

Subjective Memory Complaints of the Oldest-Old:  
Subclinical and Neuropsychological Predictors in the 90+ Study

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**Abstract**

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**Introduction:** We investigated the relationship between subjective memory complaints and objective memory and cognitive test scores, while also accounting for behavioral changes, such as depression, and physiological, i.e. biomarker, evidence of underlying dementia causing diseases in an oldest-old cohort.

**Methods:** Participants are from The 90+ Study, a population based longitudinal study of people aged 90 and older. We used data from participants who completed a 3T MRI scan and/or a High Resolution Research Tomograph (HRRT) PET scan with Florbetapir ligand. These individuals were categorized as cognitively normal or MCI based on neurological examinations during The 90+ Study. Then, we determined whether an

individual had subjective memory complaints based on the question, “Do you feel you have more problems with memory than most?” A total of 201 participants were included in the study.

**Results:** In individuals 90 years and older, the California Verbal Learning Test long delay (CVLT-LD) was found to be predicative of subjective memory complaints ( $P = .008$ ), as was white matter hyperintensities ( $P = .02$ ) and an increased Geriatric Depression Scale (GDS) score ( $P = <.001$ ).

**Discussion:** People 90 years and older that have objective long-term memory impairment, those with changes in brain pathology and those that suffer from more depressive symptoms than their peers are more likely to notice subjective changes in their memory performance. If we can understand the significance of subjective memory complaints in the 90+ population regarding subclinical and pathological changes, then we can begin to explore their relationship to the dementing process in this quickly growing population.

## Introduction

People 90 years and older, the oldest-old, are one of the fastest growing populations in the United States. The number of persons in this age group is expected to quadruple according to population projections, becoming over 8.7 million by 2050 (US Census Bureau, 2011). In many studies, higher dementia prevalence and incidence has been shown to be associated with increased age (Fiest K, et al 2016). Within the 90+ Study, incidence rates of dementia will continue to increase from 12.7% per year in the 90 to 94 age group, to 21.2% per year in the 95 to 99 age group, to 40.7% per year in the 100+ age group (Corrada MM, et al 2010). Other research, such as the Framingham Heart Study (FHS), recently showed that despite an increasing prevalence of dementia, age specific incidence of dementia has been steadily declining over the past three decades (Pase MP, et al 2017). According to the FHS, an individual's risk of developing dementia by a specific age has decreased by as much as 20% over this 30 year time period (Satzabal CL, et al 2016). Multiple other population-based studies have shown a declining age-specific risk in the United States and Europe. Higher education and better treatment of cardiovascular risk factors such as hypertension is thought to be the reason for declining age-specific risk of dementia around the world (Langa KM 2015, Rocca WA 2011). Conflicting studies, such as the ones mentioned above, give further evidence for the necessity of more research on dementia in the oldest-old population.

Together, the biomedical and public health research community must identify effective means of decreasing the incidence of underlying, dementia causing conditions (primary prevention), limiting the progression of dementia causing pathologies in order to forestall symptoms (secondary prevention), and also must explore new pathways to find effective care and cure

strategies for those who already have dementia symptoms (tertiary prevention). This is the biomedical and public health challenges of the current century.

In order to address primary and secondary prevention in Alzheimer's Disease and dementia research we must find effective means to detect disease before clinical symptoms are present or to identify the very earliest symptoms which will reliably predict progression to dementia.

We currently have available some biomarkers which can determine the existence of Alzheimer's disease *in vivo* prior to any symptoms; amyloid and tau PET, as well as cerebrospinal fluid assays for amyloid and tau proteins (Jack et al, A&D 2018; Roberts R, et al JAMA Neurol 2018). However, these are not yet widely available in ordinary clinical settings because of costs, desirability, pain and the ethical issues associated with identifying catastrophic disease without a disease modifying therapy. This is likely to change rapidly though with the acceptance of the NIA-AA research framework for Alzheimer's disease and related dementias (Jack et al 2018). The goal of the NIA-AA research framework is to advance the field of dementia and Alzheimer's research in understanding the pathophysiology of Alzheimer's disease and allow for testing of hypotheses related to development and progression of the disease in diverse populations and settings.

While some very early subjective or objective symptoms may continue to progress, others may not. Identifying which would reliably progress could lead to lower cost diagnosis and potentially intermediate endpoints for clinical trials. A study in 2012 suggested that subjective complaints may be highly correlated to the existence of AD pathology prior to any significant objective impairment (Amariglio et al., 2012). Another study suggested that subjective memory complaints (SMCs) could be markers of age related changes in the brain which may influence

future cognitive impairment (Hohman et al, 2011). Prospective studies have also found that elderly individuals with subjective memory complaints have a high risk of progression to dementia, even with normal performance on objective memory tests (Jessen et al., 2014). It is common for elderly individuals to report having memory problems. i.e., there are potentially many “worried well” because of the pervasiveness of dementia with age (Jonker et al., 2000; Reid et al., 2006; Minett et al., 2008; Perquin et al., 2015) but the validity of these reports compared to true developing cognitive impairment need further exploration.

### *Purpose of Research*

The purpose of this study is to evaluate the relationship between subjective memory complaints and objective memory and cognitive test scores, while also accounting for behavioral changes, such as depression and the physiological i.e., biomarker, evidence of underlying dementia causing diseases; specially cerebral small vessel disease, and amyloid deposition in individuals over the age of 90. Research participants in this study have normal cognition or mild cognitive impairment (MCI). We have captured “subjective memory complaints” based on the clinical interview question, “Do you feel you have more memory problems than most?” The goal of the study is to determine how strongly the subjective memory complaints are associated with objective cognitive measures, biomarker measures of disease and behavioral issues such as depression. This will be helpful in establishing low cost, easily obtained and reliable criteria for early detection of pre-dementia syndrome in the 90+ as well as other age groups, especially in population-based studies.

## *Background*

The rapid increase in the number of oldest-old individuals in our country presents public health issues that need to be addressed sooner rather than later. An aging population brings with it increased prevalence of chronic disease and disability and puts strain on those providing care, such as: family members, health and social service professionals, provider systems, and local, state, and federal governments (Brodaty H., 2009). The prevalence of Alzheimer's disease and other dementia imposes a personal, public health and budgetary crisis that affects the entire U.S. population; it is projected to worsen exponentially if effective interventions are not identified (Newcomer RJ., 2010).

In the 1980's, the University of Southern California (USC) sent out surveys to approximately 14,000 residents in a Southern California community in Laguna Woods called Leisure World. They collected data about dietary habits, exercise, and overall health. In 2003, researchers at the University of California, Irvine (UCI) began contacting participants from the USC study (aptly named the Leisure World Cohort Study) who had reached the age of 90. They initiated a research study about the oldest-old and called this new cohort *The 90+ Study*. Beginning in 2014, interested volunteers from Southern California were also permitted to join. The current cross-sectional analysis of data collected by *The 90+ Study* reflects both initial cohort members from 2003 as well as newer volunteers. As the current Senior Psychometrist of *The 90+ Study*, I was granted permission to access the data for this research by Dr. Claudia Kawas and Dr. Maria Corrada, the lead investigators, in accordance with the approval of the UCI IRB and UW IRB.

*The 90+ Study* is one of the largest longitudinal research studies of people over the age of 90 in the world; it aims to promote better quality of life in a rapidly growing population where dementia incidence and prevalence are higher than in any other age group.

## **Literature Review**

### *SMCs as a predictor of cognitive impairment*

Subjective memory complaints may predict more objective cognitive impairment and are an object of growing interest among researchers. A study of 131 elderly individuals found that those with subjective cognitive complaints (including memory specific) had objective cognitive changes that affected them on a day-to-day basis, despite having normal cognition (determined from testing) considered to be in the normal range overall (Amariglio, et al., 2012). Subjective complaints often precede and are correlated with later deficits noted on objective cognitive testing (Dufouil, et al., 2005). These and other studies suggest that subjective memory complaints may be important for early detection of cognitive symptoms and could act as harbingers of later dementia, when objective cognitive testing is not yet sensitive enough to detect such deficits.

### *SMCs and brain alterations*

“Cerebral small vessel disease (SVD) is an umbrella term covering a variety of abnormalities related to small blood vessels in the brain. Specific examples of cerebral SVD include “lacunar infarcts” (which are a type of small stroke), “white matter hyperintensities” (which are a radiological finding), and “cerebral microbleeds” (which means bleeding in the brain from a very small blood vessel) (<https://betterhealthwhileaging.net/cerebral-small-vessel-disease/>).”

Studies have found that subjective memory complaints often reflect objective alterations in brain function (Hafkemeijer et al, 2013; Palm et al, 2013). Complaints of cognitive decline have been shown to be associated with the severity of white matter lesions within the brain (Minett et al., 2005). SMCs have also been found to be a risk factor for cognitive decline and dementia (Luck et al., 2015) and may represent a pre-mild cognitive impairment stage, measurable by brain alterations (Saykin, et al., 2006). A recent study from Germany found that extensive WMHs are associated with specific impairment in memory and subjective cognitive performance, as well as attention and social cognition (Kynast J, et al. 2017).

Cerebral SVD is one of the largest contributors to cognitive decline and is related to vascular risk factors that may ultimately lead to dementia (Anouk et al, 2011). A study in 2016 showed that individuals with SMCs may be more likely to present with white matter hyperintensities (WMH), microbleeds, lacunes, etc. (Uiterwijk et al, 2016). Subjective cognitive decline and white matter hyperintensities show increased risk of clinical progression to dementia (Benedictus, et al. 2015). Vascular pathology is the second most common pathologic feature in the oldest-old and the prevalence of microinfarcts in this population is significantly increased (Bullain, 2013). The interaction between small vessel disease (and other vascular diseases) with neurodegenerative diseases such as AD and Lewy body disease in relation to the beginning stages of dementia syndrome is one of the major research puzzles we face. This interaction significantly impacts how we think of dementia prevention and the underlying disease components.

### *SMCs and Depression*

Some researchers have found that SMCs are more closely associated with depressive symptoms than with cognitive impairment (Markova et al, 2017; Zlatar et al, 2017). The results of a study in 2014 suggest that even though SMCs reflect fluctuations in memory functioning, they are also influenced by changes in depressive symptoms (Hulur, et al. 2014). The results of studies focusing on depression and SMCs reinforce their importance as predictors of subjective memory complaints (Hulur et al., 2015; Ryu, et al., 2016; Markova, 2017; Zlatar, 2017). Other research shows that depression may or may not be part of a cognitive impairment prodrome. A study of cognitively healthy Czech older adults, for instance, found that even though a higher number of subjective memory complaints in cognitively functioning individuals were most closely related to depressive symptomatology, some specific complaints instead reflected lower memory performance, depending on how the information was captured. Of particular interest, the Czech study found that worse memory in comparison to peers was significantly associated with lower memory performance (Markova H, 2017). In another recent study about depressive symptoms, subjective complaints and objective cognitive impairment, researchers found that subjective memory complaints were associated more with lower objective memory. They also reported that interactions between SMC and depressive symptoms were significant for tests of memory, executive function and global cognition, as well as psychomotor speed. Further analysis also revealed that depressive symptoms actually moderated the SMC-cognition relationship, meaning that only individuals with higher depressive symptoms showed significant SMC-cognition associations (Seo EH, et al. 2017).

## *Hypotheses*

Complaints about subjective memory problems have yet to be explored in *The 90+ Study* cohort. This study intends to understand the significance of these complaints in relation to the development of underlying disease processes, as well as, processes that ultimately lead to dementia syndrome. The specific hypotheses are as follows:

**Hypothesis 1:** Based on evidence from literature review, individuals with SMCs will not perform any worse on objective cognitive tests than individuals without SMCs.

**Hypothesis 2:** Individuals with SMCs will have more cerebral small vessel disease (SVD) than individuals without SMCs as measured by volumetric white matter hyperintensities (WMH) and based on hippocampal volume found with magnetic resonance imaging (MRI) scans.

**Hypothesis 3:** Individuals with SMCs will have more amyloid deposition than individuals without SMCs based on standardized value uptake ratio (SUVR) totals found with positron emission tomography (PET) scans.

**Hypothesis 4:** Individuals with SMCs will have higher scores on the Geriatric Depression Scale (GDS) than individuals without SMCs, indicating more depressive symptoms.

## Methods

### *Subjects*

The *90+ Study* currently consists of approximately 1800 participant's total (living and deceased) and researchers visit approximately 300 of the living participants every six months. On those (in-home or in-clinic) visits the researchers complete clinical exams and interval medical history interview, neuropsychological test battery with trained psychometricians and a nurse or physician. After testing, trained staff members give each participant a categorical diagnosis using MCI and dementia criteria (Petersen RC, 2004).

We used data from participants who completed a 3T MRI scan and/or a High Resolution Research Tomograph (HRRT) PET scan with Florbetapir ligand, for purposes of this study. These individuals were categorized as cognitively normal or MCI based on neurological examinations during *The 90+ Study*.

Table 1 summarizes the measures used in this current research to investigate subjective memory complaints in *The 90+ Study*. The independent variables include multiple objective cognitive measures, MRI measures, a PET measure, and a behavioral measure that have previously been found to be significantly associated with subjective complaints in other studies.

**Table 1. Summary of Measures**

	Measure	What it measures	Method of measurement
<b>Objective Cognitive Measures</b>			
	<i>MMSE</i>	Gross function	22 item questionnaire that examine various cognitive domains. Scores range from 0-30, with lower scores indicating more cognitive impairment
	<i>Animal Fluency</i>	Verbal retrieval and fluency	One minute to name as many animals as possible
	<i>Clocks</i> <i>(numbers and hands scores)</i>	Executive function	8-point scale (4pt- numbers, 4pt- hands) that assesses the accuracy of the placement of numbers and hands in a blank circle. The higher the total score, the better the performance
	<i>CVLT long delay</i>	Long term Memory	9 words are read aloud. After a 10-minute delay, participants recall the words.
<b>MRI Measures</b>			
	<i>MRI Scan</i>	Vascular Disease in the brain: WMH and hippocampal volume	Participants were scanned for 30-40 minutes in a 3T scanner, which shows pathological conditions in the brain and vascular imaging.
<b>PET Measures</b>			
	<i>PET Scan</i>	Density of amyloid plaques: SUVR	Participants were injected with Florbetapir ligand. The compound is used to estimate the density of $\beta$ -amyloid plaques when it binds to amyloid in the brain
<b>Behavioral Measures</b>			
	<i>GDS</i>	Depressive symptoms in elderly	The short form GDS is comprised of 15 questions and is answered with a yes or no response by the subject.

## Measures

### 1. Objective Cognitive Measures

a) *Mini-Mental State Examination (MMSE)*. General cognition was measured with the MMSE, commonly used to measure gross function (Folstein, & McHugh, 1975; Halpern & O'Connor, 2000). The questionnaire is 22 items that examine various cognitive domains including orientation, language, registration, memory, and construction. Total scores range from 0-30, with lower scores indicating more cognitive impairment. In *The 90+ Study*, the mean MMSE score is 26.4 (SD 2.7) (Bullain, 2013; Whittle, 2007).

b) *Animal Fluency*. Verbal retrieval and fluency was measured using the animal fluency test (Thurstone, 1938). Participants are given one minute to name as many animals as they can. It has been shown in previous studies that those with subjective memory complaints score lower on fluency tests (Minett, 2008), thus making this a measure worth exploring in the current study. In *The 90+ Study*, the mean number of animals named is 12.8 (SD 4.2) (Bullain, 2013; Whittle, 2007).

c) *Clocks*. Executive function was measured using the clock drawing and looking at individual scores for clock numbers and clock hands. The clock drawing test is scored on an 8-point total scale that assesses the accuracy of the placement of numbers and hands in a blank circle. The sequence of the placement of the numbers is rated from 0 to 4 points. The placement of the hands on the clock is also rated from 0 to 4 points. The higher the total score, the better the performance. In a cross-sectional study, they found that better executive function, as is measured by the clock drawing, predicted fewer SMCs (Steinberg, et al., 2013). In the 90+

Study, the mean total score for the clock drawing is 5.4 (SD 1.9) out of a total of 8 points (Bullain, 2013; Whittle, 2007).

d) *CVLT Long Delay*. Memory was measured with the California Verbal Learning Test, specifically focusing on the long delay portion of the measure. The CVLT contains nine words that are read aloud to participants. Participants recall the words immediately after they are read and responses are recorded. This is done for four consecutive trials. A 30 second delay is given and the words are recalled again by the participant and recorded. After a 10-minute delay (the long delay portion of the CVLT measure), testers ask participants to recall whatever they can from the list of words. Those responses are then recorded. A study of 98 participants (mean age 75) showed that frequent subjective complaints were associated with increased rates of decline in delayed recall on the California Verbal Learning Test (Hohman, 2011). In the 90+ Study, the mean number of words recalled after the 10-minute-long delay is 5 (SD 2.7) out of 9 total.

## **2. MRI Measures**

a) *3T MRI Scan*. The image clarity revealed by a 3T scanner is particularly beneficial for pathological conditions involving the brain, while the increased spatial resolution allows for high-quality vascular imaging. Participants of the 90+ Study were given one 3T MRI scan, conducted at Newport Diagnostics in Newport Beach, CA. They were scanned for approximately 30-40 minutes. In a study of 158 elderly individuals, white matter hyperintensity volume was more highly associated with preclinical AD than other AD biomarkers (Kandel, 2016).

Hippocampal volume was calculated using freesurfer segmentation. White matter hyperintensities were calculated at UC Davis. Segmentation was based on a modified Bayesian approach that combines image likelihood estimates, spatial priors and tissue class constraints.

The segmented WMH masks were then back-transformed in to native space for tissue volume calculation. Volumetric white matter hyperintensity may be indicative of preclinical AD, especially when associated with subjective memory complaints, thus making this measure relevant for the current study.

### **3. PET Measures**

a) *HRRT Florbetapir PET Scan*. Florbetapir ligand was used for a PET scan of *90+ Study* participants at the University of California, Irvine campus in Irvine, CA. The compound is injected and binds to amyloid in the brain, which can then be used to estimate the density of  $\beta$ -amyloid neuritic plaques. Once the scan is completed, the standardized uptake value ratio (SUVR) is used to make comparisons computing the degree of radiotracer uptake in a brain region of interest. A 2015 study conducted with 14 patients using PET imaging found that participants with subjective complaints had higher brain  $A\beta$  deposition when compared to normal aging study volunteers (Snitz, 2015). Similar studies have shown an association between subjective complaints and brain amyloid- $\beta$  deposition in healthy older adults (Snitz and Weissfield, 2015). The association between amyloid deposition in oldest-old adults with or without subjective memory complaints has yet to be determined within the 90+ population. Subjective complaints may reflect subtle changes in amyloid deposition that could be indicative of future (for those with normal cognition) or increased (for those diagnosed with MCI) cognitive decline or dementia, thus making this part of the current research essential.

### **4. Behavioral Measures**

a) *Geriatric Depression Scale (GDS)*. The short form GDS was developed in 1986 and is comprised of 15 questions used to identify depressive symptoms in elderly patients. The

questionnaire was found to have 92% sensitivity and 89% specificity when evaluated against diagnostic criteria (Sheikh & Yesavage, 1986). The short form GDS is answered with a yes or no response. If the number of “incorrect” responses total 5 or more, the participant screened positive for geriatric depression and a self-harm discussion ensues. Depression diagnoses in *The 90+ Study* are also captured by self-reported medical history, medical records from doctor’s offices and by history of prescribed antidepressant medications. Depression and subjective memory complaints have been found to be highly correlated in younger elderly and should thus be explored in the oldest-old population as well.

#### *Statistical approach*

Data were explored for each variable using the study population (n=201) and then stratified by SMC response. Hypothesis tests were performed between each independent variable and SMC response to measure magnitude of differences and explore significance of associations. To test the associations between the independent variables and SMC, we used: independent samples t-test, Mann-Whitney test, and chi-square significance test, depending on the variable. A t-test analysis reported the means of the population with SMC against those without SMC and explored the difference between the samples when the variances of two normal distributions were unknown. A Mann-Whitney test was used to compare differences between two independent groups (those with SMC and those without SMC) when the dependent variable was either ordinal or continuous and not normally distributed. We also performed chi-square tests which assessed how likely it was for an observed distribution to occur due to chance. Lastly, we ran a multiple logistic regression to compare variables as predictors of subjective

memory complaint based on each of the four hypotheses. Multiple logistic regression was used as a way to understand the effect that the independent variables had on the probability of having subjective memory complaints.

Hypothesis testing was chosen based on the nature of the variables, as follows:

- Independent samples t-tests: only where the dependent variable was normally distributed at both levels of the independent variable SMC
- Mann-Whitney tests: where the dependent variable was scale or ordinal, but not normally distributed at both levels of the independent variable SMC
- Cross-tab with Chi-square significance test: for categorical data

Approximate normality was based upon having both skew and kurtosis no more than +/- 2 from 0. Zero indicates perfect normality for both. Also, the histograms were visually inspected to see if the variable “looks” normally distributed. Correlation analyses were run, and we looked at Pearson correlation coefficients when both variables were approximately normal. If either of the variables were ordinal/not normal, we interpreted the Spearman correlation instead.

Multiple linear regressions were performed to see whether we could predict SMC from the various measures in the current study. Regression analyses were controlled for age, gender, and education. Significant predictors were combined into the same model, retaining any control that was already paired with each predictor. We then decided to explore how cardiovascular factors may have affected the significance of the previous findings. All further regression analyses were controlled for age, gender, education and cardiovascular risk factors including: heart disease (coronary heart disease (CAD), myocardial infarction (MI), atrial

fibrillation (Afib), heart valve disease (HVD), and congestive heart failure (CHF)), as well as stroke, transient ischemic attack (TIA), high blood pressure (HBP) and high cholesterol.

## **Results**

A total of 222 individuals were initially included in this research. 201 (90%) completed the SMC criteria question and either an MRI and/or PET scan. 21 participants (10%) did not answer the SMC criteria question and were excluded from analysis. Mean age of the remaining participants at the time of their scan was 94 years old (range, 90-102). Most of the participants were women (64%), Caucasian (97%), and had greater than high school education (84%). Most scans and biannual visits were not conducted on the same day with a mean of 69 days between these measures (range, 0 days-852 days). 137 of these participants (61%) had normal cognition and the other 64 (29%) were diagnosed MCI by 90+ Study examiners.

Heart disease, including a history of: coronary artery disease, myocardial infarctions, atrial fibrillation or other arrhythmias, heart valve disease, and congestive heart failure, was found in 165 (82%) of participants in the study population. This was followed by high blood pressure (62%), high cholesterol (39%), transient ischemic attacks (19%), and stroke (12%) (Table 2).

Participants with SMCs were diagnosed less with heart disease (50% vs 87%) and less with high cholesterol (31% vs 41%) than participants without SMCs. The SMC “yes” group had more incidences of strokes (19% vs 11%) and transient ischemic attacks (23% vs 18%) than those without subjective memory complaints. High blood pressure stayed constant throughout all groups with 62% having been diagnosed with the disease (Table 2).

Table 2 summarizes general characteristics of the 201 participants used for this study, including the information presented above.

**Table 2.** *Characteristics of participants with brain scans and SMC response: The 90+ Study*

<b>Characteristic</b>	<b>All Participants</b> (N=201) Mean (SD) [range]	<b>SMC: Yes</b> (N=26) Mean (SD) [range]	<b>SMC: No</b> (N=175) Mean (SD) [range]
Age at 90+ Study brain scan, years	93.9 (2.98) [90-102]	92.7 (2.26) [90-99]	94.1 (3.04) [90-102]
Interval between MMSE and brain scan, days	69.4 (76.97) [0-852]	77.8 (44.07) [9-192]	68.1 (80.7) [0-852]
	<b>Number (%)</b>	<b>Number (%)</b>	<b>Number (%)</b>
<b>Gender</b>			
Women	128 (64%)	14 (54%)	114 (65%)
Men	73 (36%)	12 (46%)	61 (35%)
<b>Race</b>			
Caucasian	194 (97%)	26 (100%)	168 (96%)
Not Caucasian	7 (3%)	0 (0%)	7 (4%)
<b>Education</b>			
≤High school	33 (16.4%)	2 (8%)	31 (17.7%)
Vocational/Some college	62 (30.8%)	10 (38%)	52 (29.7%)
College or higher degree	105 (52.3%)	14 (54%)	91 (52%)
Missing	1 (0.5%)	N/A	1 (0.6%)
<b>Cognitive Diagnosis</b>			
Normal	137 (68%)	9 (35%)	128 (73%)
MCI	64 (32%)	17 (65%)	47 (27%)
<b>Medical history at time of MMSE *</b>			
Heart Disease †	165 (82%)	13 (50%)	152 (87%)
Stroke	24 (12%)	5 (19%)	19 (11%)
Transient ischemic attack	38 (19%)	6 (23%)	32 (18%)
High blood pressure	124 (62%)	16 (62%)	108 (62%)
High cholesterol	79 (39%)	8 (31%)	71 (41%)
*Participants can have more than one of these medical conditions			
† Heart disease includes a history of any of the following: coronary artery disease, myocardial infarction, atrial fibrillation or other arrhythmias, heart valve disease, and congestive heart failure.			

Table 3 shows the characteristics of the study participants in relation to the various measures used to examine subjective memory complaints.

**Table 3:** *Characteristics of Study Participants and Measures*

<b>Measure</b>	<b>All Participants (N=201)</b> Mean (SD) [range]	<b>SMC: Yes (N=26)</b> Mean (SD) [range]	<b>SMC: No (N=175)</b> Mean (SD) [range]
<b>Objective Cognitive Measures</b>			
MMSE Missing	27.56 (2.18) [18-30] N/A	26.6 (2.69) [21-30] N/A	27.71 (2.07) [18-30] N/A
Animals Missing	15.26 (4.76) [6-30] 1	13.38 (1.08) [7-30] N/A	15.6 (.35) [6-25] 1
Clocks Numbers Hands Missing	3.36 (0.96) [0-4] 2.76 (1.29) [0-4] 19	3.36 (0.94) [0-4] 2.68 (1.07) [1-4] 1	3.36 (0.97) [0-4] 2.77 (1.33) [0-4] 18
CVLT Long Delay Missing	6.13 (2.52) [0-9] 2	4.04 (.6) [0-9] N/A	6.45 (.17) [0-9] 2
<b>MRI Measures</b>			
WMH Missing	17.66 (13.22)[1.09-64.8] 96	21.89 (17.36) [3.53-64.8] 13	17.06 (12.54) [1.1-49.1] 83
Hippocampal Volume Missing	5.55 (0.75) [3.75-7.30] 96	5.39 (.98 ) [3.83-7.26] 13	5.58 (0.72) [3.75-7.3] 83
<b>PET Measures</b>			
SUVr Missing	0.77 (0.08) [0.60-0.93] 67	.80 (.087) [.65-.91] 14	0.77 (.075) [.60-.93] 53
<b>Behavioral Measures</b>			
GDS Missing	2.09 (2.12) [0-10] N/A	4.23 (.46) [1-8] N/A	1.78 (.143) [0-10] N/A

## Hypothesis Testing Results

### Hypothesis One: Objective Cognitive Measures

To test the hypothesis that participants with SMC would not perform any differently on objective cognitive testing, we used a Mann-Whitney test. Using this test allowed us to compare the means of two groups (those with SMCs and those without SMCs) to explore whether individuals with SMCs had significantly lower scores overall. People that answered “yes” to the SMC question had a lower mean rank on the MMSE and animal fluency tests than those without memory complaints (Table 4). Analysis showed a magnitude difference of 1.1-point between the MMSE scores of those with memory complaints and those without when tested in a two-group comparison, adjusted for age and gender. Animal fluency had a magnitude difference of 2.2 points between those with SMC and those without SMC.

Table 4 shows the results of the nonparametric Mann-Whitney test we ran for non-normal neuropsychological dependent variables. Two of these measures were found to be significant: MMSE ( $p=0.03$ ) and animal fluency ( $p=0.01$ ). Clock numbers were not significantly associated with SMC. In addition, we ran a t-test for clock hand scores as it was approximately normally distributed. Those without SMCs performed better on the clock hands but Table 5 shows that this measure was not significantly associated. The composite measure of MMSE was used to assess the association between overall cognitive performance and SMC, while individual measures were tested separately to represent different cognitive domains.

**Table 4.** Mann-Whitney U Tests of Differences by SMC Group

	Mean Ranks	N	U	Z	p
MMSE	SMC Yes = 78.69 SMC No = 104.31	26 175	1695	-2.13	<b>.03</b>
Animal Fluency	SMC Yes = 73.31 SMC No = 104.56	26 174	1555	-2.57	<b>.01</b>
Clock: Numbers	SMC Yes = 89.68 SMC No = 91.79	25 157	1917	-.21	.83
WMH	SMC Yes = 60.62 SMC No = 51.92	13 92	499	-.96	.34
Geriatric Depression	SMC Yes = 155.65 SMC No = 92.88	26 175	854	-5.26	<b>&lt;.001</b>

Participants with SMCs scored lower on a 0 to 9-point scale when given a long-term memory task. Better performance on the test is indicated by a higher score. The SMC “yes” group had a mean score of 4 while the SMC “no” group had a mean score of 6.5 out of 9 (Table 5). The analysis showed a 2.4 magnitude difference between the CVLT long delay scores of those with memory complaints and those without memory complaints. An independent samples t-test for approximately normally distributed dependent variables showed that those with subjective memory complaints perform worse on the CVLT long delay. This variable is significantly associated with subjective memory complaints ( $p=.001$ ) based on the results of a Welch’s t-test with unequal variances.

Table 5 shows the results of the independent samples t-tests that report the means of the population with SMC against those without SMC. It also shows the difference between the samples when the variances of two normal distributions are unknown.

**Table 5: Independent-Samples t-tests by SMC Groups**

	SMC = No			SMC = Yes			Mean Dif.	<i>t</i>	<i>p</i>
	<i>M</i>	<i>SD</i>	<i>n</i>	<i>M</i>	<i>SD</i>	<i>n</i>			
Clock: Hands	2.78	1.33	157	2.68	1.07	25	.10	.35	.73
CVLT Long Delay	6.45	2.28	173	4.04	3.05	26	2.41	4.79	<b>.001</b>
Hippocampal Vol.	5.57	0.72	92	5.39	0.98	13	.18	.82	.42
SUVR	.77	.08	122	.80	.09	12	-.03	-1.41	.16

*Hypothesis Two: MRI Measures*

Using a nonparametric Mann-Whitney test for non-normal dependent variables, we found that individuals with SMCs had more white matter hyperintensities than those without SMCs, but the difference was not statistically significant ( $p=.36$ ) (Table 4). Total hippocampal volume was approximately normally distributed and we used t-tests to explore the association with subjective memory complaints. Those without SMCs had more hippocampal volume than those with SMCs. Table 5 shows that this variable was not statistically significant.

These results suggest that WMH and hippocampal volume are not associated with SMCs in this population.

*Hypothesis Three: PET Measures*

Using an independent samples t-test, results showed that individuals with subjective memory complaints had slightly higher SUVR scores (mean 0.8) than individuals without subjective memory complaints (mean 0.78). Table 5 shows that this finding was not statistically significant though and further suggests that SMCs are not associated with SUVR scores of 90+ participants.

#### *Hypothesis Four: Behavioral Measures*

*90+ Study* participants with subjective memory complaints had higher scores on the geriatric depression scale (mean 4.23) than participants without SMCs (mean 1.78), indicating they were more likely to have depressive symptoms (Table 3). The magnitude of the difference of means between those with SMC and without SMC in relation to GDS score was 2.4 points. A Mann-Whitney test was used to examine whether subjective memory complaints were associated with depressive symptoms. This association was found to be significant ( $p < .001$ ) (Table 4). The results indicate that a higher GDS score is associated with subjective memory complaints in this study population.

#### **Multiple Logistic Regression Results**

To see whether we could predict SMC from the various measures in the current study, we performed multiple logistic regressions. Table 6 shows that the CVLT- long delay was a significant predictor of SMC, even when controlling for age, gender, education and all other objective cognitive tests. For every 1-point decrease in CVLT- long delay score, the OR for SMC increased by .75. In other words, a lower CVLT score means an increased possibility of an individual having subjective memory complaints. Of the objective cognitive measures, CVLT long delay was shown to be the best predictor of subjective memory complaint in participants of *The 90+ Study*.

In a multiple variable regression for MRI measures, white matter hyperintensities (p-value .05) as well as age (p-value .02) were found to be significant predictors of SMC when controlled for age, gender, education and hippocampal volume. Higher white matter hyperintensities were

able to predict subjective memory complaints in the *90+ Study* population. Hippocampal volume and gender trended towards significance with a p-value of .07, as well.

In the PET measure, SUVR was not predictive of SMC.

For behavioral measures, GDS was shown to be a significant predictor of SMC. For every 1-point decrease in the GDS score, the OR for SMC increased by 1.54. The higher the geriatric depression score (more depressive symptoms), the more risk an individual is at for having SMCs in this 90+ Study population. In other words, individuals are at a 54% greater risk of having SMCs for every 1-point increase in the GDS score.

Table 6 shows results of the multiple linear regressions that were performed to see whether the outcome of SMC could be predicted from the various measures in the current study, adjusted for age, gender and education.

**Table 6: Multiple Logistic Regressions Predicting SMC Likelihood: Combined Models**

<b>Objective Cognitive Testing</b>					
	Estimate(SE)	Wald $\chi^2$	df	Sig.	Odds Ratio
MMSE	-.14 (.12)	1.33	1	.25	.87
Animals	-.08 (.06)	1.74	1	.19	.92
Clock numbs	.18 (.27)	.45	1	.50	1.20
Clock hands	-.03 (.21)	.02	1	.89	.972
CVLT- LD	-.29 (.11)	7.04	1	<b>.008</b>	.75
Age	-.14 (.11)	1.68	1	.19	.87
Gender	-.23 (.52)	.20	1	.65	.79
Education	.23 (.14)	2.81	1	.09	1.25
<i>Omnibus <math>\chi^2 (8) = 26.5, p &lt; .001</math>. Nagelkerke pseudo <math>R^2 = .248</math>.</i>					
<b>MRI Measures</b>					
WMH	.05 (.03)	4.0	1	<b>.05</b>	1.05
Hippo	-.94 (.52)	3.34	1	.07	.39
Age	-.31 (.14)	5.2	1	<b>.02</b>	.73
Gender	-1.58 (.88)	3.24	1	.07	.21
Education	-.23 (.15)	2.50	1	.11	.79
<i>Omnibus <math>\chi^2 (5) = 13.26, p &lt; .04</math>. Nagelkerke pseudo <math>R^2 = .23</math>.</i>					
<b>PET Measure</b>					
SUVR	6.29 (4.15)	2.29	1	.13	537
Age	-.08 (.11)	.47	1	.50	.93
Gender	-.22 (.64)	.12	1	.73	.80
Education	-.30 (.15)	.04	1	.84	.97
<i>Omnibus <math>\chi^2 (4) = 2.76, p &lt; .6</math>. Nagelkerke pseudo <math>R^2 = .05</math>.</i>					
<b>Behavioral Measures</b>					
GDS	.43 (.09)	21.22	1	<b>&lt;.001</b>	1.54
Age	-.18 (.10)	3.34	1	.07	.84
Gender	-.50 (.49)	1.07	1	.30	.61
Education	.03 (.12)	.08	1	.78	1.03
<i>Omnibus <math>\chi^2 (4) = 30.35, p &lt; .000</math>. Nagelkerke pseudo <math>R^2 = .26</math></i>					
All variables adjusted for age, gender and education					

It has been suggested in other studies that cardiovascular risk factors may be instrumental in the development of dementia (Fillit, 2008). We decided to run more regression analyses based on this knowledge, controlling for cardiovascular factors. Table 7 shows the results of these further regression analyses. When controlling for age, gender, education and cardiovascular factors with the objective cognitive measures, CVLT long delay was again the only significant predictor of subjective memory complaints in the 90+ Study participants (p-value .008).

When we re-ran the regression and controlled for age, gender, education and cardiovascular factors in the MRI measures, we found that white matter hyperintensities (p-value .02), age (p-value 0.02) and gender (p-value .007) were all significant predictors of SMC. The significance of gender may be due to the difference of cardiovascular factors and the effects they have in the brains of males versus females.

When we re-ran PET measures in a regression that was controlled for age, gender, education and cardiovascular factors, we found that the variables remained insignificant and did not predict SMC in this population.

We ran another regression with the behavioral measure, GDS, and controlled for age, gender, education and cardiovascular factors and found that once again, the GDS was a very strong, significant predictor of SMC in this study population (p-value <.001).

Table 7 shows the results of this second set of multiple linear regressions that were performed to see whether SMC could be predicted from the various measures in the current study when adjusted for age, gender, education and cardiovascular risk factors.

**Table 7: Multiple Logistic Regressions Predicting SMC Likelihood:  
Adjusted for Cardiovascular Factors**

<b>Objective Cognitive Testing</b>					
	Estimate(SE)	Wald $\chi^2$	df	Sig.	Odds Ratio
MMSE	-.13 (.13)	1.1	1	.30	.88
Animals	-.05 (.06)	.73	1	.39	.95
Clock numbers	.24 (.26)	.80	1	.37	1.27
Clock hands	.06 (.22)	.07	1	.79	.94
CVLT- LD	-.32 (.12)	7.05	1	<b>.008</b>	.73
Age	-.13 (.11)	1.41	1	.24	.87
Gender	-.29 (.57)	.26	1	.61	.75
Education	.25 (.14)	3.15	1	.08	1.29
CAD	-2.8 (.92)	.09	1	.76	.76
MI	-1.03 (1.2)	.74	1	.39	.36
Afib	-.73 (.68)	1.13	1	.29	.48
HVD	.39 (1.03)	.14	1	.70	1.48
CHF	-.41 (1.15)	.13	1	.72	.66
Stroke	.34 (.73)	.22	1	.64	1.41
TIA	.61 (.66)	.87	1	.35	1.84
HBP	.56 (.56)	.98	1	.32	1.74
High Cholest	-.76 (.60)	1.6	1	.21	.47
<i>Omnibus <math>\chi^2</math> (17) = 32.92, p &lt; .012. Nagelkerke pseudo R<sup>2</sup> = .30.</i>					
<b>MRI Measures</b>					
WMH	.08 (.04)	5.32	1	<b>.02</b>	1.08
Hippo	-1.2 (.64)	3.53	1	.06	.30
Age	-.43 (.18)	5.52	1	<b>.02</b>	.65
Gender	-4.11 (1.51)	7.38	1	<b>.007</b>	.02
Education	-.24 (.20)	1.43	1	.23	.79
CAD	-.07 (1.65)	.002	1	.97	.94
MI	.14 (1.5)	.009	1	.93	1.15
Afib	-19.85 (7683.61)	<.001	1	.10	<.001
HVD	.36 (1.69)	.05	1	.83	1.44
CHF	-20.14 (9476.91)	<.001	1	.10	<.001
Stroke	1.04 (1.09)	.91	1	.34	2.83
TIA	-1.41 (1.2)	1.41	1	.23	.25
HBP	2.04 (1.07)	3.64	1	.06	7.68
High Cholest	-1.62 (1.07)	2.31	1	.13	.20
<i>Omnibus <math>\chi^2</math> (15) = 30.14, p &lt; .011. Nagelkerke pseudo R<sup>2</sup> = .47</i>					

<b>PET Measures</b>					
SUVR	6.43 (4.15)	2.4	1	.12	622.7
Age	-.10 (.11)	.774	1	.38	.91
Gender	-3.6 (.73)	.24	1	.63	.70
Education	-.001 (.16)	<.001	1	.10	.10
CAD	-.09 (1.32)	.004	1	.95	.92
MI	.09 (1.29)	.005	1	.94	1.10
Afib	-1.28 (1.15)	1.24	1	.27	.28
HVD	-18.84 (12133.22)	<.001	1	.10	<.001
CHF	-.30 (1.17)	.07	1	.80	.74
Stroke	.51 (.95)	.28	1	.60	1.66
TIA	.41 (.83)	.25	1	.62	1.51
HBP	.84 (.74)	1.29	1	.26	2.31
High Cholest	-1.3 (.93)	1.96	1	.16	.27
<i>Omnibus <math>\chi^2(13) = 10.83, p &lt; .63</math>. Nagelkerke pseudo <math>R^2 = .17</math></i>					
<b>Behavioral Measures</b>					
GDS	.46 (.1)	20.52	1	<b>&lt;.001</b>	1.58
Age	-.16 (.1)	2.42	1	.12	.85
Gender	-.70 (.53)	1.74	1	.19	.50
Education	.03 (.12)	.07	1	.79	1.03
CAD	-.17 (.90)	.04	1	.85	.84
MI	-.99 (1.15)	.74	1	.39	.37
Afib	-.50 (.70)	.51	1	.48	.61
HVD	.10 (1.01)	.01	1	.92	1.11
CHF	-1.6 (1.28)	1.58	1	.21	.20
Stroke	.59 (.69)	.72	1	.40	1.80
TIA	.47 (.62)	.57	1	.45	1.60
HBP	.44 (.55)	.63	1	.43	1.55
High Cholest	-.59 (-.56)	.95	1	.33	.58
<i>Omnibus <math>\chi^2(13) = 35.94, p &lt; .000</math>. Nagelkerke pseudo <math>R^2 = .33</math></i>					
All variables adjusted for age, gender, education and cardiovascular factors					
Cardiovascular risk factors include: heart disease (coronary heart disease (CAD), myocardial infarction (MI), atrial fibrillation (Afib), heart valve disease (HVD), and congestive heart failure (CHF)), as well as stroke, transient ischemic attack (TIA), high blood pressure (HBP) and high cholesterol					

## **Discussion**

Subjective memory complaints need to be further explored in the 90+ population as they may provide insight into the beginning stages of dementia and Alzheimer's Disease. This research study aimed to find associations between SMCs and relevant subclinical and neuropsychological measures and was based on the underlying idea that SMCs may be the result of changes in an individual at the start of the dementing process.

Hypothesis testing showed that participants with SMCs generally performed worse on neuropsychological testing, had lower hippocampal volumes, more WMH, more amyloid deposition and had more depressive symptoms than those without SMCs, even if some of these findings were not statistically significant.

Regression analysis, when adjusted for age, gender and education, showed that lower scores on the CVLT long delay, more WMHs in the brain and a higher GDS score in this research population could predict subjective memory complaints. The direction of some of these associations is unclear, however. A person who is struggling with neuropsychological tests, for example, may be reflecting on their performance and answering "yes" to subjective memory questions as a direct result. The relationship between SMCs and GDS may represent the way in which depression can alter an individual's perception of themselves. It also may indicate that subjective memory complaints and depression are a result of cognitive changes that an individual is experiencing. Further research needs to be done to fully understand the implications of this finding as depression may be a prodromal response to recognition of declining cognition or may be otherwise involved in the beginning of the dementia syndrome.

Increased white matter hyperintensities were shown to predict subjective memory complaints in this population and this finding is particularly interesting because it suggests that changes in the brain may be causing, at least in some significant way, subjective memory complaints.

Further regression analyses showed that, when also adjusted for age, gender, education and cardiovascular risk factors, CVLT-long delay, WMHs and the GDS were still significant predictors of SMC. Overall, the three strongest predictors of subjective memory complaints in this study have consistently been the CVLT long delay, white matter hyperintensities and the geriatric depression scale. These findings ultimately suggest that individuals in this study population with objective cognitive impairment in the long delay memory test, those with measurable changes in the brain due to WMHs and those with more depressive symptoms are more likely to have subjective memory complaints.

It would be useful in future studies to test longitudinal associations of SMCs in those with repeat brain scans. Tracking the changes in brain structure of those with SMCs versus those without SMCs overtime may be a better indicator of the relevance of SMCs and their relationship with subclinical brain pathologies. There were a lot of missing data in these measures and the smaller sample sizes may have impacted the results of the study. Re-running these hypotheses tests with more MRI and PET scan data may potentially show better associations.

One measure that was not explored in this current study was APOE (apolipoprotein E). APOE is considered the strongest risk factor for AD and greatly influences age at onset. Evidence has shown though that APOE4 (which puts an individual at higher risk of AD) has a negligible effect regarding dementia in individuals over the age of 90 (Corrada M., 2013). It is therefore very

possible that there would be no difference in proportions found between groups within in this study. An association may exist between APOE and biomarkers however and thus should be further explored in future studies of this nature.

### **Limitations**

Subjective memory complaint data was self-reported by the 90+ study participants in the presence of neuropsychological testers and not verified by informants. Participants could have different interpretations for the question, “Do you feel you have more memory problems than most?” or may have been tailoring answers to tester expectations. The SMC question also may not have been sensitive enough to fully access the complaints that each of these 201 participants had. If they believed they had memory complaints but did not think it was worse than others their age, they might have responded with a “no” instead of a “yes.”

Another limitation to this study was the amount of missing data we had for the various measures. Missing data for neuropsychological variables were coded for vision problems, general fatigue during testing, and running out of time to complete all the necessary tasks. The large amount of missing data for MRI scans was in part due to not receiving an additional 47 scans in time for the write up of this paper. The other missing MRI scans were due to participants having pacemakers or other metal in their body that would have interfered with the MRI machine. 67 individuals were lost to follow-up or had not yet completed the PET scan by the cut-off point used in this study.

Partly due to missing data, our largest limitation in this study was the sample size. Even though this study included 201 participants, we were missing much needed data on many of the

individuals. With a small sample size, the concern lies in whether we over-estimated the magnitude of an association when an association is present. In general, when the number of observations in a study is small and researchers attempt to adjust for many factors, the models can produce inaccurate or unreliable results. Data from this study could, therefore, be used to design a larger confirmatory study of the oldest-old, further exploring the importance of subjective memory complaints in relation to dementia and Alzheimer's disease in this population.

## **Conclusion**

Our study ultimately shows that 90 years and older individuals that have objective, long-term memory impairment, those with changes in brain pathology and those that suffer from more depressive symptoms are more likely to notice subjective changes in their memory performance. These results provide more evidence for existing literature that has found that objective memory impairment, cardiovascular risk factors and depression is associated with subjective memory complaints. This study expands on current research as it specifically focuses on a particular population that has yet to be explored for the significance of SMCs and their underlying meaning.

Populations throughout the world are living longer and dementia and Alzheimer's disease continue to be a significant public health concern. Previous studies suggest that subjective memory complaints may be indicative of future cognitive impairment, thus making continued research on this topic essential. However, information on SMCs in the oldest old is very limited

and should further be investigated beyond the scope of this current research study. If we can understand the significance of subjective memory complaints in the 90+ population regarding subclinical and pathological changes, then perhaps we can understand their relationship to future dementia in this quickly growing group of individuals.

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