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### Dementia and Primary-Care Health Measures:Hearing, Gait, and Markers of Inflammation

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Dementia and Primary-Care Health Measures:  
Hearing, Gait, and Markers of Inflammation

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### Abstract

Dementia is a syndrome associated with declining cognitive function that has a variety of types and causes, and is encountered frequently in general medical practice. Researchers are actively exploring possible risk factors for dementia. The St. Louis University Mental Status (SLUMS) exam is a dementia-screening exam used in primary care visits to detect cognitive impairment that may be a sign of dementia. This study compared scores on the SLUMS exam to other measures recorded in a typical primary care visit in 86 patients of age 65 and older to look for correlations between indicators of health, such as physical examination measures and complete blood count panels, and cognitive impairment, as measured by score on the SLUMS exam. Abnormal gait was associated with a lower score on the SLUMS exam compared to normal ( $p=.006$ ), failure of the hearing test in both ears was associated with a lower score on the SLUMS exam compared to patients passing the hearing test in one or both ears ( $p=.046$ ), red blood cell count was positively correlated with SLUMS exam score ( $p=.020$ ), white blood cell count was negatively correlated with SLUMS exam score ( $p=.003$ ), and serum albumin levels were negatively correlated with SLUMS exam score ( $p=.002$ ). These data support the view that both physical impairments and markers of an inflammatory response are related to dementia.

*Keywords:* dementia, cognitive impairment, inflammation, hearing, gait, albumin, white blood cells, red blood cells

## **Introduction**

Dementia is estimated to affect 14.7% of the US population aged 70 years and older, and to cost an estimated \$159 billion to \$215 billion nationwide (Hurd, Martorell, Delvande, Mullen and Langa, 2013). Worldwide, nearly 35.6 million people live with dementia, a number that is expected to triple by 2050 (World Health Association). Primary care visits frequently use screening tools such as the Mini-Mental Status Exam (MMSE) or St. Louis University Mental Status (SLUMS) exam to assess cognitive impairment and screen for dementia in elderly patients. An advantage of the SLUMS exam is that it differentiates dementia from mild neurocognitive impairment (MNCI), which may precede dementia in younger patients, so it has a broader assessment of cognitive impairment (Tariq, Tumosa, Chibnall, Perry and Morley, 2006). In order to consider physical and biological factors associated with cognitive impairment, this study analyzed primary-care health measures to find associations to scores on the SLUMS screening exam. The five variables that were selected for analysis were hearing, abnormal gait, white blood cell count, serum albumin levels, and red blood cell count. It is hypothesized that results from this study will find associations with these variables to SLUMS exam score that are support evidence of associations of the variables to scores on the MMSE and clinical diagnoses.

## **Vascular Risk Factors**

Hypertension, dyslipidemia, and diabetes have been shown to increase risk for both vascular dementia and Alzheimer's disease (Kloppenborg, van den Berg, Kappelle, and Biessels, 2008). These factors frequently occur together in what is known as the "metabolic syndrome." However, these variables were not considered in this analysis, as the data collected came from patients under a physician's care, whose hypertension, dyslipidemia,

and diabetes were actively controlled for by medications that may lower blood pressure, cholesterol, and blood glucose. Launer et al. (2000) found that blood pressure showed no association with dementia risk in men treated with anti-hypertensive medications.

Therefore, it is predicted that there will be no association in this study due to effects of medications.

### **Hearing**

Hearing loss has been shown to be more prevalent in populations with dementia, and to correlate with greater cognitive impairment as measured by the MMSE in both groups with and without dementia (Uhlmann, Larson, Rees, Koepsell and Duckert, 1989). Lin et al. (2011) performed a longitudinal study using data from the Baltimore Longitudinal Study of Aging, and found that during a median follow-up of 11.9 years, the risk of all-cause dementia increased with greater baseline hearing loss. Uhlmann, et al. hypothesize that hearing loss may be a risk factor to target for dementia prevention, as hearing loss decreases stimuli from the environment processed in the brain, and may also affect an individual's social interactions, possibly leading to social isolation. Another explanation is that the pathology that affects dementia may also affect cortical structures that process auditory stimuli. However, Uhlmann, et al. observed a relationship between hearing loss and cognitive impairment that was independent of age, which would not be expected for an age-related neurodegeneration process.

Lin et al. (2011) found hearing loss to be prospectively related to dementia. In this study, risk of dementia was only associated with hearing loss at thresholds greater than 25 dB, which is the threshold determined at which hearing loss will begin to impair verbal conversation (Lin et al., 2011), suggesting the importance of social interaction and

environmental enrichment in maintaining intact cognitive function. As hearing loss in both ears is much more functionally disabling, this study will compare hearing loss in both ears to intact hearing in one or both ears to determine if there is an association to cognitive impairment according to score on the SLUMS screening exam. It is predicted that hearing loss in both ears will have a lower score on the SLUMS screening exam than intact hearing in one or both ears.

### **Gait**

Recent studies suggest abnormal gait to be a predictor of non-Alzheimer's dementia. Verghese et al. (2002) used data from the Bronx Aging Study to compare dementia diagnoses for subjects with neurologic gait abnormalities to patients whose gait was normal after a median follow-up period of 6.6 years. Verghese et al. found that subjects with abnormal gaits were more likely to have non-Alzheimer's dementia, but not more likely to have Alzheimer's disease. Diagnoses were made by clinical and neuropsychological evaluations and confirmed by postmortem examinations in the 14.5 percent of subjects who died. It is hypothesized that gait disturbances are an effect of lesions in the brain related to vascular dementia that precede the appearance of cognitive decline (Hennerici et al., 1994).

Other studies have used quantitative gait analysis to look at different factors of gait such as speed, variability, and trunk accelerations. Patients with dementia show a slower walking speed, greater stride time and stride time variability, and more irregular trunk accelerations than both older and younger cognitively intact controls (Ijmker and Lamoth, 2012). Ijmker and Lamoth suggest that considering these patterns may provide an additional tool for early diagnosis of dementia. Due to a small sample, this study will only

define gait as abnormal versus normal in comparing scores on the SLUMS screening exam.

It is predicted that abnormal gait will be associated with lower scores on the SLUMS screening exam.

### **Inflammation**

Inflammation is commonly studied by measuring levels of inflammatory proteins in blood plasma such as c-reactive protein (CRP) and interleukin-6 (IL-6). IL-6 is a pro-inflammatory cytokine, and CRP is a positive acute phase protein. Inflammation is associated with an increased risk for cardiovascular disease, and moderately high IL-6 and CRP levels have been associated to increased mortality in the elderly (Harris, et al., 1999). High levels of IL-6 are also shown to be associated with an increased risk of non-Alzheimer's dementia (Sundelöf et al., 2009), likely due to cardiovascular disease mechanisms leading to vascular dementia. IL-6 is known to cross the blood-brain barrier to modulate immune and inflammatory responses that may result in neurodegeneration. Chronic increases in peripheral inflammation increase central inflammatory responses in the brain, which are hypothesized to drive chronic neurodegeneration (Perry, Cunningham and Holmes, 2007).

Marsland et al. (2014) found IL-6 and CRP were higher in subjects with decreased cognitive function in the areas of spatial reasoning, short term memory, verbal proficiency, learning and memory, and executive function, and that higher levels of IL-6 and CRP were also associated with lower cortical gray and white matter volumes according to MRI volumetric measurements, while controlling for age, sex, race, education, BMI and nicotine and alcohol use. This study suggests that inflammation may accelerate cognitive decline by affecting brain morphology.

As blood tests for IL-6 and CRP are not typically performed in primary-care visits, this study will examine if white blood cell count and serum albumin levels can predict inflammation associated with cognitive decline.

### **White Blood Cell Count**

The American Heart Association lists white blood cell count as an inflammatory maker that is a potential predictor of cardiovascular risk, although they recommend high-sensitivity C-reactive protein as having the greatest utility (Pearson, et al., 2003). White blood cell count is also indicated as an independent predictor of cardiovascular disease events, stroke and all-cause mortality in women and was found to be a comparable assessor of cardiovascular risk as CRP (Margolis, et al., 2005). As vascular risk factors and stroke increase the risk for development of vascular dementia, (Ross et al., 1999), it is likely that white blood cell count can also predict vascular dementia risk. Shad, Aghazadeh, Ahmad and Kress (2013) found that blood levels of monocytes and neutrophils are elevated above the normal range in patients diagnosed with Alzheimer's disease, irrespective of patient age and sex, and suggest that white blood cells may serve as key peripheral markers for early diagnosis of Alzheimer's disease. It is predicted in this study that higher white blood cell counts will be correlated to lower scores on the SLUMS screening exam.

### **Serum Albumin Levels**

Serum albumin is a negative acute phase protein that decreases in serum level as inflammation and positive acute phase proteins, such as CRP, increase. In a previous study, serum albumin level was shown to correlate with scores on the MMSE (Dik, et al., 2005). However, these results were somewhat inconclusive, as the association lost significance



after adjustment for age. Dik et al. also did not find any association between Il-6 and MMSE score or CRP and MMSE score, which disagrees with the findings of several other studies (Teunissen et al., 2003), (Marsland et al., 2014). A major limitation of the Dik et al. study was also nonresponse and loss of follow-up, which may have accounted for lost associations because of selective loss to follow-up.

More recent studies have found further evidence of a possible relationship between serum albumin levels and amount of cognitive decline. Ng, Niti, Feng, Kua and Yap (2009) found low serum albumin levels to be associated to cognitive impairment and decline in a population of 2, 611 elderly Chinese from the Singapore Longitudinal Aging Study. The Ng et al. study also found an association between low albumin levels and cognitive decline to be especially strong in individuals with the APOE-4 genotype, suggesting a genetic vulnerability.

Low albumin levels was found to be an independent risk marker for cognitive decline, as defined by a decrease in 3 points on the MMSE in a population of 873 Japanese aged 70 and older (Taniguchi et al., 2014). The Taniguchi et al. study and the Ng et al. study also emphasize the role of serum albumin in nutrition. As albumin can be consumed through dietary proteins, there is the potential to explore the effects of protein supplementation on cognitive effects in the elderly.

It is predicted in this study that low serum albumin levels will be associated with a lower score on the SLUMS screening exam.

### **Red Blood Cell Count**

Taniguchi et al. (2014) was the first study to show that red blood cell count was an independent predictor for cognitive decline on the MMSE after adjusting for confounders.

Taniguchi et al. suggest that this may be mediated by nutrition; for example low iron intake leads to smaller red blood cells. In addition, nutritional intake is related to albumin levels in the blood, which Taniguchi et al. also found to be related to cognitive decline in the same study. Low nutritional status is also related to frailty and low body weight. Qizilbasch et al. (2015) recently found in a retrospective cohort study of two million subjects that underweight people (BMI <20 kg/m<sup>2</sup>) had a 34 percent higher risk of dementia than those of a healthy weight, and very obese people (BMI >40 kg/m<sup>2</sup>) had a 29 percent higher risk of dementia than those of a healthy weight. Although these results do not support previous studies of Body Mass Index (BMI) predicting dementia risk, they do suggest that nutritional status may play a very important role in cognitive decline, and red blood cell count is a possible way to predict relevant nutrition. It is predicted in this study that low red blood cell count will be associated with a low score on the SLUMS exam.

### **The Current Study**

This study is designed to extend the current research on dementia by analyzing several possible contributing variables to cognitive impairment in the same population. This study will use the SLUMS screening exam to estimate level of cognitive impairment. The goal of this study is to better understand what other markers regularly measured in a primary care visit are associated with cognitive impairment, so that a more complete diagnostic picture for dementia can be formed that includes considering cognitive testing, physical examination and biomarkers from blood work. Previous studies have found associations of hearing, gait, white blood cell count, serum albumin, and red blood cell counts to either the MMSE or clinical diagnoses, but not the SLUMS exam, which provides a broader and more detailed assessment of cognitive impairment. It is hypothesized that the

SLUMS exam will follow the same patterns of association to hearing, gait, white blood cell count, serum albumin, and red blood cell counts as previous studies that use the MMSE or clinical diagnoses, as described in the above sections.

## Methods

### Participants

Archival data were collected from electronic medical records at Goodwin Community Health, Somersworth, NH. A report was generated for all patients 65 and older with a score on the SLUMS exam, N=86. Data for SLUMS scores and other measures were transferred to a de-identified data file. Approval was given from the University of New Hampshire Institutional Review Board for the Protection of Human Subjects in Research (IRB) and the Chief Information Officer at Goodwin Community Health. A HIPAA privacy regulation waiver was obtained. Mean age of the participants was 70.74 years and subjects were primarily white. There were significantly more females (N=71) than males (N=15).

Table 1

#### *Sample Demographics*

	<b>Males</b>	<b>Females</b>
<b>N</b>	15	71
<b>Mean SLUMS Score</b>	23.4	24.6
<b>Mean Age</b>	70.5	70.8
<b>Mean BMI</b>	29.3	31.0
<b>Mean Blood Pressure</b>	127/73	126/70
<b>Mean Cholesterol</b>	173.5	200.4

**Measures**

The six variables analyzed were SLUMS exam score, hearing, gait, white blood cell count, serum albumin level and red blood cell count. The SLUMS exam has a score from 0-30, with scores from 1-20 indicating dementia (N=17), 21-26 indicating mild neurocognitive impairment (N=32), and 27-30 indicating normal cognitive function (N=37). Scoring assumed that all patients had a high school education. The mean SLUMS was 24.35, SD=5.09.

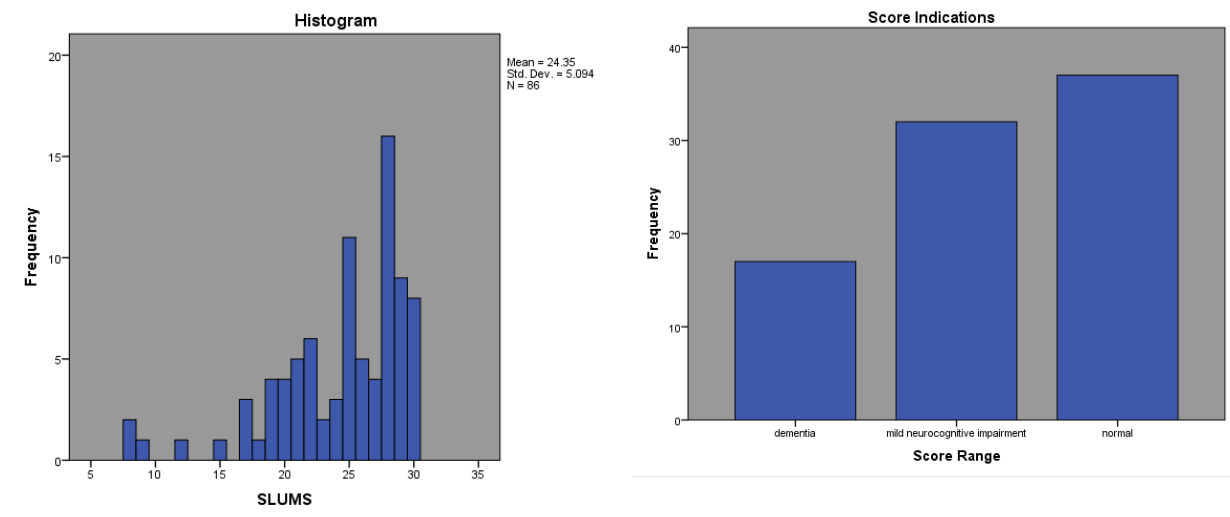


Figure 1: Frequency of SLUMS scores and frequency of the three indications.

Hearing loss was measured by a hearing test of each ear, with the possibility to pass or fail the test. Data from patients with a hearing aid were not included. Hearing data were available for 45 patients. If a patient passed the test in one or both ears, the patient was placed into the some hearing group (N=14). If a patient failed the test in both ears, the patient was placed into the hearing loss in both ears group (N=31).

Gait was determined by the patient's provider and documented by the physician's comments in the chart. Gait data was available for 71 patients. Patients described as normal gait were placed in the normal gait group (N=60). Any gait that was not described as normal was placed in the abnormal gait group (N=11).

White blood cell count (M=7.09, SD=2.03), serum albumin level (M=4.19, SD=0.47), and red blood cell count (M=4.47, SD=0.45) were all measured by routine blood tests. Statistical analysis was performed using SPSS.

## Results

### Hearing

To evaluate whether SLUMS score differed between groups with hearing loss in both ears and no hearing loss or loss in one ear, an independent samples t-test was performed. SLUMS scores were approximately normally distributed with no extreme outliers. The group with hearing loss in both ears had a significantly lower SLUMS score (M=22.26, SD=5.38) than the group with no hearing loss or hearing loss in one ear (M=25.43, SD=3.03).  $t(43)=2.055, p=.046$ , two-tailed. This was approximately a 3 point difference on the SLUMS score between the two hearing groups, a difference large enough to have clinical significance. Eta-squared=0.09, which corresponds to a small effect size.

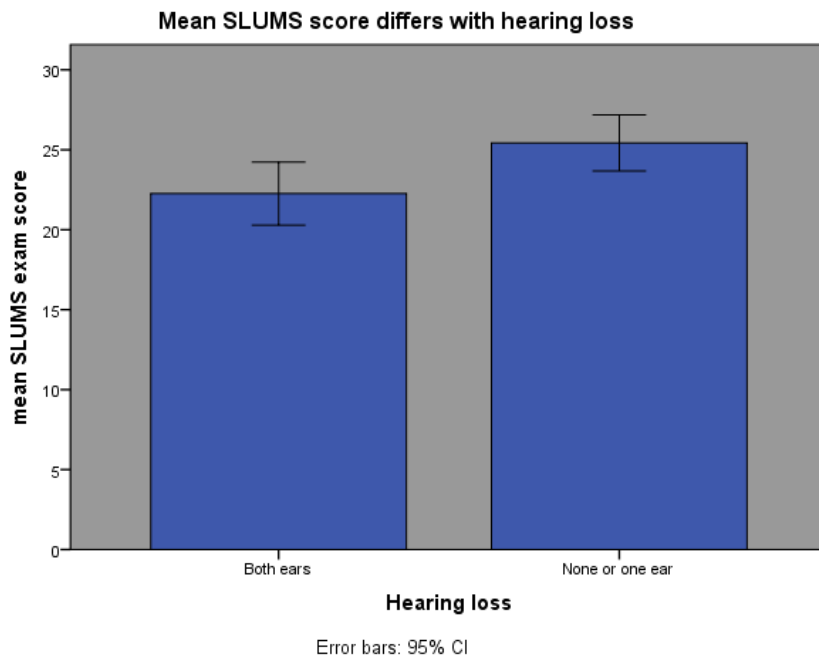


Figure 2: Mean SLUMS scores for the two hearing groups.

## Gait

To evaluate whether SLUMS score differed between the group with normal gait and the group with abnormal gait, an independent samples t-test was performed. SLUMS scores were approximately normally distributed with no extreme outliers. The group with abnormal gait had a significantly lower SLUMS score ( $M=20.45$ ,  $SD=6.76$ ) than the group with normal gait ( $M=24.87$ ,  $SD=4.34$ ).  $t(69)=2.82$ ,  $p=.006$ , two-tailed. This was approximately a 4.4 point difference on the SLUMS score between the two gait groups, a difference large enough to have clinical significance  $\text{Eta-squared}=0.1$ , which corresponds to a small effect size.

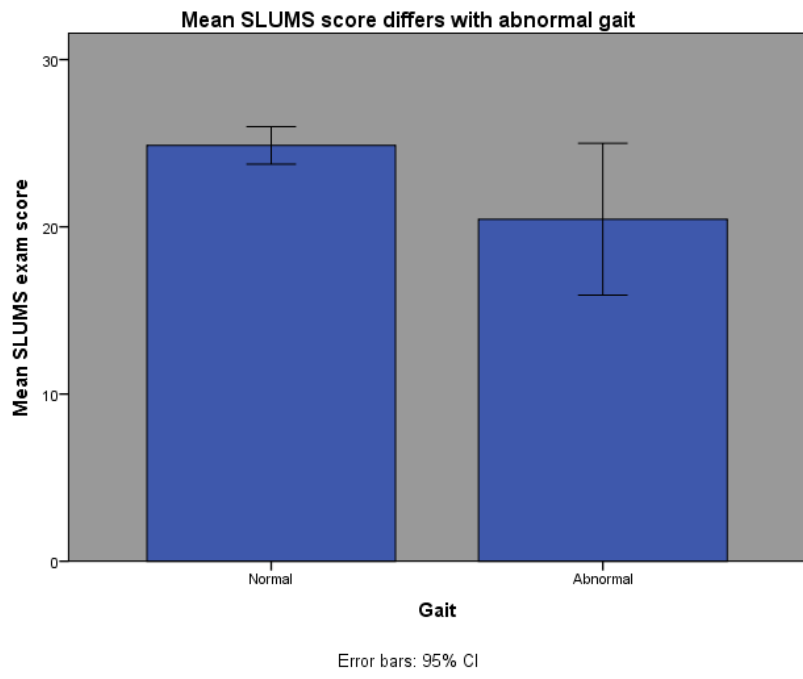


Figure 3: Mean SLUMS scores for the abnormal and normal gait groups.

### White Blood Cell Count

To evaluate whether SLUMS score could be predicted by white blood cell count, a bivariate linear regression analysis was performed. Scores for both the SLUMS score and white blood cell count (white blood cells per liter) were approximately normally distributed with no extreme outliers. A scatter plot indicated the relation between X and Y was negative and there were no extreme bivariate outliers. The regression was statistically significant,  $r=.331$ ,  $r^2=.110$ ,  $F(76)=9.234$ ,  $p=.003$ .

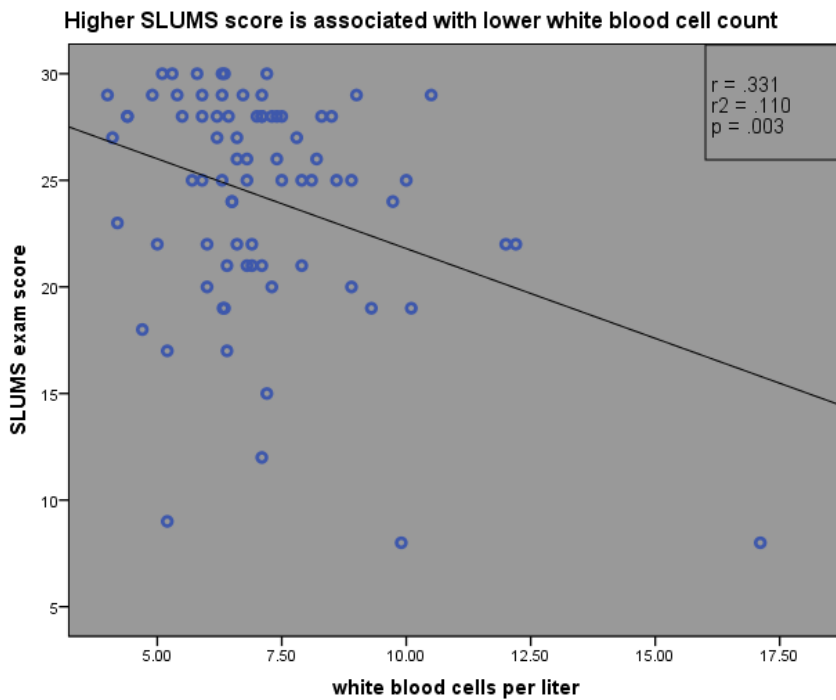


Figure 4: SLUMS score is negatively correlated to white blood cell count.

### Serum Albumin Level

To evaluate whether SLUMS score could be predicted by serum albumin level, a bivariate linear regression analysis was performed. Scores for both the SLUMS score and serum albumin level (mg/dl) were approximately normally distributed with no extreme outliers. A scatter plot indicated the relation between X and Y was negative and there were no extreme bivariate outliers. The regression was statistically significant,  $r=.343$ ,  $r^2=.117$ ,  $F(81)=10.638$ ,  $p=.002$ .



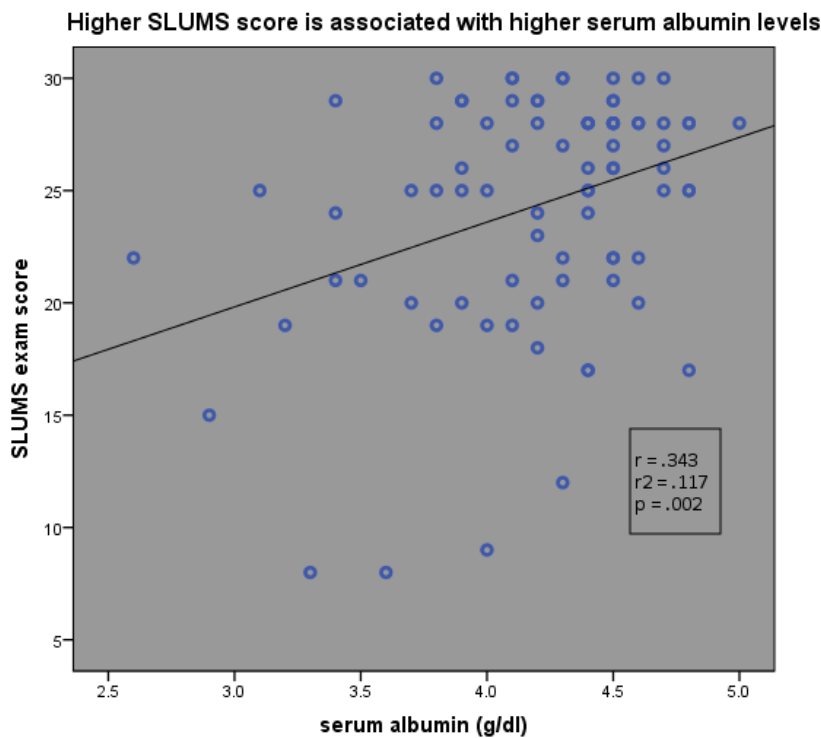


Figure 5: SLUMS score is positively correlated to serum albumin levels.

### Red Blood Cell Count

To evaluate whether SLUMS score could be predicted by red blood cell count, a bivariate linear regression analysis was performed. Scores for both the SLUMS score and red blood cell count (red blood cells per liter) were approximately normally distributed with no extreme outliers. A scatter plot indicated the relation between X and Y was negative and there were no extreme bivariate outliers. The regression was statistically significant,  $r = .264$ ,  $r^2 = .070$ ,  $F(76) = 5.626$ ,  $p = .02$ .

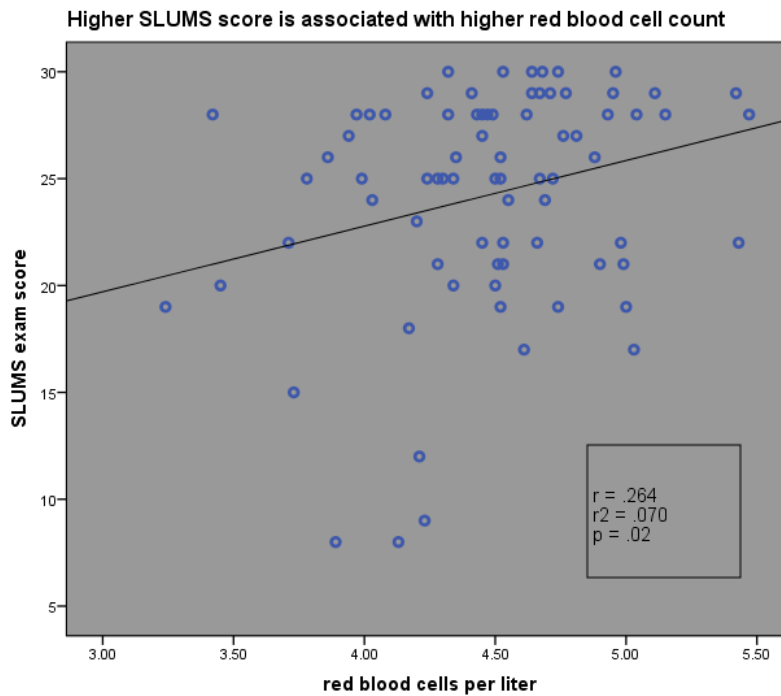


Figure 6: SLUMS score is positively correlated to red blood cell count.

### Multiple Linear Regression Analysis

A multiple linear regression analysis was performed for the predictors of white blood cell count, serum albumin, red blood cell count, age and sex. Age and sex were not significant predictors of SLUMS score. The overall regression including the predictors of white blood cell count, serum albumin, red blood cell count, age, and sex was statistically significant,  $R = .535$ ,  $R^2 = .286$ ,  $F(5,73) = 5.44$ ,  $p < .001$ .

A second linear analysis was also performed for the predictors of hearing, gait, age and sex. Sex was not a significant predictor of sex. The overall regression including the predictors of hearing, gait, age and sex was statistically significant,  $R = .685$ ,  $R^2 = .410$ ,  $F(4,40) = 7.961$ ,  $p < .001$ .

### Discussion

The results of this study show an association between scores on the SLUMS screening exam and hearing loss, abnormal gait, white blood cell count, serum albumin levels, and red blood cell count. The associations were also still significant when controlling for age and gender, indicating that the effects seen were not part of the normal aging process but are associated with cognitive impairment more severe than the effects of normal aging.

The results were consistent with previous research. Patients with hearing loss in both ears had a mean SLUMS exam score lower than patients with hearing loss in one or neither ear. This supports previous research that found a negative association between hearing loss and score on the MMSE. Patients with abnormal gait had a mean SLUMS exam score lower than patients with normal gait, supporting previous research that found gait to be a predictor of non-Alzheimer's dementia. As this study did not consider clinical diagnoses, it suggests that abnormal gait is associated with greater cognitive impairment than normal gait, which suggests a more broad association than non-Alzheimer's dementia.

White blood cell count and serum albumin level have been shown to be reliable predictors of systemic inflammation. In this study, high counts of white blood cells and low levels of serum albumin, both of which are indicative of inflammation, were associated with poorer scores on the SLUMS screening exam. This supports previous studies that examined the relationship between dementia and inflammation using markers of inflammation such as c-reactive protein and interleukin-6. If the same results can be predicted by white blood cell count and serum albumin levels, it is of clinical significance, as in many doctor's office

testing for CRP and IL-6 is not readily available, however blood tests are almost universally performed.

Red blood cell count was positively correlated with SLUMS exam score. Patients with a low red blood cell count performed more poorly on the SLUMS exam. This is an important contribution to dementia research as very few studies have to this date been done that have examined this connection. It is an important connection to nutritional status, and low red blood cell count can also be a sign of anemia and poor oxygen delivery to the brain.

In clinical applications, it is useful to have several different markers to use for determining diagnosis. This study suggests a tentative picture for diagnosis of dementia that includes considering cognitive abilities, physical abilities and biomarkers of the blood. Further research is needed to confirm these associations and determine if they change before or after cognitive symptoms begin to appear. However, this knowledge could be extremely useful to improve early diagnoses of dementia and other disorders associated with cognitive impairment in an elderly population.

This study was limited by a small sample size from only one location, and it was simply a correlational study. It also did not control for factors such as medications and chronic health conditions. Future research could be improved by a larger, more diverse sample size, a longitudinal design, and controlling for potential confounding factors.

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