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An Examination of Traumatic Brain Injury as a Risk Factor for Psychiatric Symptoms in Alzheimer's Disease Patients

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An Examination of Traumatic Brain Injury as a Risk Factor for Psychiatric Symptoms in Alzheimer's Disease Patients

CAPSTONE PROJECT PAPER

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By
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Abstract:

Introduction:
Dementia is a major public health issue both in the United States and worldwide. Alzheimer's disease (AD) is widely considered to be the most prevalent type of dementia. While the hallmark AD symptom is profound memory loss, patients also commonly experience changes in personality and behavior. These changes often include depression, anxiety, social withdrawal, mood swings, irritability and aggression, changes in sleeping habits, and delusions.

Background:
Several studies have established a mechanistic link between traumatic brain injury (TBI) and the development of AD. However, it is unknown whether TBI contributes to the personality/behavior changes observed in many AD patients. The current study examined a possible association between TBI and psychiatric conditions in patients who present with clinically diagnosed dementia due to AD.

Methods:
Participants in the current study were sampled from the National Alzheimer's Coordinating Center dataset. Only participants who had AD at the time of their most recent assessment were included in the study (N=10,511). Logistic regression was used to analyze the association between TBI and adverse psychiatric outcomes (defined as presence of psychosis or agitation/aggression) in patients with AD. Confounding variables, including age, gender, education, and dementia severity, were included in final regression models.

Results:
Agitation/Aggression:
This study found an association with alcohol abuse (OR: 1.87), age group of 65-74 (OR: 1.41), and having active diabetes in both the mild (OR: 1.21) and moderate (OR: 1.25) states of AD. A remote history of seizure in moderate AD had one of the strongest associations with increased odds of agitation/aggression (OR: 2.24). In those with severe AD and agitation/aggression, a protective association was found in those age 85+ (OR: 0.66), and in those with a recent history of urinary incontinence (OR: 0.59).
Psychosis:
The lowest educational attainment group had the highest risk of developing psychosis, with mild AD & 0-12 years of education (OR: 1.67), those with moderate AD & 0-12 years of education (OR: 1.76), in those with moderate AD & 13-16 years of education (OR: 1.53). At a mild stage of AD there was a suggestive association with urinary incontinence (OR: 1.20). In addition, being age 85+ at a severe stage of AD had a suggestive protective association (OR: 0.67).

Conclusion:
No significant association was found between TBI and psychiatric symptoms in persons with AD. However, there was evidence of an association between age, diabetes, alcohol abuse, urinary incontinence and seizures with agitation/aggression. Age, education level, and a recent history of incontinence are associated with increased odds of developing psychosis.

Introduction:

Dementia is a major public health issue not only in the United States but also worldwide. While there are several types of dementia, Alzheimer's disease (AD) is generally considered to be the most prevalent.[1] The Diagnostic and Statistical Manual of Mental (DSM) Disorders V classifies AD into two categories: major neurocognitive disorder (ND) and mild neurocognitive disorder.[2] These two categories can be further subdivided into probable and possible cases. A probable diagnosis of AD is assigned – either through genetic testing or familial history – based on evidence of the AD genetic mutation.[2] In addition, a probable case must have a clear presentation of memory decline and decline of at least one other cognitive function. A possible diagnosis of AD is given when there is no evidence of an AD genetic mutation but there is clear evidence of memory and information retention issues as well as steady cognitive decline without extended plateaus.[2] Both possible and probable diagnoses must present without evidence of mixed etiology.[2] While this is how AD is classified by the DSM-V, it is important to note that this is only one form of diagnostic classification. There are several methods that clinicians use to diagnose AD. Some of these methods include a thorough medical history, mental status testing, physical and neurological exams, imaging scans, and blood tests to rule out other types of dementia.[3]

Traditionally, the hallmark AD symptom is memory loss. However, people with AD also commonly experience disorientation; difficulty with spatial relationships, speaking and writing, judgment, planning, and/or carrying out familiar tasks; and changes in personality and behavior. These behavior and personality changes are generally characterized by symptoms such as depression, anxiety, social withdrawal, mood swings, distrust, irritability and aggression,

changes in sleeping habits, wandering, loss of inhibition, and delusions.[1] Memories established early in life are often the last to be lost during the course of the disease.[1]

AD places a heavy cognitive disease burden on the U.S. population, with 60-90% of all dementia cases being attributed to AD.[2] The overall prevalence of dementia increases with age.[2] Of the people diagnosed with AD, 7% are between the ages of 65 and 74, 53% are between the ages of 75 and 84, and 40% are 85+ years old.[2] In 2013, as defined by the ICD-9, AD was one of the 15 leading causes of death in the U.S.[4] In 2013, there were 84,767 total deaths attributed to AD.[4,5] Mortality increased from 1999 to 2013,[4] with the majority of deaths occurring between the ages of 75 and 84; for people older than 85 there was an increase in mortality rates until 2008.[4] Mortality in the 75-84 age range has begun to decline; in 1999, the mortality rate of AD was 129.5 deaths per 100,000 people, with the rate peaking in 2008 at 192.5 deaths per 100,000 people and later declining to 171.6 deaths per 100,000 people in 2013.[4] Additionally, deaths among those older than age 85 have begun to decrease, with the all-time highest death rate to date occurring in 2008 at 1,002.2 deaths per 100,000 people.[4] By 2013, this rate had decreased to 929.5 deaths per 100,000 people.[4] The age-adjusted rate increased from 16.5 deaths per 100,000 people in 1999 to 25.8 deaths per 100,000 people in 2008, with a slight decrease between 2008 and 2013 to 23.5 deaths per 100,000 people.[4]

Although there does not appear to be any single definitive cause of AD, it is generally agreed that several risk factors contribute to the development of disease.[1] Genetic and physiological risk factors for AD include age, genetic susceptibility (apolipoprotein E4 or APOE), Down's syndrome, vascular problems, and environmental risk factors, including traumatic brain injuries (TBI).[2] Upon autopsy, individuals with AD often show evidence of cortical atrophy and high levels of amyloid-predominant neuritic plaques and/or tau-predominant

neurofibrillary tangles.[2] These plaques and tangles are thought to contribute to brain shrinkage through neuron death, which causes many of the symptoms of AD.[6]

The purpose of this study was to assess the potential link between TBI history and psychiatric conditions in patients who present with medically diagnosed dementia due to AD. It evaluated the association between AD-related psychiatric symptoms or diagnosed psychiatric illnesses and reported TBIs.

Literature Review:

This literature review was conducted using PubMed, an online repository of medical and health-related peer-reviewed journals articles maintained by the National Institutes of Health. The main key words employed in the literature review were: Alzheimer's disease, psychiatric conditions, traumatic brain injuries, dementia, increased risk, risk factors, and increased odds.

A TBI is the loss or alteration of consciousness, with or without prograde and retrograde amnesia, that involves immediate physical and neurological symptoms ranging from mild to severe.[7] TBIs can cause several types of chronic physical, cognitive, and behavioral issues. The most common form of brain injury is an acute mild TBI or concussion.[7] Several epidemiological studies have tried to establish a mechanistic link between a TBI as an exposure and the development of AD as an outcome. These studies have produced conflicting results. Both a study in Japan by Kondo et al. and a study in Kentucky by Abner et al. found an increased risk of developing AD to be associated with a history of head injury, though results varied slightly between studies.[8,9] Using a case control study to examine risk factors for AD, Kondo et al. found that a head injury with a loss of consciousness (LOC) increased the odds of developing AD 5.5 times as compared with having no history of head injury with a LOC ($p<0.001$).[8] Abner et al. found that the odds of developing dementia among those with a history of TBI was only

significantly increased in males (OR 1.47, 95% CI 1.03 to 2.09); and the odds of developing AD in women with a history of TBI was increased but not found to be statistically significant (OR 1.18, 95% CI 0.83 to 1.68).[9] Two studies, the Rotterdam study and the Adult Changes in Thought study found that there was no statistically significant association between the development of AD and having a history of head injury.[9] Plassman et al. had a mixed result with increased rates in those with moderate (HR=2.32, p-value<0.05) and severe head injury (HR=4.51, p-value<0.05), however decreased risk in those with mild head injuries (HR=0.76, p-value>0.05), though the latter was not found to be statistically significant.[12]

Hyperphosphorylated tau, the main component in neurofibrillary tangles, is one of the pathological hallmarks of AD. Higher levels of tau are found in those who died with AD than in those who did not. A study by Jeromin et al. found that soldiers with a self-reported history of TBI had higher blood levels of Tau than those who had not experienced a TBI (p=0.03).[13] While an elevated tau level is expected in individuals with TBI, it was initially believed that these levels only remained high for a few hours immediately following the injury.[13] However, the study by Jeromin et al. indicated that these levels remained elevated for up to 3-18 months.[13] This study also found that the severity of total post-concussive symptoms was significantly correlated with total Tau concentrations in those with self-reported TBI (p=0.003).[13] Furthermore, the study indicated that people who suffered multiple TBIs maintained long-term elevated tau levels. The level of measured tau was directly correlated with the severity of symptoms experienced. The long-term health effects of elevated tau levels are currently unknown, but it is possible that elevated tau levels could be associated with a history of TBI and increased risk of AD, as elevated tau is thought to be one of the risk factors in AD development.

However, a major limitation to this study is that it does not report whether the Tau measured was the phosphorylated Tau found in neurofibrillary tangles.

Another study used mice with AD as a model and induced TBIs to observe the resulting changes in behavior. This study specifically examined how ß-amyloid (the main component in neuritic plaques) contributes to the neuro-inflammatory response post-concussive injury.[2,14] This study showed a difference in the recovery of mice with higher levels of ß-amyloid as compared with mice with lower levels of ß-amyloid.[14] This finding suggests a possible correlation between TBIs and AD-associated outcomes. Although there is some research on this connection between TBIs and AD outcomes, further analysis would help improve prediction of negative health outcomes for AD sufferers.

AD, an already burdensome disease, becomes more difficult to manage when the patient also suffers from neuropsychiatric symptoms (NPS).[15] Some studies have found that those with AD who suffer from NPS will have an expedited decline, both functionally and cognitively.[16,17] They also have been known to have a lower quality of life, often with earlier institutionalization and accelerated mortality rates.[18-22] Those who suffer from delusions or agitation had an increased risk of being institutionalized as compared to those who did not have delusions or agitation, with a hazard ratio of 5.74 (95% CI: 1.94-16.96) and 4.70 (95% CI: 1.07-20.70), respectively.[22] The presence of overwhelmed caregivers was often found to be a main mediating variable for institutionalization in those with delusions and or agitation.[22] Those suffering from hallucinations were found to have an increased mortality rate: HR=2.59 (95% CI: 1.09-6.16).[22] Some studies have found that NPS are predictors for the future onset of dementia in those with mild cognitive impairment (MCI).[23] A longitudinal study of a cohort who presented with MCI at the time of study found that those who had NPS were at an increased risk of developing AD:

HR=1.35 (95% CI: 1.09-1.66).[23] Due their close linkage with adverse health events and decreased quality of life of those with AD, NPS have been shown to be important targets for prevention.[15] Currently, most research on the association between NPS and AD conceptualizes NPS as a predictor of AD. Limited research has explored the risk factors for those who have AD and subsequently develop NPS.

Psychosis, defined as suffering from hallucinations and delusions, is a common occurrence in patients with AD, with one study reporting a prevalence of 41%.[24] Psychosis rates in patients with AD have been shown to be higher in those who reside in nursing facilities, with more than 66% suffering with symptoms for a time period longer than 10 weeks.[24] Imaging studies indicate that NPS symptoms can be caused by the neurodegeneration of areas associated with these psychiatric symptoms.[24] Single photon emission tomography (SPECT) scans have shown that patients suffering with dementia and psychosis usually manifest with preferential involvement of the frontal lobe and/or the limbic regions, as well as hypoperfusion in the parietal lobe.[24] There also tended to be gender differences when examining perfusion positron emission tomography (PET) scans, with females having lower perfusion in the right inferior-lateral frontal cortex and inferior temporal regions as compared to those who were not psychotic and males having higher perfusion in the right striatum.[24] SPECT scans also have shown decreased blood flow to the frontal and temporal regions of the brain in those suffering with agitation.[24]

However, research has shown that neuropathological explanations are not sufficient to explain why NPS happen in those with AD.[24] It is likely that a combination of factors (e.g., environmental, biological abnormalities, psychiatric history, family history, genetic susceptibility) contribute to NPS.[24] Neuropathological studies on psychosis have shown an increased deposition of neuritic plaques and neurofibrillary tangles in the areas associated with

varying psychotic symptoms when patients with AD are autopsied.[24] In a prospective clinicopathologic study, those who had AD confirmed by autopsy were found to have less severe neuron loss in the parahippocampal gyrus and non-significant lower neuron numbers in the serotonergic dorsal raphe nucleus than patients who had no NPS symptoms.[25]

Studies have shown concussions, or TBIs, to be linked not only with cognitive impairment but also with psychiatric symptoms. Sports-related head injuries have been demonstrated to be highly associated with MCI and depression in retired football players.[26] A prospective longitudinal study that examined symptoms and recovery time in those who suffered from a mild TBI found that a subset population of people with persistent symptoms post-injury suffered from psychological symptoms such as depression, traumatic stress, and low resilience.[27] A cross-sectional study on collegiate athletes concluded that athletes with a history of concussion displayed changes in their frontal-alpha and frontal-beta asymmetry by an electro encephalogram, which are indicative of increased general mood disturbances when compared to the controls ($p < 0.05$).[28] These findings also were correlated with self-reported depression and anxiety in those who suffered from frontal-alpha asymmetry and self-reported anger/aggression in those with alterations in beta-asymmetry.[28] However, these correlations were found to be significant only in the athletes who had a history of concussion.[28]

While the current literature address NPS and their effects in people with AD on multiple levels, continued research is needed on NPS predictive risk factors. This would aid in a holistic understanding of the potential causes and risk factors for these symptoms in those with dementia due to AD. In addition, this would aid in a more personalized approach in symptom prevention and management, as well as aid in the enhancement of quality of life.

Methods:

Study Design and Data

This study used a cross-sectional design to examine whether those with AD and a history of TBI had increased odds of NPS, primarily psychosis and agitation/aggression. These two conditions were chosen because they often are the primary psychiatric conditions that cause a person with AD to enter into early institutionalization.[15]

Data for this project were obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set and Neuropathology databases (December 2014 freeze) with full neuropsychiatric inventory. Dr. Erin Abner of the University of Kentucky's College of Public Health and Sanders-Brown Center on Aging submitted the data request on December 7, 2015, with approval granted the same day. Data then were downloaded from the NACC's online portal. Data in this study are representative of Version 1 & 2 of the protocols conducted by the NACC. The NACC Uniform Dataset consists of annual examinations of study participants, or by a co-participant (usually a family member or close friend), at each of the ~30 federally funded Alzheimer's Disease Centers (ADCs). All locations have different qualifying criteria for participation in the study. Participants may have any cognitive status. The total number of assessments included in the original data set amounted to 103,710, with 105 variables. Each individual participant could have multiple data lines due to annual follow-up visits to assess cognitive function. All research activities were approved by an Institutional Review Board (IRB) at the research center at which the participant was recruited and followed. All subjects provided written informed consent. No IRB approval was needed for this secondary analysis of the de-identified NACC data.

Variable Selection

Data for the current study were limited to the most recent clinical assessment available. Participants were limited to those with a clinical diagnosis of AD dementia at the last assessment (N=10,511). Variables of interest were retained, and several new variables were generated, including dementia due to AD, categorical educational attainment, categorical age groups, presence of agitation/aggression, psychosis, and TBI, and a new variable for race that collapsed Asian and Pacific Islander categories due to low numbers. TBI was defined as the participant having indicated that during their lifetime they had suffered from a recent (current) or remote (historically far-off) head injury, which had resulted in a brief loss of consciousness (LOC), an extended LOC, or a chronic deficit. All those who indicated no to the three types of head injury reported on were coded as having no history of TBI. In contrast, those who answered yes to one or multiple types were coded as having a history of TBI. Levels of education were categorized as 0-12 years (12=High School Diploma), 13-16 years (16=Bachelors Degree), 17-18 years (18=Masters Degree), and 18< years (18+ =Doctoral Degree). These ranges were chosen to reflect common U.S. educational attainment levels. In addition, the age groups were categorized as <65, 65-74, 75-84, and 85+ because these are the same groupings used by the CDC to report incidence and prevalence rates of AD in the U.S. The remaining variables then were assessed for missing-ness using frequency counts. Variables of interest included: AD status; AD severity; TBI status; psychosis status; agitation/aggression status; medical history related to incontinence, stroke, seizure, bypass, hypertension, heart attack, use of psychiatric drugs, smoking status, and alcohol or non-prescription drug use/abuse; and demographics such as age, gender, race, and years of educational attainment. No variable of interest had greater than a 15% missing rate, thus all variables were included in the analysis.

Statistical Analysis

Logistic regression, with dependent variables of agitation/aggression and psychosis, was used to estimate odds ratios for risk factors of interest. Initially, a bivariate analysis of each variable of interest was conducted for both dependent variables. Using the outcomes of these bivariate analyses, a complete model was generated. The model was further refined using backwards elimination to establish which variables should be kept in the final regression model. Based on these results, history of heart disease, history of cardiac bypass, and history of hypertension were eliminated from the model. Diabetes, history of drug abuse, and history of alcohol abuse were retained in the model, despite backwards elimination indicating they may not be necessary. This decision was made because diabetes, drug use, and alcohol abuse have a close relationship with an outcome of interest (agitation/aggression). Models were run with educational attainment and age as both categorical and continuous variables. Both education and age had higher significance levels when modeled as categorical rather than continuous variables; therefore, these two variables were run categorically. The final models then were run using selected variables. Due to wide confidence intervals, a secondary analysis of the model was conducted to identify unnecessary variables. This secondary analysis suggested that smoking status, prescription psychiatric drug use, gender, and race should be removed from the model in an effort to increase power. Akaike's Information Criterion was used to compare the models. Due to minimal change in these numbers as well as minimal changes in confidence intervals, these variables were excluded from the final model. Each model then was stratified by AD severity, which is associated with prevalence of NPS, using the Clinical Dementia Rating Global (CDRGLOB) score, ranging from 1 to 3 (1=mild dementia, 2=moderate dementia, 3=severe dementia), to generate six separate outputs. Additional variables were created for TBI, psychosis, and agitation/aggression to represent at which visit each participant was diagnosed with

psychosis, agitation/aggression, and/or TBI. The frequency of each was calculated to ensure that the majority of TBIs occurred at or before the diagnosis of psychological symptoms, which helped to ensure that exposure preceded the onset or diagnosis of psychological disorders.

Results:

Table 1.1 is a summary of participant demographics. The participants were 43.7% male and 56.3% female. In addition, those with TBI tended to be, at 60% to 40% female. The number of participants was highest in the age group of 75-84 years (41.5%) and lowest in the age group of less than 65 years (10.9%). While the percentage of people ages 75-84 is representative of the average percentage with AD in this age group, the number of participants in the age group of 65-74 years is higher than average at 21.8%, and the age group of 85+ years is lower than average at only 25.8%.[2] The percentage of white participants is high in this study, with 80.4% of the study participants identifying as white and only 11.6% identifying as black or African American, 0.7% as American Indian, 1.9% as Asian/Pacific Islander, and 3.2% as multiracial. Only 10.2% of study participants reported having suffered from a TBI. Of those that reported a TBI, the highest rate was in the participants who reported a TBI with a brief loss of consciousness (75.4%). Educational attainment was evenly distributed among those who had a high school education or less (38.0%) and those who had a college degree (37.4%). The proportion of substance abuse among those who had experienced a TBI was higher than among those who had not. Of those who had experienced a TBI, 11.0% reported abusing alcohol and 1.8% reported abusing drugs.

Table 2.1-2.2 shows the bivariate, crude values of all variables that were ultimately included in the adjusted models. All results are presented in odds ratios and stratified by AD

severity (mild, moderate, and severe). In those with mild AD and agitation and aggression, there were significantly increased odds of being in the age group of 65-74 years (OR=1.42, p-value=0.004) and having diabetes (OR=1.24, p-value=0.03), when compared to those age <65 and those who never had diabetes. There also was a marginally significant between abuse of alcohol, both recent (OR=1.60, p-value=0.09) and remote (OR=1.30, p-value=0.07) when compared to those who had no history of alcohol abuse. In those with moderate AD and agitation and aggression, there were increased odds of having diabetes, when compared to those who had no diabetes (OR=1.26, p-value=0.05). Conversely, being in the age group of 85+ years had a protective effect (OR=0.75, p-value=0.04), when compared to those in age group <65. In those with severe AD and agitation and aggression, there was a decrease in odds of having a history of seizures both recent (OR=0.62, p-value=0.01) and remote (OR=0.64, p-value=0.05), and having urinary incontinence (OR=0.66, p-value=0.0002), using those with no history of seizures or urinary incontinence as a comparison group. In addition, there is a suggested association with those 85 and older (OR=0.75, p-value=0.07) using those in age group <65 as a control.

In those with mild AD and psychosis, there were increased odds of having urinary incontinence (OR: 1.23, p-value=0.04), when compared to those with no history of urinary incontinence. Those with moderate AD had increased odds of being aged 65-74 (OR=1.38, p-value=0.05), having 0-12 years of education (OR=1.38, p-value=0.001), and having 13-16 years of education (OR=1.25, p-value=0.01) when using those in age group <65 and educational attainment of 18+ years as controls. Having a remote history of urinary incontinence appears to have a protective affect (OR=0.65, p-value=0.07), when compared to those who had no history of incontinence in those with moderate AD. Those with severe AD had increased odds of having 0-12 years of education (OR=1.58, p-value=0.01), diabetes (OR=1.38, p-value=0.02), and a

suggested association with alcohol abuse (OR=6.66, p-value=0.09) using 18+ years of education, no history of diabetes, and no history of alcohol abuse as comparison groups.

Tables 3.1 presents the association between agitation and aggression and TBI, stratified by severity of Alzheimer's disease as mild, moderate, and severe. Those with mild AD and agitation/aggression had an increased odds of being in age group 65-74 (OR=1.41, p-value=0.007) when compared to those in age group <65, and those with recent alcohol abuse, using those with no history of alcohol abuse for comparison (OR=1.87, p-value=0.04). There was also a suggestive association in this group with those who had a recent history of diabetes compared to those with no diabetes, with increased odds of 21% (OR=1.21, p-value=0.07). In those with moderate AD and agitation/aggression, there was a suggestive association between diabetes (OR=1.25, p-value=0.08), a remote history of seizures (OR=2.24, p-value=0.05), and remote urinary incontinence (OR=1.18, p-value=0.08), when compared to those who had no history of those conditions. In those with severe impairment due to AD, both those in age group 85+ (OR=0.66, p-value=0.07) and a recent history of seizures (OR=0.59, p-value=0.03) appeared to have a protective association with agitation/aggression, when compared to those who were in age group <65 and had no history of seizures.

Table 3.2 evaluates the association between psychosis and TBI, stratified by the severity of AD (mild, moderate, and severe). In this adjusted model, those with mild AD and psychosis had an increased odds of being having and educational attainment of only 0-12 years (OR=1.67, p-value=0.001) and recent urinary incontinence (OR=1.20, p-value=0.09), as compared to those who had 18+ years of education and no urinary incontinence. While urinary incontinence was not statistically significant, there was a suggestive association. Those with moderate AD and psychosis had increased odds of being in age group 65-74, when compared to those who were

<65 years, with a 45% increased odds (OR=1.45, p-value=0.03). In addition those with moderate AD and psychosis had and increased odds of having only 0-12 and 13-16 years of educational years, 76% increased odds (p-value=0.001) and 53% increased odds (p-value=0.01), respectively. In those with severe AD and psychosis ages 85+ appeared to have a suggestive protective association, with an OR of 0.67 (p-value=0.07) when compared to those <65 years of age.

Discussion:

The purpose of this study was to assess whether TBI was a potential risk factor for psychiatric symptoms in AD patients. There does not appear to be any significant association between TBI and agitation/aggression at any level of AD severity. However, there are several covariates that appeared to be significantly associated with agitation/aggression. It should be noted that while an association was not found with TBI, this study had a pervasive statistical power issue, increasing the probability of a Type II error—failure to find an association when one actually exists.

When AD was mild, there was a strong association with alcohol abuse and agitation/aggression symptoms. However, this association disappeared as the severity of the AD increased from moderate to severe. This result could occur because as the severity of AD increases, the likelihood of a person having access to substances, or the faculties to maintain an addiction, likely decrease. In contrast to those still actively abusing alcohol, as it is known that a symptom of alcohol abuse is mood instability, and therefore it is likely that the abuse of alcohol itself could be the cause of the agitation/aggression symptoms.

Those with mild AD also had increased odds in being in the age group 65-74; this could be because people of this age are entering a time where independence post retirement becomes important. However, with a diagnosis of AD, a person might feel they are losing their gained

independence faster than those others of their age group. In addition, a loss of cognitive function can be a big lifestyle change, causing anger and aggression. Another reason this age group could be experiencing higher agitation/aggression could be the lack of properly trained elder care workers working with those at this level of AD.

There also was an association between having active diabetes and having agitation/aggression in both the mild and moderate states of AD. One explanation of this association could be that when diabetes is not managed appropriately, diabetic shock may cause mood instability, which could be misdiagnosed as a neuropsychiatric symptom caused by AD. Though this association was not statistically significant, it could be a clinically significant association.

A remote history of seizure with AD had one of the strongest associations with an odds ratio of 2.24 for agitation/aggression, in those with moderate AD compared to those who did not have a history of seizures. An explanation of this association could be that if seizures are severe enough, it can cause brain damage affecting the centers of the brain responsible for agitation and aggression symptoms. However, without more informed medical history on the severity of seizures this association cannot be explored.

In those with severe AD and agitation/aggression, a protective association was found in those age 85+ and in those with a recent history of urinary incontinence. This is likely due to the fact that old age, urinary incontinence, and severe AD are all likely factors to cause institutionalization; therefore they are likely receiving superior medical care as well as be highly medicated to control their symptoms.

Psychosis was not significantly associated with TBI. In addition, those in the lowest educational attainment group had the highest risk of developing psychosis, with 67% increased

odds in people who had mild AD and 0-12 years of education, 76% increase in odds in people who had moderate AD and 0-12 years of education, and 53% increase in odds in those who had 13-16 years of education. These findings could be attributed to the protective effect of education and cognitive reserve, indicated by several studies; the higher the level of educational attainment, the more protective cognitive reserve appears to be.[30]

At a mild stage of AD there is suggestive association between urinary incontinence and having psychosis, with an increased odds of 20%. While not statistically significant, the p-values were relatively close to 0.05. A study by Choudhury et al found that there was a statistically significant increase in odds of having urinary incontinence in those with psychosis, as compared to those who did not have psychosis, however it is important to note that no participants with dementia participated in this study.[29] Lastly, it appears that being age 85+ at a severe stage of AD has a suggestive protective association in moderate AD. This result could be explained by an increase in care. As those who are older and at a more severe stage of AD are more likely to be institutionalized; therefore, it could be hypothesized that these individuals are receiving better care than those who are younger and not incontinent.

Limitations

This study had many limitations. One main limitation was a lack of statistical power, due to the small number of participants who reported a TBI (effect variable). There also was a large amount of information bias. While the data provides information on TBIs with LOC or chronic deficit, it does not record data on brain injuries without an LOC or TBIs that did not cause noticeable deficits. In addition to this limitation, once a TBI is recorded, NACC does not record the amount of TBIs each individual has incurred. This protocol could have led to an underreporting of the amount of TBIs that were actually experienced. In addition to a possible underreporting of TBIs, there also is no information on how each TBI was acquired. Loss to

follow-up with this particular population may have been a problem due to the fact that all participants are sampled at different times, leaving an incomplete picture of developed symptoms as participants progress into worsening AD.

Selection bias also was problem, as a large proportion of people participating in the study were white and college-educated. Therefore, the study population is not representative of the overall population. Recall bias also could have played a role in this study, as information was not always ascertained from the original participant, with some information provided by a co-participant. In addition, there is a testing bias regarding the participants' TBI status because no medical confirmation of a TBI was required for version 1 and 2 of the NACC study, making it difficult to know whether participants had repeated head injury.

Future Directions

This study evaluated the association between several potential variables and psychological symptoms among AD patients. However, there are several directions that future studies could take to further the understanding of TBIs and NPS in people with AD. One area of importance would be examining the cellular and molecular changes that occur in patients who have had a TBI and exploring whether there is a difference in those who had the exposure and those who did not. The number of TBIs someone has experienced also is important, as this factor addresses whether there is a dose-response curve with the number of TBIs and the severity of symptoms experienced. A longitudinal prospective cohort study is also an area for future research, as this design would allow a time to event to be calculated. Lastly, a study that removes TBIs, which occurred after psychiatric symptoms started, could assess the time trend of the exposure (TBI) and the outcome (psychosis and agitation/aggression). For the purpose of this study, agitation and aggression were the only psychiatric symptoms analyzed, but an expansion of psychological symptoms experienced could reveal other important connections, as there are

many types of NPS that impact patients and caregivers. By expanding the types of symptoms analyzed, there is the potential to enhance the holistic understanding of the effect of TBIs on neuropsychological outcomes.

Conclusion:

This study did not find an association between TBI and psychiatric symptoms in persons with AD. However, there appears to be an association with age (65-74 years), active diabetes, active alcohol abuse, recent urinary incontinence, and a remote history of seizures and an increase in the odds of having agitation/aggression. However, those with severe AD and a recent history of seizures have decreased odds of developing agitation/aggression. In those with psychosis, education 0-12 years in patients with mild AD, and in those with moderate AD age 65-74 years, education 0-12 years and 13-16 years, had increased odds of developing psychosis. The limitations of this study reduce its ability to accurately assess possible associations between TBI and psychiatric conditions in persons with AD.

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Appendix

Figure 1: Study participant breakdown

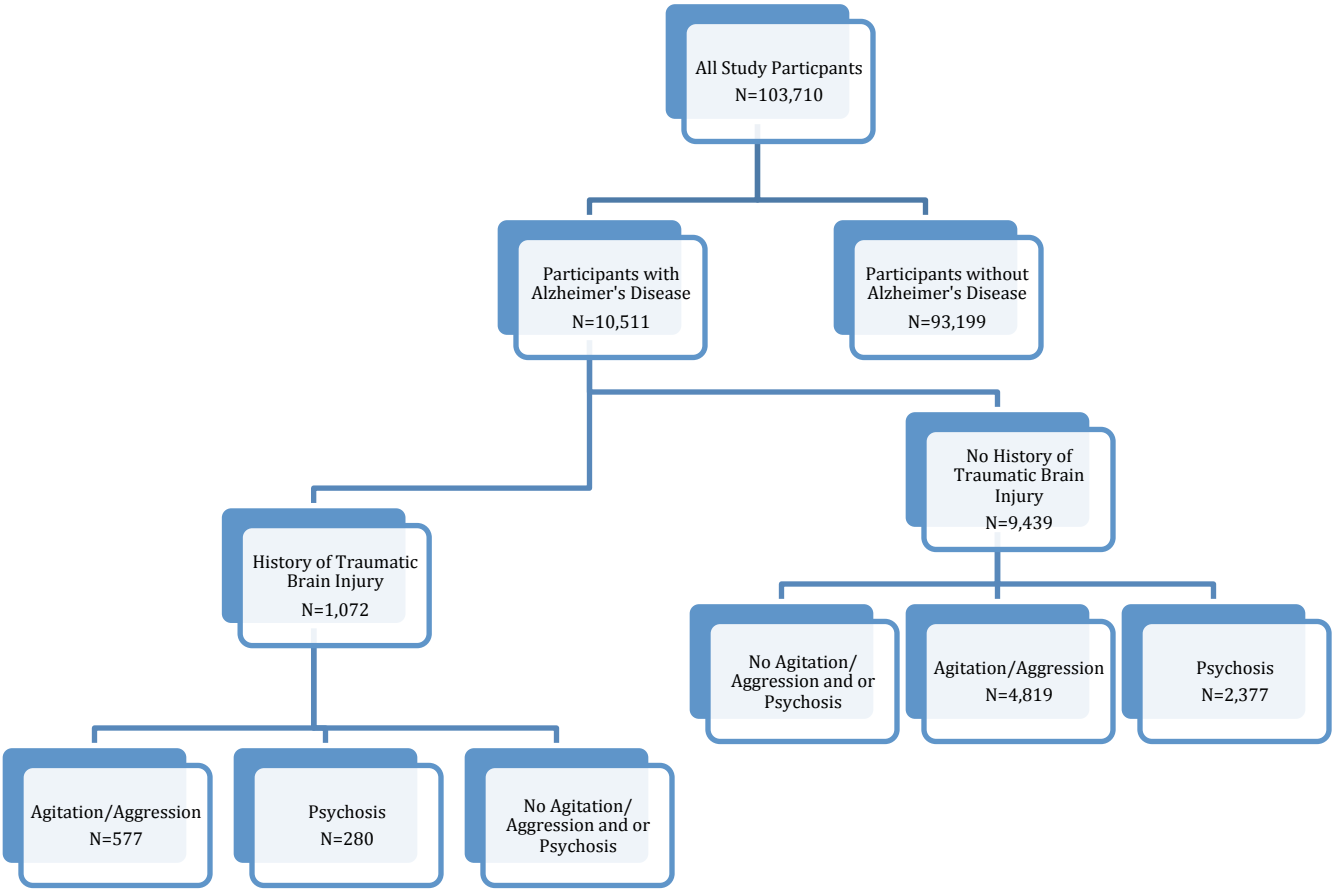

Table 1.1: Study Population Demographics

	TOTAL (N=10,511) n (%)	TBI Positive (N=1,072) n (%)	TBI Negative (N=9,439) n (%)
Sex			
Male	4, 596 (43.7)	646 (60.3)	3, 950 (41.8)
Female	5, 915 (56.3)	426 (39.7)	5, 489 (58.2)
Age			
<65	1, 143 (10.9)	158 (14.7)	985 (10.4)
65-74	2, 294 (21.8)	263 (24.5)	2, 031 (21.5)
75-84	43.62 (41.5)	382 (35.6)	3, 980 (42.2)
85+	2, 712 (25.8)	269 (25.1)	2,443 (25.9)
Race (NACCHIHR)			
White	8, 451 (80.4)	926 (86.3)	7, 525 (79.7)
Black or African American	1, 223 (11.6)	71 (6.6)	1, 152 (1.6)
American Indian or Alaska Native	74 (0.7)	9 (0.8)	65 (0.7)
Asian/ Pacific Islander	199 (1.9)	10 (0.9)	189 (2.0)
Multiracial	337 (3.2)	39 (3.6)	298 (3.2)
Years of Education			
0-12 yrs (12=High School Diploma)	3, 997 (38.0)	355 (33.1)	3, 642 (38.6)
13-16 yrs (16=Bachelors Degree)	3, 935 (37.4)	415 (38.7)	3, 520 (37.3)
17-18 yrs (18=Masters Degree)	1, 497 (14.2)	174 (16.2)	1, 323 (14.0)
18< (Doctoral Degree)	1, 082 (10.3)	128 (11.9)	954 (10.1)
TBI Exposure			
Brief Loss of Consciousness	808 (7.7)	808 (75.4)	--
Extended Loss Consciousness	292 (2.8)	292 (27.2)	--
Chronic Deficit	66 (0.6)	66 (6.2)	--
Alzheimer's Disease Status			
Mild (CDGLOB=1)	3,737 (35.6)	377 (35.2)	3, 360 (35.6)
Moderate (CDGLOB=2)	2,779 (26.4)	272 (25.4)	2, 507 (26.6)
Severe (CDGLOB=3)	2,103 (20.0)	222 (20.7)	1, 881 (19.9)
Medical History			
History of Stroke	760 (7.2)	77 (7.2)	683 (7.2)
Hypertension	5, 274 (50.2)	499 (46.5)	4, 775 (50.6)
Diabetes	1, 559 (14.8)	155 (14.5)	1, 404 (14.9)
Seizures	500 (4.8)	98 (9.1)	402 (4.3)
Urinary Incontinence	4, 029 (38.3)	471 (43.9)	3, 558 (37.7)
Substance Abuse History			
Alcohol Abuse	767 (7.3)	118 (11.0)	649 (6.9)
Drug Use	96 (0.9)	19 (1.8)	77 (0.8)
Smoking Status			
Ever Smoker	4, 552 (43.3)	534 (49.8)	4, 018 (42.6)
Never Smoked	5, 823 (55.4)	527 (49.2)	5, 296 (56.1)
Psychological State			
Agitation & Aggression	5, 396 (53.3)	577 (53.8)	4, 819 (51.1)
Psychosis	2, 657 (26.3)	280 (26.1)	2, 377 (25.2)

Table 2.1: Bivariate analysis of agitation and aggression by severity of Alzheimer's disease.

	AD with Mild Impairment CDRGLOB=1			AD with Moderate Impairment CDRGLOB=2			AD with Severe Impairment CDRGLOB=3		
	N	**OR (95% CI)**	**p-value**	**N**	**OR (95% CI)**	**p-value**	**N**	**OR (95% CI)**	**p-value**
Head Injury (TBI) Exposure									
TBI Positive	191	1.06 (0.85-1.32)	0.59	169	1.21 (0.94-1.57)	0.15	124	1.07 (0.80-1.43)	0.67
No History of TBI	1678	--	--	1472	--	--	1000	--	--
Age									
<65	196	--	--	173	--	--	133	--	--
65-74	474	1.42 (1.12-1.81)	0.004	334	1.16 (0.87-1.56)	0.32	241	0.97 (0.69-1.36)	0.85
75-84	829	1.13 (0.91-1.41)	0.26	675	1.02 (0.78-1.33)	0.90	415	0.90 (0.66-1.22)	0.49
85+	22.87	0.97 (0.76-1.23)	0.79	414	0.75 (0.57-0.99)	0.04	335	0.75 (0.55-1.03)	0.07
Education									
0-12 yrs	736	1.16 (0.92-1.46)	0.20	654	1.16 (0.88-1.52)	0.29	449	0.99 (0.71-1.38)	0.96
13-16 yrs	680	0.94 (0.74-1.18)	0.57	572	1.11 (0.84-1.46)	0.46	405	0.85 (0.61-1.18)	0.32
17-18 yrs	263	0.96 (0.74-1.26)	0.78	225	1.26 (0.91-1.74)	0.17	163	0.96 (0.66-1.40)	0.83
18+ yrs	190	--	--	145	--	--	107	--	--
Health Conditions									
Diabetes (Recent)	270	1.24 (1.02-1.50)	0.03	227	1.26 (1.00-1.59)	0.05	157	1.11 (0.85-1.45)	0.44
Diabetes (Remote)	31	1.20 (0.71-2.04)	0.50	24	0.91 (0.49-1.67)	0.75	18	0.79 (0.40-1.54)	0.48
No Diabetes	1565	--	--	1341	--	--	945	--	--
History of Stroke	1618	1.13 (0.87-1.47)	0.35	149	1.14 (0.87-1.50)	0.35	86	1.11 (0.75-1.63)	0.61
No History of Stroke	136	--	--	1248	--	--	613	--	--
History of Seizures (Recent)	23	0.94 (0.53-1.68)	0.84	29	0.93 (0.53-1.62)	0.79	66	0.62 (0.440.87)	0.01
History of Seizures (Remote)	33	1.24 (0.74-2.10)	0.42	30	1.76 (0.90-3.44)	0.10	39	0.64 (0.41-1.00)	0.05
No History of Seizures	1,801	--	--	1,532	--	--	1,011	--	--
Incontinence (Recent)*	389	1.07 (0.91-1.25)	0.44	593	1.05 (0.90-1.24)	0.53	802	0.66 (0.53-0.83)	0.0002
Incontinence (Remote)*	69	1.11 (0.80-1.55)	0.53	53	0.96 (0.63-1.47)	0.85	22	0.74 (0.38-1.44)	0.37
No Incontinence*	1394	--	--	945	--		297	--	--
Substance Use									
Alcohol Abuse (Recent)	35	1.60 (0.93-2.77)	0.09	13	1.14 (0.47-2.75)	0.78	3	1.11 (0.19-6.67)	0.91
Alcohol Abuse (Remote)	124	1.30 (0.98-1.71)	0.07	105	0.99 (0.73-1.35)	0.96	83	1.12 (0.79-1.59)	0.53
No Alcohol Abuse	1703	--	--	1471	--	--	1033	--	--
Drug Abuse (Recent)	2	0.63 (0.10-3.74)	0.61	1	0.35 (0.03-3.87)	0.39	0	N/A	N/A
Drug Abuse (Remote)	14	0.77 (0.38-1.57)	0.47	13	2.28 (0.74-6.99)	0.15	8	0.59 (0.23-1.489)	0.26
No Drug Abuse	1851	--	--	1575	--	--	1113	--	--

Table 2.2: Bivariate analysis of psychosis by severity of Alzheimer's disease.

	AD with Mild Impairment CDRGLOB=1			AD with Moderate Impairment CDRGLOB=2			AD with Severe Impairment CDRGLOB=3		
	N	**OR (95% CI)**	**p-value**	**N**	**OR (95% CI)**	**p-value**	**N**	**OR (95% CI)**	**p-value**
Head Injury (TBI) Exposure									
TBI Positive	74	0.97 (0.74-1.26)	0.80	103	1.15 (0.89-1.49)	0.30	86	1.17 (0.87-1.56)	0.31
No History of TBI	688	--	--	860	--	--	649	--	--
Age									
<65	73	--	--	93	--	--	89	--	--
65-74	175	1.22 (0.90-1.65)	0.20	208	1.38 (1.02-.86)	0.04	150	0.87 (0.62-1.22)	0.42
75-84	342	1.28 (0.96-1.69)	0.09	416	1.25 (0.95-.64)	0.12	289	0.99 (0.73-1.35)	0.96
85+	172	1.19 (0.88-1.61)	0.26	246	0.97 (0.72-1.29)	0.81	207	0.73 (0.53-1.00)	0.05
Education									
0-12 yrs	341	1.70 (1.26-2.30)	0.0005	425	1.71 (1.26-2.30)	0.001	344	1.58 (1.13-2.22)	0.01
13-16 yrs	271	1.23 (0.91-1.66)	0.19	350	1.51 (1.11-2.04)	0.01	246	0.96 (0.68-1.36)	0.83
17-18 yrs	88	1.01 (0.71-1.44)	0.97	118	1.29 (0.91-1.83)	0.16	83	0.81 (0.54-1.20)	0.29
18+ yrs	62	--	--	70	--	--	62	--	--
Health Conditions									
Diabetes (Recent)	113	1.18 (0.94-1.48)	0.16	810	1.14 (0.91-1.44)	0.26	116	1.38 (1.06-1.79)	0.02
Diabetes (Remote)	9	0.73 (0.36-1.50)	0.40	136	0.80 (0.42-1.54)	0.50	14	1.15 (0.58-2.29)	0.68
No Diabetes	638	--	--	13	--	--	603	--	--
History of Stroke	55	1.06 (0.77-1.44)	0.73	85	0.98 (0.74-1.30)	0.89	58	0.98 (0.67-1.41)	0.89
No History of Stroke	664	--	--	760	--	--	434	--	--
History of Seizures (Recent)	13	1.50 (0.78-2.86)	0.22	21	1.28 (0.73-2.25)	0.39	56	1.10	0.59
History of Seizures (Remote)	12	0.99 (0.52-1.88)	0.98	15	1.01 (0.54-1.92)	0.97	25	0.74	0.21
No History of Seizures	729	--	--	923	--	--	645	--	--
Incontinence (Recent)*	177	1.23 (1.01-1.49)	0.04	366	1.07 (0.91-1.27)	0.39	535	0.85 (0.69-1.05)	0.14
Incontinence (Remote)*	24	0.75 (0.48-1.17)	0.21	24	0.65 (0.40-1.04)	0.07	14	0.85 (0.43-1.68)	0.63
No Incontinence*	557	--	--	569	--	--	186	--	--
Substance Use									
Alcohol Abuse (Recent)	12	1.03 (0.54-1.97)	0.92	5	0.57 (0.21-1.56)	0.27	4	6.66 (0.74-59.65)	0.09
Alcohol Abuse (Remote)	49	1.11 (0.80-1.54)	0.53	63	0.99 (0.72-1.35)	0.93	53	1.04 (0.73-1.47)	0.83
No Alcohol Abuse	698	--	--	888	--	--	674	--	--
Drug Abuse (Recent)	0	<0.001 (<0.001 >999.999)	0.96	1	0.91 (0.08- 10.08)	0.94	0	N/A	N/A
Drug Abuse (Remote)	8	1.31 (0.58-2.94)	0.51	6	1.00 0.37-2.70)	0.99	7	1.05 (0.41-2.72)	0.92
No Drug Abuse	753	--	--	949	--	--	727	--	--

Table 3.1: Multivariate analysis of agitation and aggression by severity of Alzheimer's disease

	AD with Mild Impairment CDRGLOB=1		AD with Moderate Impairment CDRGLOB=2		AD with Severe Impairment CDRGLOB=3	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Head Injury (TBI) Exposure						
TBI Positive	1.11 (0.89-1.41)	0.35	1.05 (0.78-1.42)	0.74	0.99 (0.64-1.54)	0.97
No History of TBI	--	--	--	--	--	--
Age						
<65	--	--	--	--	--	--
65-74	1.41 (1.10-1.81)	0.007	1.19 (0.87-1.84)	0.27	1.11 (0.68-1.80)	0.68
75-84	1.12 (0.89-1.41)	0.35	1.07 (0.80-1.43)	0.64	0.82 (0.53-1.27)	0.37
85+	0.94 (0.73-1.21)	0.62	0.80 (0.59-1.09)	0.16	0.66 (0.42-1.04)	0.07
Education						
0-12 yrs	1.15 (0.90-1.46)	0.26	1.18 (0.87-1.59)	0.28	1.04 (0.63-1.69)	0.89
13-16 yrs	0.93 (0.73-1.18)	0.55	1.12 (0.83-1.52)	0.46	0.87 (0.53-1.42)	0.57
17-18 yrs	0.99 (0.75-1.01)	0.93	1.28 (0.90-1.84)	0.18	0.78 (0.44-1.39)	0.40
18+ yrs	--	--	--	--	--	--
Health Conditions						
Diabetes (Recent)	1.21 (0.99-1.49)	0.07	1.25 (0.97-1.61)	0.08	1.02 (0.72-1.46)	0.90
Diabetes (Remote)	1.08 (0.62-1.89)	0.78	0.99 (0.50-1.95)	0.98	0.87 (0.33-2.29)	0.77
No Diabetes	--	--	--	--	--	--
History of Stroke	1.19 (0.91-1.55)	0.20	1.20 (0.90-1.60)	0.20	1.30 (0.86-1.97)	0.21
No History of Stroke	--	--	--	--	--	--
History of Seizures (Recent)	1.02 (0.55-1.90)	0.94	0.89 (0.47-1.69)	0.72	0.59 (0.37-0.96)	0.03
History of Seizures (Remote)	1.52 (0.86-2.68)	0.15	2.24 (1.01-4.99)	0.05	0.74 (0.36-1.54)	0.42
No History of Seizures	--	--	--	--	--	--
Incontinence (Recent)*	1.06 (0.89-1.26)	0.55	1.18 (0.98-1.41)	0.08	0.88 (0.66-1.18)	0.38
Incontinence (Remote)*	1.15 (0.79-1.66)	0.47	1.04 (0.65-1.68)	0.87	0.68 (0.28-1.69)	0.41
No Incontinence*	--	--	--	--	--	--
Substance Use						
Alcohol Abuse (Recent)	1.87 (1.03-3.40)	0.04	1.45 (0.55-3.86)	0.45	0.73 (0.12-4.53)	0.73
Alcohol Abuse (Remote)	0.77 (0.36-1.65)	0.15	0.87 (0.62-1.23)	0.44	1.22 (0.71-2.09)	0.47
No Alcohol Abuse	--	--	--	--	--	--
Drug Abuse (Recent)	0.17 (.02-1.75)	0.14	0.85 (0.05-13.71)	0.91	NA	NA
Drug Abuse (Remote)	0.77 (0.36-1.65)	0.50	1.99 (0.61-6.46)	0.25	0.46 (0.14-1.51)	0.20
No Drug Abuse	--	--	--	--	--	--

*Urinary Incontinence

Table 3.2: Multivariate analysis of psychosis by severity of Alzheimer's disease.

	AD with Mild Impairment CDRGLOB=1		AD with Moderate Impairment CDRGLOB=2		AD with Severe Impairment CDRGLOB=3	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Head Injury (TBI) Exposure						
TBI Positive	0.94 (0.71-1.26)	0.68	1.22 (0.90-1.65)	0.20	1.02 (0.67-1.55)	0.93
No History of TBI	--	--	--	--	--	--
Age						
<65	--	--	--	--	--	--
65-74	1.24 (0.90-1.71)	0.19	1.45 (1.04-2.02)	0.03	0.87 (0.55-1.37)	0.55
75-84	1.28 (0.95-1.72)	0.11	1.29 (0.95-1.76)	0.10	0.94 (0.62-1.43)	0.78
85+	1.16 (0.83-1.61)	0.39	1.00 (0.72-1.38)	0.98	0.67 (0.43-1.04)	0.07
Education						
0-12 yrs	1.67 (1.22-2.28)	0.001	1.76 (1.27-2.45)	0.001	1.45 (0.91-2.31)	0.12
13-16 yrs	1.23 (0.90-1.69)	0.19	1.53 (1.10-2.13)	0.01	0.85 (0.53-1.36)	0.49
17-18 yrs	0.96 (0.66-1.40)	0.85	1.29 (0.88-1.91)	0.20	0.65 (0.37-1.14)	0.13
18+ yrs	--	--	--	--	--	--
Health Conditions						
Diabetes (Recent)	1.13 (0.89-1.43)	0.34	1.11 (0.86-1.42)	0.43	1.11 (0.79-1.56)	0.55
Diabetes (Remote)	0.77 (0.37-1.59)	0.47	0.89 (0.44-1.80)	0.74	0.96 (0.36-2.52)	0.93
No Diabetes	--	--	--	--	--	--
History of Stroke	1.01 (0.73-1.39)	0.95	0.94 (0.70-1.25)	0.49	0.98 (0.66-1.44)	0.90
No History of Stroke	--	--	--	--	--	--
History of Seizures (Recent)	1.153 (0.77-3.03)	0.22	1.38 (0.73-2.64)	0.32	1.47 (0.90-2.39)	0.12
History of Seizures (Remote)	1.20 (0.62-2.32)	0.59	1.21 (0.61-2.43)	0.58	0.63 (0.30-1.34)	0.23
No History of Seizures	--	--	--	--	--	--
Incontinence (Recent)*	1.20 (0.97-1.48)	0.09	1.14 (0.95-1.37)	0.17	0.91 (0.69-1.20)	0.50
Incontinence (Remote)*	0.75 (0.46-1.23)	0.26	0.65 (0.38-1.11)	0.11	1.30 (0.53-3.21)	0.57
No Incontinence*	--	--	--	--	--	--
Substance Use						
Alcohol Abuse (Recent)	1.09 (0.55-2.15)	0.81	0.46 (0.15-1.40)	0.17	4.93 (0.54-45.51)	0.16
Alcohol Abuse (Remote)	1.08 (0.76-1.54)	0.65	0.89 (0.63-1.28)	0.54	1.18 (0.72-1.96)	0.51
No Alcohol Abuse	--	--	--	--	--	--
Drug Abuse (Recent)	<0.001 (<0.001- >999.999)	0.97	1.99 (0.12-32.03)	0.63	N/A	N/A
Drug Abuse (Remote)	1.67 (0.72-3.90)	0.24	0.66 (0.20-2.14)	0.49	0.92 (0.28-2.99)	0.88
No Drug Abuse	--	--	--	--	--	--

*Urinary Incontinence

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Biographical Sketch

Jennifer Walch was born in Cherokee, Iowa, and moved shortly thereafter. Having lived all over the United States, from Texas to New Mexico and places in between, she now calls the Central Coast of California her home. She received her Bachelor of Science degree from University of California in Cell Biology in 2010. Currently, she is pursing her Master's in Public Health and Epidemiology degree from the University of Kentucky.

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