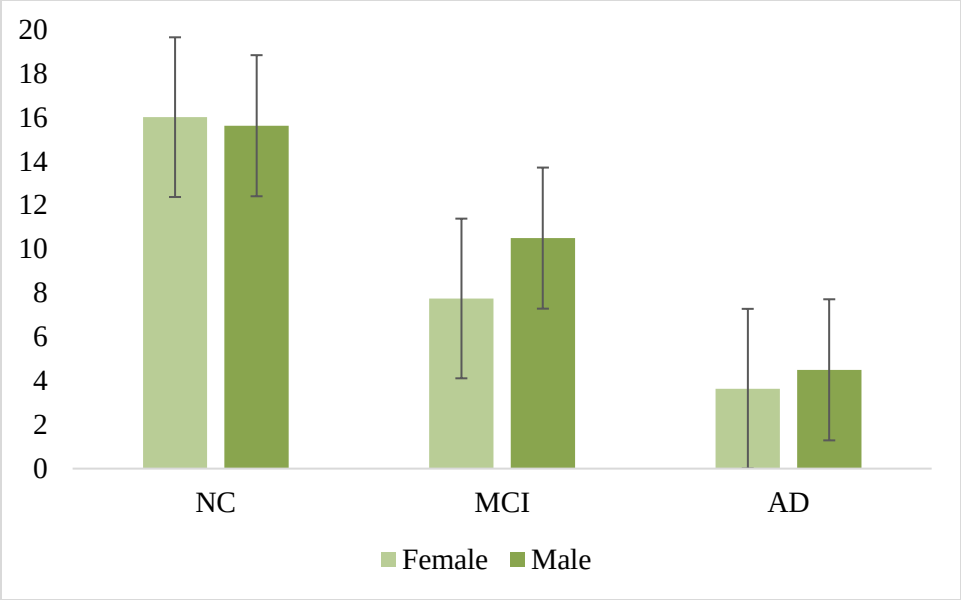

Figure 5. Bar graph displaying the effect of sex on delayed recall score of the Craft Story 21 test in Study 2. AD = Alzheimer's disease; MCI = mild cognitive impairment; NC = normal cognition.

Chapter 4: Unraveling Clusters of Influential and Sex-Specific Risk Factors in the Progression to Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting cognition and daily functioning. With increasing incidence and the prevalence of AD expected to grow by more than 14 million by 2050 in the United States, early detection of cognitive change is crucial to enhancing quality of life and outcomes (Alzheimer's Association, 2019). Early detection is particularly needed for women, who make up two-thirds of the estimated 5.8 million Americans living with AD, are typically diagnosed at later stages, and have faster rates of cognitive decline after diagnosis (Alzheimer's Association, 2019; Hebert, Weuve, Scherr, & Evans, 2013). The higher prevalence and differences in disease trajectory in women cannot solely be explained by greater longevity (Seshadri et al., 1997). While reasons for such discrepancies are not fully understood, the literature suggests that unique genetic, biological, and environmental mechanisms related to AD pathology are at play (Andrew & Tierney, 2018; Mosconi et al., 2018; Viña & Lloret, 2010).

Historically, research studies have not directly assessed the effect sex has on the etiology, presentation, and treatment outcomes of AD (Carter, Resnick, Mallampalli, & Kalbarczyk, 2012; Nebel et al., 2018). Only recently has biological sex been recognized as a significant factor related to differences in disease trajectories and phenotypes. Therefore, a significant gap exists in the literature. In fact, the Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease recently highlighted this gap by developing a list of high priority areas of research in sex and gender differences in AD (Nebel et al., 2018). Our study begins to address components from two of the priority research areas: 1) potential sex differences in genetic risk factors for AD and 2) the effects of sex differences on the clinical detection and diagnosis of AD.

If we can better understand how sex influences the risk, development, and trajectory of AD, we may be able to better identify those who are at greatest risk and improve diagnosis, clinical outcomes, and health equity for both sexes.

Regarding the trajectory of disease progression, verbal memory (VM) has been identified as a critical factor in the early detection of AD. As a decline in VM is indicative of eventual progression to AD, assessments of VM are used to screen for and diagnose AD (Albert, Moss, Tanzi, & Jones, 2001; Bondi et al., 1994; McKhann et al., 1984). Across the lifespan, women with normal cognition perform better than men on assessments of VM (Aartsen, Martin, & Zimprich, 2004; van Hooren, 2007). Emerging evidence suggests that this female VM advantage may be a form of sex-specific cognitive reserve (Beinhoff, Tumani, Brettschneider, Bittner, & Riepe, 2008).

Cognitive reserve theory suggests that those with higher levels of education, higher IQ, higher occupational complexity, and other advantageous variables possess a larger neural network which allows maintained cognitive functioning despite neuropathologic changes (Stern, 2002). However, once this fallback capacity has been depleted, such compensatory networks can no longer overcome the neuropathologic changes and a more rapid cognitive decline ensues (Stern, 2012). Due to the lifelong female advantage in VM and potential domain-specific cognitive reserve, it is important to understand the effect of sex on VM performance. Therefore, more research is needed to better identify the most influential factors for sex-specific trajectories of cognitive change leading to AD.

Mild Cognitive Impairment (MCI)

The transition from normal healthy aging to AD is gradual, involving subtle cognitive changes which occur over many years prior to diagnosis (Albert et al., 2011; Sachdev et al.,

2012). While cognitive change is strongly associated with increasing age, MCI typically indicates pathological rather than normal cognitive decline (Chen, Cheng, Lin, Lee, & Chou, 2018). In the 1990s, MCI was assumed to be a memory disorder, as only an objective decline in the memory domain was necessary for diagnosis (Petersen et al., 1999).

Since then, the research literature and clinical presentation have revealed significant heterogeneity within MCI and thus the definition has evolved (Petersen et al., 2001). Currently, there is no international consensus on the exact number of subtypes (Diaz-Mardomingo, Garcia-Herranz, Rodriguez-Fernandez, Venero, & Peraita, 2017; Petersen, 2004; Petersen et al., 2001; Petersen & Negash, 2008). However, clinicians and researchers accept that MCI includes subtypes classified by cognitive domain affected (memory, non-memory, or both), number of cognitive domains affected (single or multiple), and etiology of cognitive decline.

Subtypes based on affected cognitive domain include amnestic MCI (aMCI) and non-amnestic MCI (naMCI). aMCI involves primary impairment of episodic memory and naMCI involves primary impairment of non-memory cognitive domains (i.e., executive function/attention, language, visuospatial). Additionally, individuals may have single domain or multiple domain MCI (see Figure 1). Yet, within these subtypes of MCI, there is still significant heterogeneity that is not understood.

Understanding subtypes of MCI is critical as aMCI is predictive of future development of AD while naMCI is indicative of other types of pathology (Albert et al., 2011; Twamley, Ropacki, & Bondi, 2006). Many individuals have characteristics of both aMCI and naMCI , providing evidence that individual disease trajectories are far from linear (Sachdev et al., 2012). Thus, there is a need to better understand the various subtypes of MCI. Assessing cognition,

disease severity, daily functioning, depressive symptoms, and etiology of disease are all important diagnostic components and will facilitate further characterization of MCI subtypes.

Cognition. Episodic memory is the ability to learn and retain new information and a key component affected in aMCI (Pleizier et al., 2012). While episodic memory incorporates both verbal and non-verbal memory, VM assessments are better at differentiating AD from other types of dementias (e.g., frontotemporal dementia). Thus, VM assessment is a central marker in detecting aMCI and differentiation of dementia type (Albert et al., 2011; Pleizier et al., 2012). Though VM is important, it is essential to assess the function of other cognitive domains due to the heterogeneity in early cognitive presentation.

Other cognitive domains which may be impaired in aMCI include executive function/attention, language, and visuospatial skills. Studies have reported that significant impairment in tasks requiring executive functions and attentional control are indicative of preclinical AD and may be reliable predictors of future progression to AD (Perry & Hodges, 1999; Rapp & Reischies, 2005). In the earliest stages of AD, language impairment is subtle and becomes progressively impaired (Verma & Howard, 2012). Visuospatial skills, such as driving and spatial navigation, can become severely impaired in AD and affect independence of daily functioning (Pai & Jacobs, 2004). While there may be significant heterogeneity within the presentation of cognitive profiles in aMCI, the literature indicates that cognitive domains are interconnected and non-memory domains may rely on memory systems to function normally (Mapstone, Steffenella, & Duffy, 2003; Verma & Howard, 2012).

While global assessment of cognition is important for a general snapshot of cognitive function and care planning, researchers and clinicians agree that in-depth neuropsychological assessment is an essential part of MCI diagnosis (Klekociuk, Summers, Vickers, & Summers,

2014; Petersen et al., 2014). Unfortunately, the lack of standardization regarding which domains should be assessed and which domain-specific tests should be used makes comparison across studies difficult and further complicates our understanding of distinct features of MCI subtypes (Petersen et al., 2014; Pusswald et al., 2013). Thus, for early detection to be most effective, it is imperative to identify specific features of aMCI subtypes.

Disease severity, daily functioning, and depressive symptoms. Other factors associated with aMCI include but are not limited to severity of disease, ability to function independently, and depressive symptoms (Albert et al., 2011; Morris, 1993). These variables are particularly important as they demonstrate the interconnected relationships among cognition, functional abilities, and emotional state. As disease severity progresses, so, too, does a decline in the ability to function independently, which may also influence mood (Diaz-Mardomingo et al., 2017).

Etiology. Etiology and clinical presentation are essential to the differentiation of MCI subtypes. Categories of etiology include degenerative, vascular, traumatic, psychiatric, or other causal nature (Albert et al., 2011). MCI may be a precursor to dementia of varied etiologies, including but not limited to AD, vascular dementia, frontotemporal dementia, and Parkinson's disease. It is important to note that individuals may have mixed etiology dementia, thus further complicating early diagnosis as there may be considerable overlap in clinical and pathological features of subtypes of MCI (Albert et al., 2011). Currently, the only way to definitively determine Alzheimer's dementia etiology is on post-mortem autopsy (Braak & Braak, 1991; Markesbery, 1997). Because there is no in vivo objective test to definitively determine etiology of MCI, comprehensive assessment and synthesis of all available information is imperative.

Biomarkers of AD

In addition to functional and clinical presentation, inclusion of genetic and neuropathologic biomarkers increases diagnostic and etiological accuracy, particularly in cases of atypical cognitive presentation (Petersen et al., 2009). The two hallmark biomarkers of AD include intracellular neurofibrillary tau tangles and extracellular amyloid-β (Aβ) plaques (Jack et al., 2013; Yankner, 1996). The initial formation of tau and Aβ buildup, causing neuronal injury and atrophy, are found within the medial temporal lobe (Lupton et al., 2016). Neurodegeneration within the medial temporal lobe is the earliest degenerative marker of AD (Braak & Braak, 1991). In particular, hippocampal volume (HV) decline is apparent in aMCI and is strongly associated with a decline in VM abilities (Jack et al., 2013; Likeman et al., 2005). As early detection is key to improving outcomes, assessing HV in the presence of other biomarkers may give insight into profiles of greatest risk for progression to AD.

The apolipoprotein E-ε4 (APOE-ε4) allele is the strongest identified genetic risk factor for AD (Farrer et al., 1997; Genin et al., 2011; Lupton et al., 2016). In MCI and AD, research demonstrates that APOE-ε4 carriers have smaller HVs and more cognitive decline than non-carriers; however, the same associations are not found in healthy adults (Hohman et al., 2018; Hostage, Roy Choudhury, Doraiswamy, & Petrella, 2013). This lack of a relationship in healthy adults suggests a disease-specific interaction of genetic and degenerative processes.

Through genome wide association studies, triggering receptor expressed on myeloid cells 2 (TREM2) has been recently identified as another genetic risk factor for AD (Jay, von Saucken, & Landreth, 2017; Jonsson et al., 2013). TREM2 is a distinct biomarker as it is associated with the immune system. Relative to AD, preliminary evidence suggests that TREM2 becomes activated once the neurodegenerative process has begun, promoting debris clearance of Aβ plaques and lipoproteins (Yeh, Wang, Tom, Gonzalez, & Sheng, 2016). New research to better

understand how TREM2 functions in the presence of AD pathology has used measures of soluble TREM2 in the cerebrospinal fluid (CSF) as a surrogate marker for upregulation of TREM2 activity in the brain (Suárez-Calvet et al., 2016). A study by Ewers et al. (2019) suggests that this upregulation of scavenging activity may act in a protective manner, subsequently leading to slower cognitive decline and neurodegeneration in the context of AD.

The inclusion of multiple genetic and degenerative biomarkers in studies of aMCI has been limited. The failure to include these biomarkers and assess their relationship to cognitive markers (e.g., VM) may be another factor contributing to the lack of understanding of the heterogeneity within MCI (Albert et al., 2011). Simultaneously assessing early biomarkers and cognitive markers of AD may further elucidate the temporal evolution of neurodegenerative changes which are associated with the onset and progression of cognitive and functional symptoms.

Sex Differences in MCI and AD

As stated above, women are disproportionately affected by AD. Across the lifespan, women have about a 12% lifetime risk of developing AD whereas men only have about a 6% risk. This increased risk is not solely due to the greater longevity of women (Seshadri et al., 1997). Interestingly, men are more likely to be diagnosed with MCI. Though the reasons for such differences are not fully understood, the literature suggests that the increased risk and varying disease trajectories are due to biological and genetic variations, as well as differences in life experiences (Andrew & Tierney, 2018; Mosconi et al., 2018; Viña & Lloret, 2010). Better understanding of the underlying biological differences and sex-specific patterns of cognitive change will reduce the risk of progression to AD by improving early clinical detection and diagnosis.

As described previously, a decline in VM is tightly associated with AD and is a significant factor in the clinical diagnosis of aMCI (Albert, Moss, Tanzi, & Jones, 2001; McKhann et al., 1984). While more studies are needed, preliminary evidence suggests that as aMCI progresses, women's cognitive reserve and VM advantage may become depleted, leading to a more rapid cognitive decline later (Sundermann et al., 2017; Sundermann et al., 2016). In contrast, men's steady cognitive decline may be more easily detected earlier in aMCI and before progression to AD. These differences in VM trajectories may help begin to explain why there is a higher incidence of MCI in men and AD in women.

Aside from VM, sex differences in other cognitive domains during aMCI are largely unstudied. Though some studies have assessed sex differences in executive function/attention, language, and visuospatial skills in MCI, results are inconsistent and likely due to the heterogeneity of etiologies within MCI (Beinhoff, Tumani, Brettschneider, Bittner, & Riepe, 2008; Elosúa, Ciudad, & Contreras, 2017; Laws, Adlington, Gale, Moreno-Martínez, & Sartori, 2007). Because of the association between VM systems and other cognitive domains, it is necessary to understand how men and women are differentially affected and how these differences can be detected at their earliest stages.

Research on sex differences in APOE-ε4 and HV in AD have recently received attention. The correlation between APOE-ε4 and AD may be stronger in women compared to men, suggesting more deleterious effects of APOE-ε4 on hippocampal atrophy (Fleisher et al., 2005). Sundermann et al. (2016) found that in aMCI, women with greater atrophy performed poorer on measures of VM than women with low to moderate levels of atrophy. However, magnitude of hippocampal degeneration did not matter in men. Taken together, the relationship between sex and memory function may be dependent upon genetic and neurodegenerative factors.

As TREM2 has only been recently identified as an important biomarker in AD, to our knowledge, there have not been any studies assessing TREM2 sex differences in humans. Recently, Stephen et al. (2019) assessed the effects of sex and APOE-ε4 genotype on TREM2 activation and clearance of Aβ plaques in mouse models of AD. They found the poorest outcomes in APOE-ε4 carriers and female mice. Clearly more research is needed to understand the modulating effect of sex related to the various biomarkers of aMCI and AD and their impact on clinical features.

It is imperative to further describe the sex-specific risk profiles in aMCI, particularly since sex-specific risk factors and outcomes have been reported in other health conditions, including stroke and cardiovascular diseases (Gerber, Weston, Killian, Jacobsen, & Roger, 2006; Petrea et al., 2009). As the progression to AD is multifactorial, simultaneous assessment of influential variables may provide more comprehensive general and sex-specific profiles of aMCI. If we understand how sociodemographic, clinical, cognitive, and biomarker variables combine into different subtypes of aMCI with probable AD etiology (aMCI-AD) while assessing the influence of sex, we will be able to better identify risk trajectories of decline and which risk trajectories are more likely based on sex. The purpose of this study is to use a large, multicenter sample of individuals with aMCI-AD to investigate if there are subtypes of risk profiles based on sex, sociodemographic, clinical, cognitive, and biomarker variables. The primary research question is: Among individuals with aMCI-AD, how do sex, sociodemographic (age, education), clinical (dementia severity, daily functioning, depressive symptoms), cognitive (global cognitive function, memory, executive function/attention, language, visuospatial skills), and biomarker (HV, APOE-ε4, soluble TREM2) characteristics group by subtypes?

Methods

Sample and Recruitment

Cross-sectional data on participants with aMCI-AD were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). ADNI is a multisite, longitudinal cohort study that began in 2003 as a public-private partnership. ADNI's main goals are to test whether clinical, neuropsychological, imaging, and biomarker assessments can be combined to measure progression to AD. To date, ADNI has four protocols: ADNI-1, ADNI-GO, ADNI-2, and ADNI-3. ADNI recruits and enrolls people with normal cognition, aMCI, and AD, and their diagnostic criteria are based on the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984; Petersen et al., 2010). The Institutional Review Boards of all sites participating in the ADNI provided review and approval of the ADNI data collection protocol. Written informed consent was obtained from all participants and all data were deidentified.

Measures

Sex, age, and level of education were assessed by self-report. Table 1 displays the clinical, cognitive, and biomarker variables, how they were assessed, and a brief description of the assessment and scoring procedures.

Clinical variables. Clinical variables included the Clinical Dementia Rating (CDR), Functional Assessment Questionnaire (FAQ), and Geriatric Depression Scale (GDS). CDR scores were collapsed into three categories for analysis: low, moderate, and high, with higher scores indicating greater dementia severity. Higher scores on the FAQ indicate less independence in ADLs. Higher scores on the GDS indicate a greater number of depressive symptoms.

Cognitive variables. Scores on assessments from each cognitive domain and global cognition were included to give a holistic picture of cognitive functioning, as well as to understand domain-specific deficits. Cognitive assessments included the Mini-Mental Status Exam (MMSE), Rey Auditory Verbal Learning Test (RAVLT) immediate and delayed recall, Trails B, Category fluency (Animals), and Clock drawing and copy. Higher scores on Trails B indicate poorer performance. Higher scores on all other cognitive assessments indicate better performance.

Biomarker variables. APOE-ε4 carrier status, HV, and soluble TREM2 concentration were included as biomarker variables. APOE-ε4 was dichotomized into carriers and non-carriers. To control for sex differences in head size, we calculated a HV ratio using the formula, hippocampal/intracranial volume x 10^3 (HpVR) (Sundermann et al., 2016; Sundermann, Tran, Maki, & Bondi, 2018). Due to the large variance across participants, soluble TREM2 values were standardized before analysis.

Data Analysis

We used Latent Class Analysis (LCA) to address our research question. LCA is a type of mixture modeling that analyzes latent classes, or subtypes, of a heterogeneous population that are unknown (Kline, 2016). The aim of LCA is to find clusters or groups of individuals with similar characteristics to parse the heterogeneity of populations (Muthén, 2002). Class membership is determined by patterns of observed indicators and each participant is assigned to the latent class to which the largest posterior probability is calculated (Muthén & Muthén, 2017). We used Mplus Version 8.3 for the analysis (Muthén & Muthén, 2017).

We completed the following six steps when selecting a model and class solutions: 1) determine the best fitting model by analyzing fit statistics, including the Loglikelihood (LL),

Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample size-adjusted BIC (SABIC); 2) analyze entropy, which follows a continuum from zero to one where values >.80 indicate that the latent classes are highly discriminating; 3) compare models using the Bootstrapped Likelihood Ratio Test (BLRT), Vuong-Lo-Mendell-Rubin likelihood (VLMR), and Lo-Mendell-Rubin (LMR) adjusted test; 4) examine the percentage of individuals in each class to ensure all classes included more than 5% of the sample (McCutcheon, 1987; Nylund, Asparouhov, & Muthén, 2007); 5) ensure the mean conditional probability scores (how closely a participant fits their class) for each latent class were greater than 70%; and 6) compare the results of each model to previous research for meaningful theoretical interpretation.

Results

We examined the number of latent classes based on sex, sociodemographic, clinical, cognitive, and biomarker variables. Our final sample included adults (n = 1124), ages 54-95 (M = 73.64, SD = 7.72), from protocols ADNI-1 (n = 463), ADNI-GO (n = 128), ADNI-2 (n = 394), and ADNI-3 (n = 139). We compared the LCA fit statistics for one, two, three, four, and five class solutions (see Table 2) and chose the four-class solution. This model had the most meaningful clinical interpretability (groups were highly differentiated) and the lowest values for the information criteria and loglikelihood (AIC = 73127.15, BIC = 73549.22, SABIC = 73282.41, LL = -36479.57) while considering both the Bootstrap LRT (p = 0.000) and Vuong-Lo-Mendell-Rubin LRT (p = 0.0001), showing the four-class model fit significantly better than the three-class model. The five-class model was not selected because it showed over-extraction and contained a class representing less than 5% of the sample. However, the five-class model was not a worse fit than the four-class model according to the Bootstrap LRT (p = 1.000) and Vuong-Lo-Mendell-Rubin LRT (p = 0.24).

Mean conditional probabilities for the four-class solution ranged from 0.91-0.94. The four classes included: LC1, *Global Decliners* (e.g., due to their low status across all indicators); LC2, *Maintainers* (e.g., due to their overall stable status across all indicators); LC3, *Cognitive Reservers* (e.g., due to having the youngest and most educated sample in addition to their higher status across all indicators); and LC4, *Functional Decliners* (e.g., due to their decreased independence in ADLs and most severe staging of dementia). The sociodemographics and characteristics of the sample are shown in Table 3.

LC1 (*Global Decliners*; *n* = 127; 11.3%) was characterized by the oldest adults (*M* = 75.73, *SD* = 7.36), predominantly male (64.5%), lower levels of education (*M* = 14.77, *SD* = 3.46), and more likely to be APOE-ε4 carriers (59.0%). Compared to the other classes, LC1 had poorer scores on most measures of cognitive performance, including global cognition, VM immediate recall, executive function/attention, language, visuospatial skills, and the 2nd lowest VM delayed recall scores. LC1 also had the 2nd least independence with ADLs (i.e., FAQ scores), moderate dementia severity rating (i.e., CDR), the 2nd fewest depressive symptoms (i.e., GDS scores), the 2nd smallest HV (i.e., HpVR), and the highest soluble TREM2 concentrations.

LC2 (*Maintainers*; *n* = 613; 54.5%) was slightly younger than LC1 (*M* = 74.77, *SD* = 7.39), predominantly male (62.6%), had higher levels of education compared to LC1 and LC4 (*M* = 15.99, *SD* = 2.64), and less likely to be APOE-ε4 carriers (46.9%). Compared to the other classes, LC2 had moderate cognitive performance, including the 2nd greatest global cognition, VM immediate and delayed recall, language, and visuospatial skills scores, and the 2nd poorest executive function/attention scores. LC2 had the 2nd greatest independence with ADLs, the least severe staging of dementia, the fewest depressive symptoms, the 2nd largest HV, and the 2nd lowest soluble TREM2 concentrations.

LC3 (*Cognitive Reservers*; *n* = 240; 21.4%) was the youngest latent class of the four (*M* = 69.33, *SD* = 7.27), the only class that was predominantly female (56.9%), had the highest levels of education (*M* = 16.88, *SD* = 2.37), and was less likely to be APOE-ε4 carriers (39.4%). Compared to the other classes, LC3 had the highest performance on all cognitive assessments. LC3 had the greatest independence with ADLs, the least severe staging of dementia, the most depressive symptoms, the largest HV, and the lowest soluble TREM2 concentrations.

LC4 (*Functional Decliners*; *n* = 144; 12.8%) was characterized by the 2nd youngest adults (*M* = 74.19, *SD* = 7.58), more likely to be male (65.0%), had the 2nd lowest levels of education (*M* = 15.70, *SD* = 2.80), and more likely to be APOE-ε4 carriers (64.4%). Compared to the other classes, LC4 had the 2nd poorest global cognition, executive function/attention, VM immediate recall, language, and visuospatial skills, and the poorest VM delayed recall scores. LC4 also had the least independence with ADLs, the most severe staging of dementia, the 2nd most depressive symptoms, the smallest HV, and the 2nd highest soluble TREM2 concentrations. Class profiles and distributions are illustrated in Figures 2-4.

Discussion

National panels of Alzheimer's experts, including scientists and clinicians, have reinforced the importance of early identification of AD-related cognitive changes in order to improve outcomes (Nebel et al., 2018). Without a definitive clinical diagnostic test for AD, identifying subtypes of aMCI based on clinical presentation is an optimal strategy to prevent or slow disease progression and provide individualized care. We investigated subtypes of aMCI-AD based on sex, sociodemographic, clinical, cognitive, and biomarker variables. While previous studies have assessed only one (e.g., cognition) or two (e.g., neuropsychiatric and cognition) indicators of aMCI subtypes, our model encompassed multiple indicators, including early

biomarkers to assess the relationship among the sociodemographic, functional, and, in particular, cognitive markers (Peraita, Chacón, Díaz-Mardomingo, & Martínez-Arias, 2015; Ezzati, Zammit, Habeck, Hall, & Lipton, 2019; Hanfelt et al., 2011). Our study parsed out the significant variability within the aMCI-AD population and revealed four subtypes. Interestingly, only one of the four subtypes included a higher female to male ratio. To our knowledge, this is the first study to include biological sex as a direct indicator within the modeling process.

Subtype Differentiation

Current diagnostic guidelines state that aMCI must involve primary decline in the memory domain, although other cognitive domains may be affected (Albert et al., 2011). Previous literature has demonstrated that VM is tightly associated with aMCI and AD (Albert, Moss, Tanzi, & Jones, 2001; McKhann et al., 1984). However, our results suggest that memory is not the sole differentiating cognitive domain. Specifically, the domains which most differentiated the groups were global cognition, VM immediate recall, language, and visuospatial skills. These findings highlight that many patients have characteristics of multiple domain aMCI. Furthermore, individual disease trajectories and the daily needs of those with aMCI may be quite variable. Therefore, it is imperative that clinicians understand the multiple characteristics associated with aMCI and incorporate a holistic approach rather than relying on assessments of VM for screening, diagnosis, and treatment.

***Global Decliners*, LC1.** LC1 was more likely to be male and displayed the poorest cognitive functioning, in addition to lower clinical and functional status compared to all other latent classes. This subtype also had distinct sociodemographic characteristics, such that they were the oldest and had the fewest years of education. Based on the cognitive reserve theory and their sociodemographic characteristics, it is not surprising that this subtype had the least

favorable overall cognitive profile and were more likely to be APOE-ε4 carriers. That is, APOE-ε4 carriers with MCI and AD have been shown to have more cognitive decline than non-carriers, in addition to having smaller HVs (Hohman et al., 2018; Hostage et al., 2013).

Additionally, this subtype had the lowest VM performance, particularly on immediate recall, the smallest HpVR, and increased levels of soluble TREM2 concentrations. As Ewers (2019) found that soluble TREM2 is associated with memory, APOE-ε4, and HV, this subtype's upregulation of soluble TREM2 may suggest further progressed neuropathology compared to the other subtypes. Additionally, it is interesting that this group reported the second least number of depressive symptoms compared to other classes. It is possible that their lower level of cognitive function may influence insight, as has been shown in other neurodegenerative disease (Banks & Weintraub, 2008; Marczinski, Davidson, & Kertesz, 2004). Thus, participants in LC1 may not have adequate insight to identify depressive symptoms.

Compared to the other latent classes, this subtype included the least number of participants. Consequently, it is possible that individuals in this subtype are not as readily identified by clinicians. Because of their sociodemographic characteristics and poorer profile across indicators, they may need more ongoing support and screening for change over time. Additionally, this subtype may require additional and intensive supports for daily functioning, such as personal care assistance. If individuals are living alone, they may need extra assistance with home making and may benefit from assisted living residency or more frequent surveillance for decline.

***Maintainers,* LC2.** LC2 was more likely to be male and displayed a maintained status across all indicators. Of all male-dominant subgroups, LC2 had the highest level of education and was less likely to be APOE-ε4 carriers. Further, compared to LC1 and LC4, this subtype

reported the least number of depressive symptoms, had the greatest VM performance, had larger HpVR, and had the lowest soluble TREM2 concentrations. These results provide evidence to support Ewers (2019) findings that less neurodegeneration in the region of the brain most associated with memory is associated with less upregulation of the brain's immune system. LC2's risk profile was most similar to the female-dominant subtype, LC3. However, in comparison, LC2's performance was poorer across all indicators, providing evidence that male and female risk profiles may vastly differ in level of performance.

Based on the relatively maintained clinical and functional status, LC2 may require less frequent monitoring from healthcare providers. Comparatively, their overall status is more stable than the other subtypes. Individuals in this subtype may benefit from recurrent assessment and intermittent visits from family or home health providers. While not intensive, periodic and consistent check-ins may allow for more sensitive detection of cognitive changes, which may require more in-depth health services or treatments. Additionally, cognitive stimulation, physical exercise, and nutrition programs may be optimal preventive strategies for this subtype.

***Cognitive Reservers,* LC3.** LC3 differed from the other subtypes as it was the only subtype more likely to be female and had the greatest performance across all indicators. This subtype was also the youngest, had the highest level of education, and was less likely to be APOE-ε4 carriers. In comparison to the other subtypes, their larger HpVR was likely associated with their greater performance on the measures of VM, particularly immediate recall, and lowest soluble TREM2 concentrations. As this subtype had the largest HpVR, their greater memory performance was expected (see Figure 5).

Interestingly, LC3 reported the greatest number of depressive symptoms yet maintained the highest cognitive and functional status. Previous studies have found that women are more

likely to report internalized symptoms (e.g., depressed or crying mood) and men are more likely to report externalized symptoms (e.g., anger or substance abuse; Mahalik & Rochlen, 2006; Price, Gregg, Smith, & Fiske, 2018). Questions included in the GDS are more focused on internalized depressive symptoms, which may be why this group scored higher. Further, a recent review noted that increased risk of depression in women may stem primarily from biological sex differences (Albert, 2015). Perhaps depressive symptoms affect men and women's cognitive functioning differently.

While LC3 displayed higher clinical, functional, cognitive statuses and a more favorable biomarker profile, their need for close monitoring and educational resources should not be overlooked. In fact, this subtype may need more frequent monitoring, as their characteristics may be less salient compared to the other latent classes. Families should be alert for subtle changes over time, otherwise symptoms may go undetected. Like LC2, intermittent check-ins may be beneficial to detect more subtle changes over time and facilitate seeking treatment in a timely manner. Cognitive stimulation, physical exercise, and nutrition programs may also be beneficial preventive measures for this subtype.

***Functional Decliners*, LC4.** LC4 was similar to LC2 across sociodemographic and cognitive characteristics. However, LC4 was differentiated by functional and biomarker characteristics. Specifically, LC4 displayed the lowest overall functional status and the least favorable biomarker profile, having the smallest HpVR and more likely to be APOE-ε4 carriers.

As functional independence affects patient and family quality of life, this subtype may need increased support and monitoring over time. Such additional care may include referrals to occupational therapists, psychologists, and other healthcare providers. These resources may facilitate increased independence and provide education for families to optimize quality of life.

As we have demonstrated, assessing more than VM is important in characterizing and differentiating profiles of aMCI. Clinically, these results have important implications. If resources or insurance do not allow for biomarker assessment, neuropsychological assessment can be the first line of screening. However, based on the Medicare Annual Wellness Visit guidelines, current clinical practices most commonly utilize assessments of global cognition to screen for and track cognitive decline over time (Borson, Scanlan, Watanabe, Tu, & Lessig, 2006; Cordell et al., 2013). However, it may be most beneficial to assess global cognition in addition to VM, language, and visuospatial skills. While adding these assessments to a standard of care visit requires more time, patients will benefit as clinicians will have a more comprehensive baseline of cognition and individualized needs for support can be addressed efficiently. Further, families will gain more detailed information about individual cognitive changes that may indicate disease progression.

Sex Differences

As we have discussed, sex may affect the presentation and outcomes in the progression to AD. Previously, other studies have either not explored the effect of sex or used sex as a covariate predictor after model selection to assess whether it had an indirect effect on the latent classes (Hanfelt et al., 2011; Sachdev et al., 2012). Our method allowed for direct assessment of the influence of sex within the modeling. LC3 was the only subtype with a greater percentage of females and displayed overall greater performance across all indicators. These characteristics provide evidence that women may have a form of cognitive reserve, allowing them to maintain greater functioning until later stages of neuropathology.

Women may have more subtle changes and may not experience challenges with ADLs until their disease is more progressed. Further, women may be more at risk of problems, such as

managing finances and avoiding scams due to subtle changes in judgement while maintaining ADLs. In addition, as the *Cognitive Reservers* reported the greatest number of depressive symptoms, women may benefit from extra social supports in the community to avoid social isolation. Finally, the "protective" effect of education may need to be considered by adjusting thresholds (e.g., cutoff points for further testing or diagnosis) on clinical, cognitive, and biomarker assessments in those with advanced education, particularly women.

Finally, as women are less likely to be diagnosed with MCI, it is conceivable that women in the ADNI cohorts categorized as normal may actually have aMCI and are overlooked due to their cognitive reserve. If clinicians can better identify this distinct profile of characteristics earlier, they may begin to prevent women's poorer prognoses (Gao, Hendrie, Hall, & Hui, 1998; Tschanz et al., 2011). Taken together, these sex-specific findings begin to address the Society for Women's Health Research Interdisciplinary Network on Alzheimer's Disease's research priority regarding the effects of sex differences on the clinical detection and diagnosis of AD.

Implications for Future Research

Soluble TREM2 concentrations were indirectly related to cognitive, and to some degree, functional status. Thus, we provide evidence supporting Ewers' (2019) findings that upregulation of the immune system may be connected to cognitive and biomarker indicators of AD. Markers of soluble TREM2 warrant future investigation as they may have implications for the development of targeted therapies.

Additionally, understanding treatment response of each subtype may help inform which specific resources each latent class benefits from the most. Having this deeper understanding will also help prevent progression, as well as screen for and detect aMCI-AD across subtypes. In turn, these strategies will inform precision medicine methodologies. Finally, by understanding the sex-

specific subtypes of aMCI-AD, we may better tailor early interventions for the aMCI-AD population.

Strengths and Limitations

This study is innovative as it is the first to directly assess the effect of sex on latent class modeling and include more than two indicators of overall status. Further, this study expands upon the first study to explore soluble TREM2's relationship with cognitive outcomes in early AD and how the brain's immune system may be reflected in cognitive functioning and biomarkers of AD. Because of our comprehensive design and stringent exclusion of aMCI with etiologies other than AD, our results help parse out the heterogeneity of the clinical syndrome.

Our study is not without limitations. Only 46% of sample had soluble TREM2 data available. However, Mplus utilizes full information maximum likelihood estimation within LCA to handle large amounts of missing data (Muthén & Muthén, 2017). Further, our design is cross-sectional. Longitudinal analysis would give insight into disease trajectories of risk profiles over time.

Conclusion

This study has provided a preliminary explanation for the heterogeneous phenotypes of aMCI-AD. Our results demonstrate that this population has various subtypes and multiple dimensions should be considered to increase sensitivity for screening and diagnosis of early AD. Further, our study suggests that men and women may have distinct risk profiles and variables other than memory are important in distinguishing among patients with aMCI-AD. As the four subtypes possess different characteristics, clinicians may consider incorporating individualized recommendations based on subtype into care plans to optimize quality of life. Finally,

information learned from this study will help advance clinical practice and aid in tailoring early interventions to meet the diverse needs of the aMCI-AD population.

Tables and Figures

Table 2.
Clinical, Cognitive, and Biomarker Variables

Variable	Assessment Name	Brief Description of Assessment	Scoring of Assessment
Clinical			
Severity of dementia	CDR	The CDR is used as a measure of severity of dementia with a score of 0 indicating normal cognitive functioning, 0.5 MCI, 0.5 or 1 mild AD, 2 moderate AD, and 3 severe AD.	The CDR includes six independent domains of function. The ratings of degree of impairment obtained on each of the six categories of function are synthesized into one global rating of dementia (ranging from 0 to 3), which is referred to as CDR sum of boxes (Morris, 1993).
Functional assessment	FAQ	The FAQ is based on an interview with a caregiver or qualified partner and a subject is rated on their ability to carry out ten complex activities of daily living: 1) manage finances, 2) complete forms, 3) shop, 4) perform games of skill or hobbies, 5) prepare hot beverages, 6) prepare a balanced meal, 7) follow current events, 8) attend to television programs, books or magazines, 9) remember appointments, and 10) travel out of the neighborhood.	Each activity is rated as 0 (does without difficulty), 1 (needs frequent advice or assistance), or 2 (someone has taken over the activity). Scores are summed across items to provide a total disability score (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982).
Depressive symptoms	GDS	The GDS is a self-report scale designed to identify symptoms of depression in the elderly.	One point is given for each appropriate positive or negative answer indicative of a symptom of depression, for a possible total of 15 points (Sheikh & Yesavage, 1986).

Cognitive

Global cognition	MMSE	The MMSE is a structured screening instrument of global cognition frequently used in AD clinical trials. The MMSE evaluates orientation to place, orientation to time, immediate and delayed recall, attention and concentration, language, and visual construction.	Scores from each domain are added together for a total score ranging from 0 to 30 with lower scores indicating poorer performance and greater cognitive impairment (Folstein, Folstein, & McHugh, 1975).
Memory	RAVLT	The RAVLT is a list learning verbal memory task. On each of five learning trials, 15 unrelated words (all nouns) are presented orally at the rate of one word per second and immediate free recall of the words is elicited.	The number of correctly recalled words on each trial is recorded. Following a 20-minute delay filled with unrelated testing, free recall of the original 15-word list is elicited. The total possible score is 75 points for immediate recall and 15 points for delayed recall (Rey, 1964).
Executive function/attention	Trails Making Part B	This assessment consists of 25 circles, either numbered (1 through 13) or contain letters (A through L). The subject must draw a line connecting the circles while alternating between numbers and letters in an ascending order (e.g., A to 1; 1 to B; B to 2; 2 to C) as quickly as possible. Trails Making Part B requires considerable cognitive flexibility in shifting from number to letter sets under time pressure.	The time to complete the assessment (300 second maximum) is the primary measures of interest with higher scores indicating poorer performance (Reitan, 1958).
Language	Category fluency (Animals)	In this measure of verbal fluency, the subject is asked to generate examples from a semantic categories (animals) in successive one-minute trials.	The primary performance measure is the number of correct, unique examples generated for the category (Butters, Granholm,

			Salmon, Grant, & Wolfe, 1987).
Visuospatial skills	Clock drawing and copy	The subject is given a blank sheet of paper and instructed to "Draw a clock, put in all of the numbers, and set the hands for 10 after 11." After that task is completed, the "copy" condition ensues in which the subject attempts to copy a drawing of a clock with the hands set at ten past eleven.	A quantitative score (maximum total score = 10) is derived for each drawing (Cahn et al., 1996).
<u>Biomarker</u>			
HV	Structural MRI	HV was assessed via structural MRI on a 1.5T scanner according to a standardized protocol (Jack et al., 2008). HV data were analyzed using FreeSurfer version 4.3 or 5.1 (https://surfer.nmr.mgh.harvard.edu) at the University of California-San Francisco (Hsu et al., 2002). To control for sex differences in head size, we calculated a HV ratio, hippocampal/intracranial volume x 10^3 (HpVR) (Sundermann et al., 2016; Sundermann et al., 2018).	
APOE-ε4 genotype	Blood analysis	APOE-ε4 genotyping was performed at the University of Pennsylvania (Alzheimer's Disease Neuroimaging Initiative, 2017). Specific APOE-ε4 genotyping is described in detail at http://www.adni-info.org. For the purposes of our study, subjects were categorized as carriers if they possessed at least one ε4 allele and non-carriers if they did not possess any ε4 alleles.	
Soluble TREM2	CSF analysis	CSF was analyzed by ADNI for soluble TREM2 levels using the MSD ELISA (Haass Group) protocol with minor changes. Detailed information about the soluble TREM2 assays can be found at http://adni.loni.usc.edu (Alzheimer's Disease Neuroimaging Initiative, 2017).	

Note. APOE-ε4 = apolipoprotein E; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale; HV = hippocampal volume; MMSE = Mini-Mental Status Exam; MRI = magnetic resonance imaging; RAVLT = Rey Auditory Verbal Assessment Test; TREM2 = triggering receptor expressed on myeloid cells 2.

Table 3.
LCA Model Fit Statistics

	One Class	Two Class	Three Class	Four Class [a]	Five Class [b]
LL	-37967.78	-37125.82	-36735.04	-36479.57	-36164.72
AIC	75995.56	74347.64	73602.09	73127.15	72533.44
BIC	76146.30	74588.82	73933.72	73549.22	73045.96
SABIC	76051.01	74436.36	73724.08	73282.41	72721.98
Entropy	--	0.83	0.87	0.87	0.88
VLMR	--	-37967.78	-37125.82	-36735.04	-36158.25
VLMR 2 Times the Loglikelihood Difference	--	1683.92	781.55	510.94	-12.94
VLMR Difference in Number of Parameters	--	18	18	18	21
VLMR Mean	--	97.88	50.98	43.49	-18058.61
VLMR *p*-value	--	0	0.0002	0.0001	0.24
LMR	--	1670.71	775.42	506.93	-12.86
LMR *p*-value	--	0	0.0002	0.0001	0.24
BLRT	--	-37967.78	-37125.82	-36735.04	-36158.25
BLRT 2 Times the Loglikelihood Difference	--	1683.92	781.55	510.94	-12.94
BLRT Difference in Number of Parameters	--	18	18	18	21
BLRT *p*-value	--	0	0	0	1.00

Note. [a] = selected class solution; [b] = solution contained latent classes with <5% of the sample; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; BLRT = Bootstrapped Likelihood Ratio Test; LCA = latent class analysis; LL = Loglikelihood; LMR = Lo-Mendell-Rubin adjusted test; SABIC = sample-size adjusted BIC; VLMR = Vuong-Lo-Mendell-Rubin likelihood.

Table 4.
Participant Characteristics

Variable	Total N	% (n)	Mean (SD)	Range
Age	1123	--	73.64 (7.72)	54-95
Sex (male)	1124	58.9 (662)	--	--
Education (years)	1124	--	16.00 (2.78)	4-20
Race = White	1124	92.9 (1044)	--	--
Race = Non-White	1124	7.1 (80)	--	--
APOE-ε4 (carriers)	1053	48.9 (515)	--	--

Note. APOE-ε4 = apolipoprotein E-ε4.

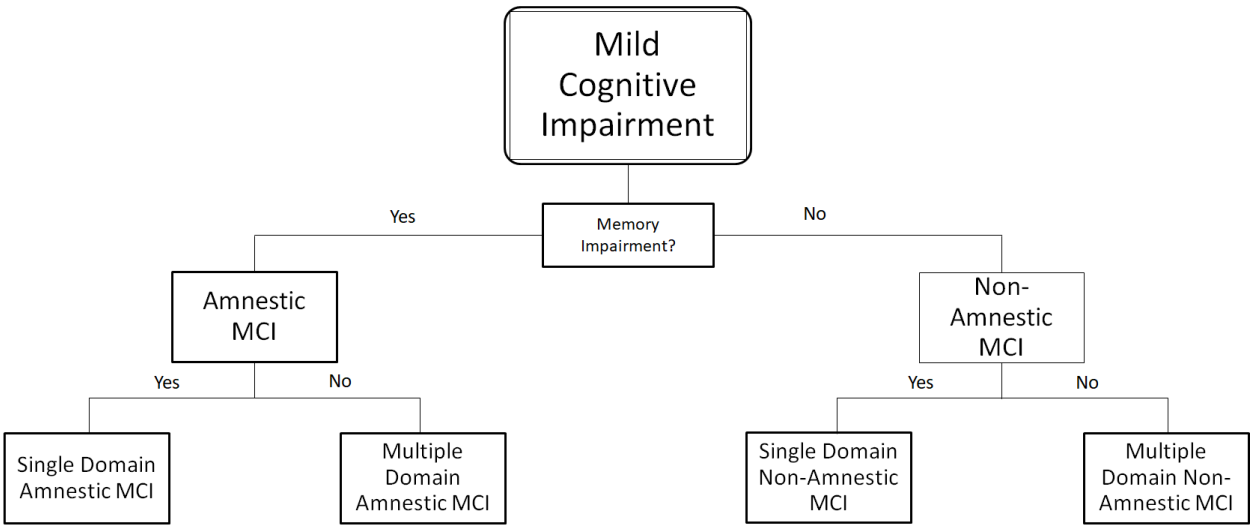

Figure 1. Subtypes of mild cognitive impairment based on cognitive domain affected. MCI = mild cognitive impairment.

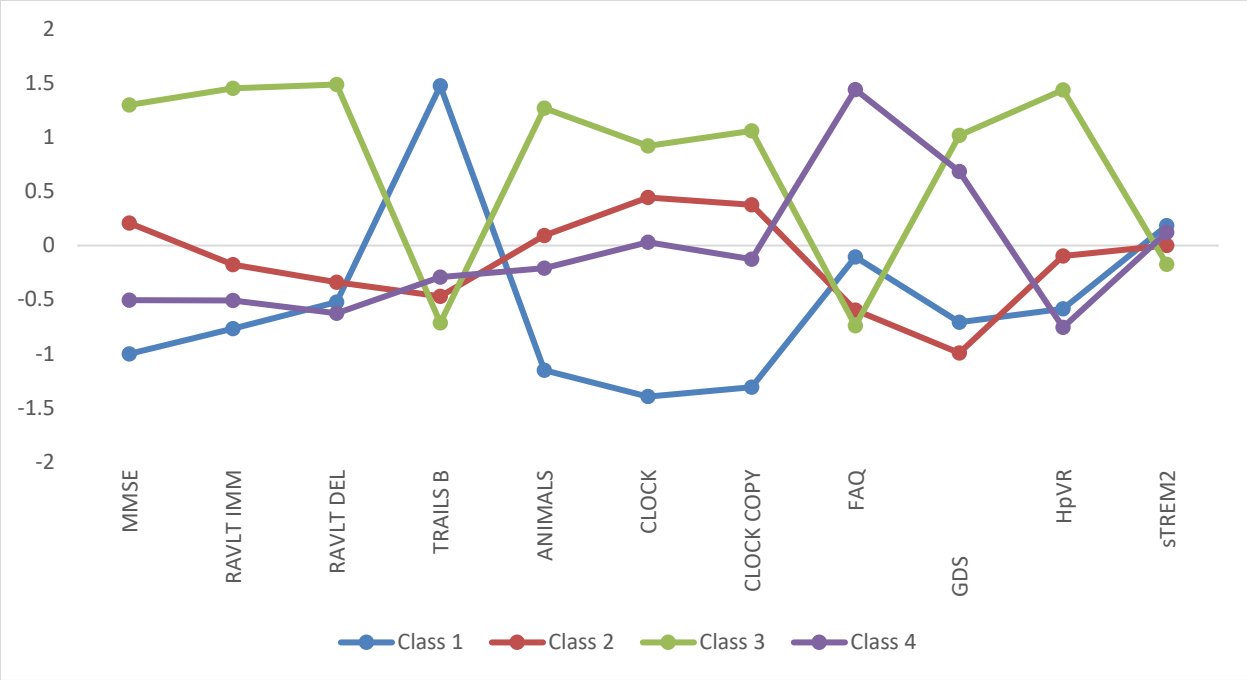

Figure 2. Profiles of the subtypes (latent classes) in the 4-class model. Scores have been transformed to z-scores for ease of comparison. Class 1 = LC1, *Global Decliners*; Class 2 = LC2, *Maintainers*; Class 3 = LC3, *Cognitive Reservers*; Class 4 = LC4, *Functional Decliners*; GDS = Geriatric Depression Scale; HpVR = hippocampal/total intracranial volume x 10^3 ratio; FAQ = Functional Assessment Questionnaire; MMSE = Mini-Mental Status Exam; Trails B = Trails Making Park B; sTREM2 = soluble triggering receptor expressed on myeloid cells 2 concentration; RAVLT DEL = Rey Auditory Verbal Learning Test delayed recall; RAVLT IMM = Rey Auditory Verbal Learning Test immediate recall.

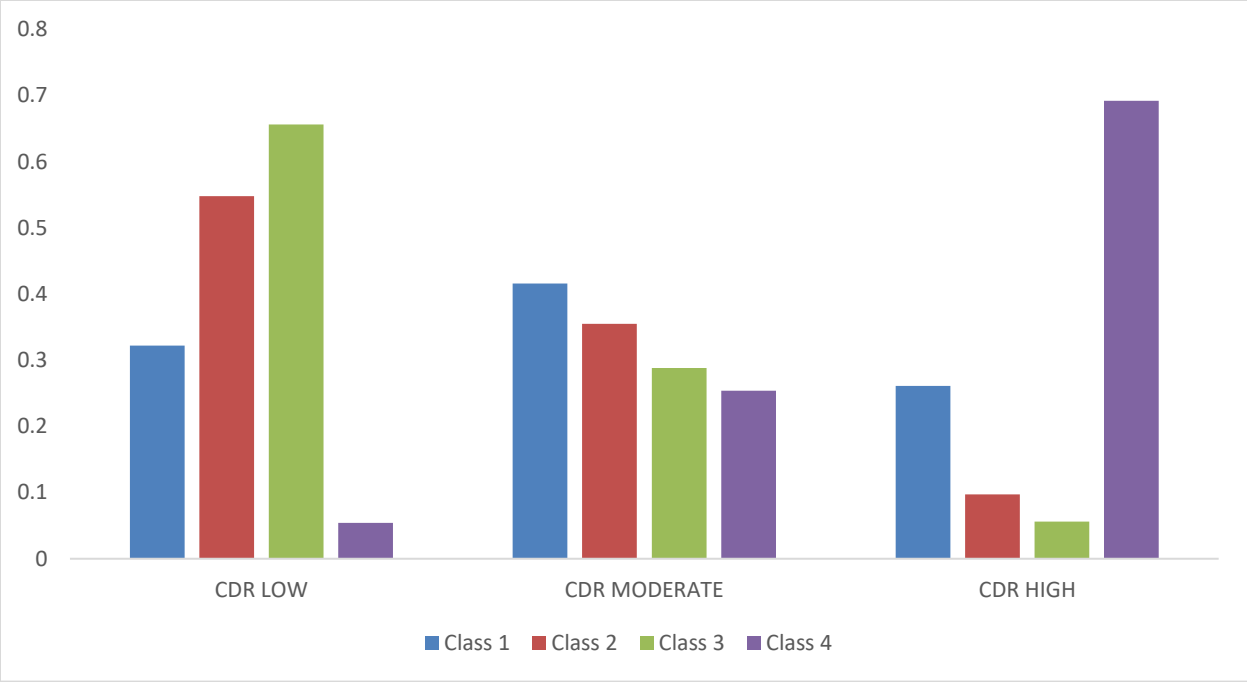

Figure 3. Distribution of mean CDR scores by latent class. CDR = Clinical Dementia Rating; Class 1 = LC1, *Global Decliners*; Class 2 = LC2, *Maintainers*; Class 3 = LC3, *Cognitive Reservers*; Class 4 = LC4, *Functional Decliners*.

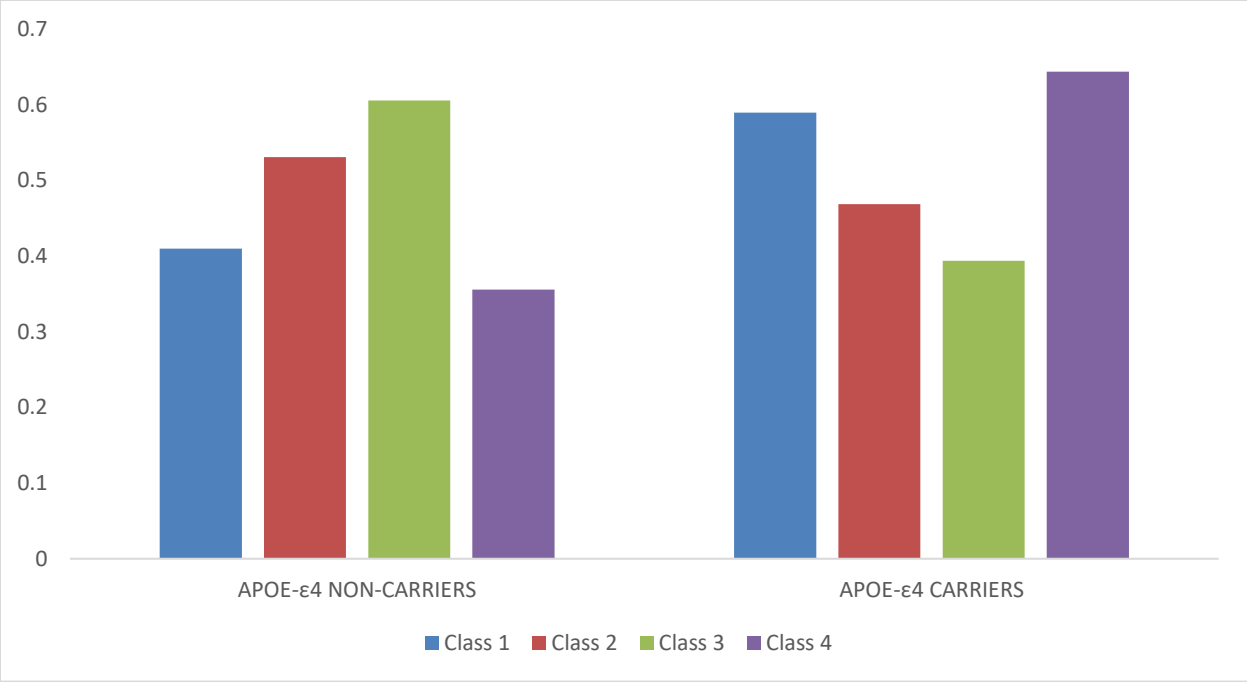

Figure 4. Distribution of APOE-ε4 carriers by latent class. APOE-ε4 = apolipoprotein E-ε4; Class 1 = LC1, *Global Decliners*; Class 2 = LC2, *Maintainers*; Class 3 = LC3, *Cognitive Reservers*; Class 4 = LC4, *Functional Decliners*.

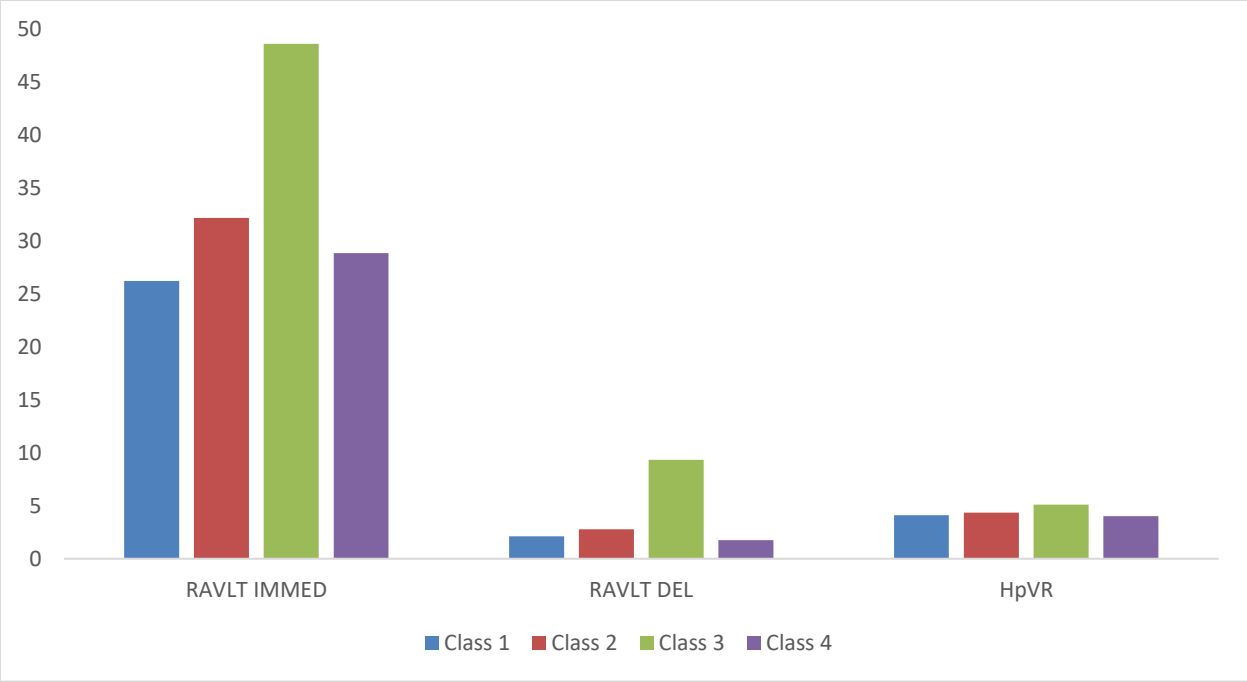

Figure 5. Memory systems by latent class. Class 1 = LC1, *Global Decliners*; Class 2 = LC2, *Maintainers*; Class 3 = LC3, *Cognitive Reservers*; Class 4 = LC4, *Functional Decliners*; HpVR = hippocampal/total intracranial volume x 10^3 ratio; RAVLT DEL= Rey Auditory Verbal Learning Test delayed recall; RAVLT IMM = Rey Auditory Verbal Learning Test immediate recall.

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Chapter 5: Overall Conclusions

For many years, the field of research did not account for differences in diseases manifestation and presentation between men and women. Only recently has it come to light that in other chronic conditions, such as cardiovascular disease and stroke, there are differences in symptoms and disease presentation between men and women. Regarding Alzheimer's, sex differences have largely been unstudied. The purpose of my dissertation study was to use a large sample of individuals with aMCI to investigate if there are subtypes of risk profiles based on sex, sociodemographic, clinical, cognitive, and biomarker variables. My results demonstrated that the aMCI-AD population has various subtypes and multiple indicators should be considered to increase sensitivity for screening and diagnosis of early AD. Additionally, my study suggests that men and women may have distinct risk profiles and variables other than memory are important in distinguishing among patients with aMCI-AD.

The findings from my three comprehensive exams and dissertation study build off one another, explore a largely untapped area of research, and provide the groundwork for an exciting line of research regarding sex differences in the progression to AD. With increasing incidence and the prevalence of AD expected to grow by more than 14 million by 2050 in the United States, this is an important area of research. Results obtained from my studies can help inform precision medicine methodologies to improve outcomes and the quality of life of individuals with aMCI-AD.

Appendix A: Results from Alternate Latent Class Analyses

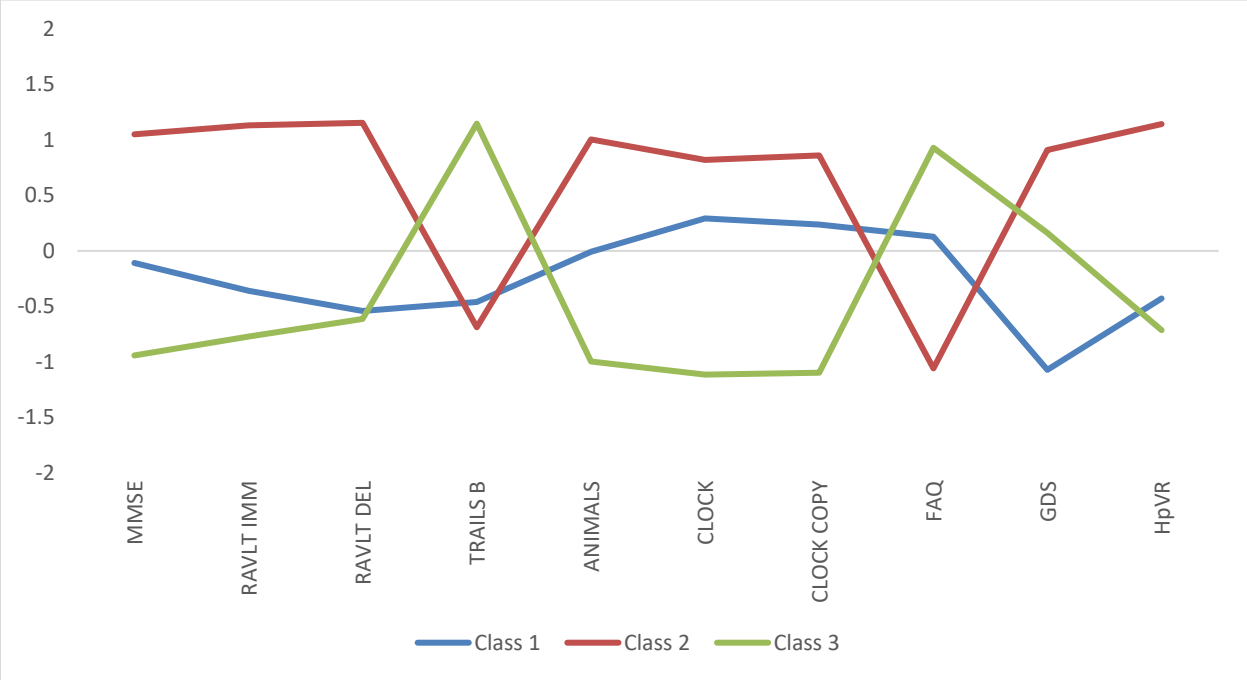

Figure 1. Profiles of the subtypes (latent classes) in the 3-class model which does not include soluble TREM2. Scores have been transformed to z-scores for ease of comparison. GDS = Geriatric Depression Scale; HpVR = hippocampal/total intracranial volume x 10^3 ratio; FAQ = Functional Assessment Questionnaire; MMSE = Mini-Mental Status Exam; Trails B = Trails Making Park B; RAVLT DEL = Rey Auditory Verbal Learning Test delayed recall; RAVLT IMM = Rey Auditory Verbal Learning Test immediate recall.

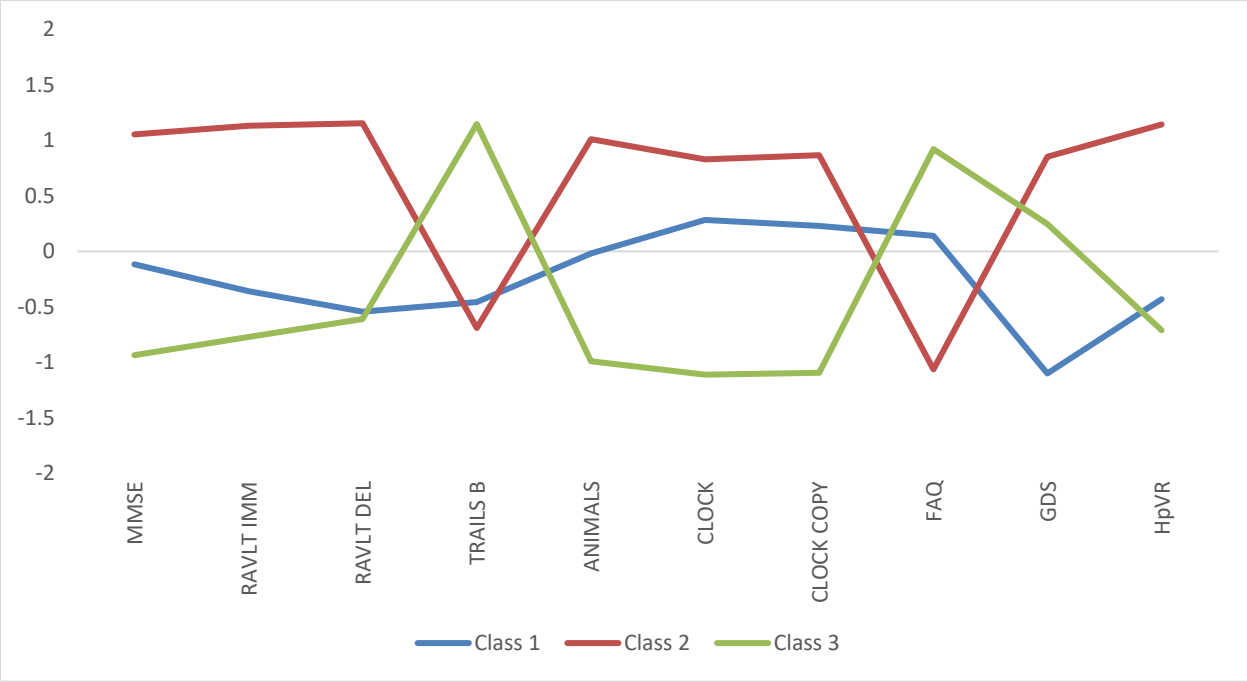

Figure 2. Profiles of the subtypes (latent classes) in the 3-class model without sex and soluble TREM2. Scores have been transformed to z-scores for ease of comparison. GDS = Geriatric Depression Scale; HpVR = hippocampal/total intracranial volume x 10^3 ratio; FAQ = Functional Assessment Questionnaire; MMSE = Mini-Mental Status Exam; Trails B = Trails Making Park B; RAVLT DEL = Rey Auditory Verbal Learning Test delayed recall; RAVLT IMM = Rey Auditory Verbal Learning Test immediate recall.