Considering Biological Sex in The Development of Dementia

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ABSTRACT

Dementia is a neurological, cognitive disease characterized by a patient's impaired memory and judgment, often seen during the geriatric stages of life. It is estimated that close to 10.7% of people worldwide over the age of 65 have some form of diagnosed dementia. This large percentage creates undue financial and caretaking burdens on family members and heavily impacts healthcare systems. While a cure for dementia is not known, researching this condition paves the way for treatments that could help millions of families. However, for these treatments to be effective, one should consider demographic information, such as biological sex, as a key variable in their studies. The correlation of demographic differences to the development of dementia has yet to be thoroughly studied. To investigate potential sex differences in dementia-related cognitive decline, we used data from The Aging, Dementia, and TBI Study from the Allen Institute for Brain Science that included a variety of patient cognitive assessments—such as the Braak and the NIA-Reagan criteria. Our results indicate a significant correlation between biological sex and the severity of neurodegeneration. Our findings suggest that sex as a biological variable should be given deep consideration when assessing the prognosis of neurodegenerative disorders in human patient populations.

INTRODUCTION

Dementia is a neurocognitive disease that impairs memory and judgment and is often observed in the late stages of natural aging. It is thought to be caused by an excess of non-functioning proteins that build up in the brain, impairing regions and leading to malfunctions, including cognitive, memory loss, and disorientation [1]. The most common form of dementia is Alzheimer's disease, which is further characterized by the rapid deterioration and malfunction of one's memory abilities [1]. Furthermore, there are also other types of dementia, including Huntington's disease—where the nerve cells in the brain break down [2]—and Vascular dementia—a type of dementia that occurs when blood vessels in the brain are damaged [3]—each with their own symptom profiles and hypothesized causes [4]. The variation in types of dementia creates a challenge for scientists to develop any one treatment for all. There is an urgent need to devise treatments for this family of diseases, as dementia affects not only the diagnosed but also their loved ones, who are most often their caretakers or the ones spending thousands of dollars on care services. There are also societal impacts that come with the disease, with research and treatment also affecting global economies and healthcare systems. Treatment for dementia is limited, often serving just to diminish individual symptoms as there is no cure for the disease. Some current treatments for dementia include acetylcholinesterase inhibitors—donepezil, rivastigmine, and Reminyl—which are medicines that prevent an enzyme from breaking down acetylcholine [5]. There is also memantine, a medicine that blocks the effects of excessive glutamate [5]. However, it is unknown how the efficacy of these treatments relates to demographic information, such as biological sex. Addressing these knowledge gaps regarding dementia will advance research to eventually reach a cure for dementia and help

millions of families affected by the disease. One of the most significant challenges to developing treatment for dementia is the possible implications biological sex could have. Biological sex poses a challenge because if there is a difference, then doctors will have to curate specific treatments for each biological sex. Previously, the risk of developing dementia differed between men and women, which is an important starting point [6]. Research has shown women have two times the risk of developing dementia [7]. On average, females typically live longer than males, greatly increasing their chances of developing the disease [7]. What are the biological sex differences in the development of dementia, and what are their implications? Researching the differences is crucial to finding a cure and treatment for the neurodegenerative disease. It will also help advance the development of personalized therapies focusing on helping patients. We will focus on how tests about the development of dementia—specifically Braak staging and the NIA-Reagan criteria—are different in males and females.

METHODS

The Aging, Dementia, and TBI study from the Allen Institute for Brain Science includes three data sets used in the current study to examine the differences between sexes: Donor Information, Protein and Pathology Quantifications, and Description of Stains, which explains the histological methods used in the quantifications used in the former dataset [8]. The dataset was found online. There were 107 donors in the study, all over the age of 77 [8]. Using the Donor Information data set from the Aging, Dementia, and TBI study, we isolated females and males by first sorting the sex column of the data set. There are different types of indicating tests for dementia, and we specifically used the Braak Staging and the NIA-Reagan criteria as a metric for the risk of developing dementia. The National Institute on Aging (NIA)-Reagan's neuropathologic criteria, which relies on neurofibrillary tangles and neuritic plaques, ranging from lowest to highest based on the amount of each [9]. Braak Stages go from I to IV, evaluating the progression of neurofibrillary tangle growth within the medial temporal lobe memory circuit from the lowest to the highest stage [10]. Using the averages of Braak stages and NIA-Reagan values from males and females, we created bar graphs to examine the differences between biological sexes in the development of dementia. Using alpha-synuclein immunohistochemistry, we further focused on the temporal cortex's deterioration, a key memory formation region. Each comparison between males and females will undergo a Student’s two-sample t-test [11], assuming equal variance between groups to test for statistical differences between the means of the two groups.

RESULTS

After creating graphs of the Braak staging method and the NIA-Reagan criteria, females were found to have greater values in both indicating methods. Females also had a higher average number of alpha-synuclein proteins in the temporal cortex.

Figure 1

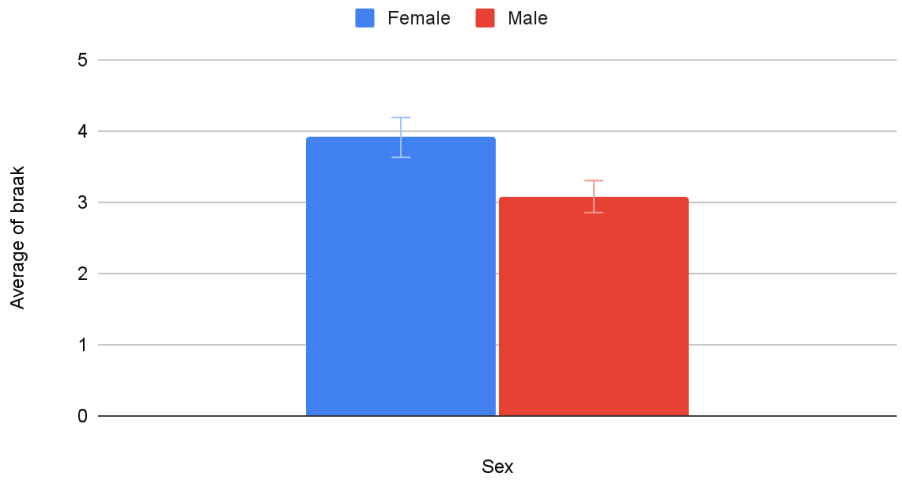
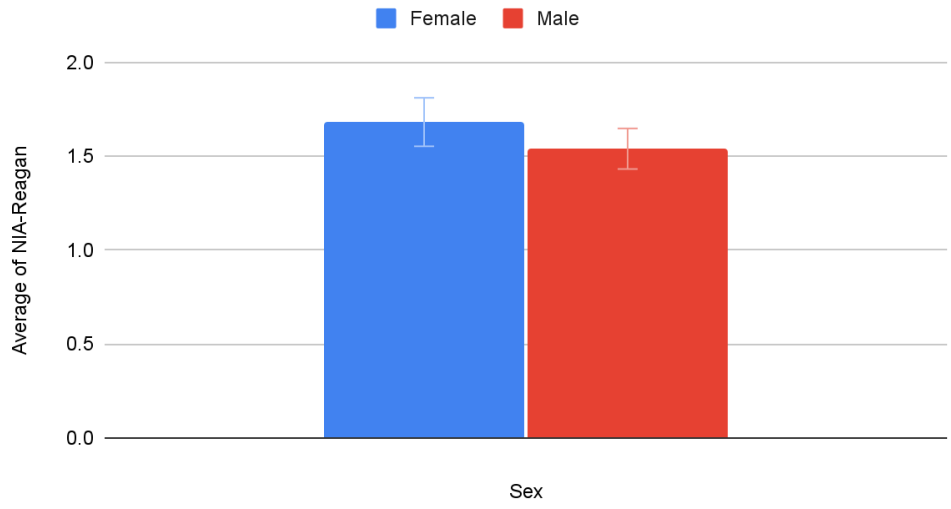


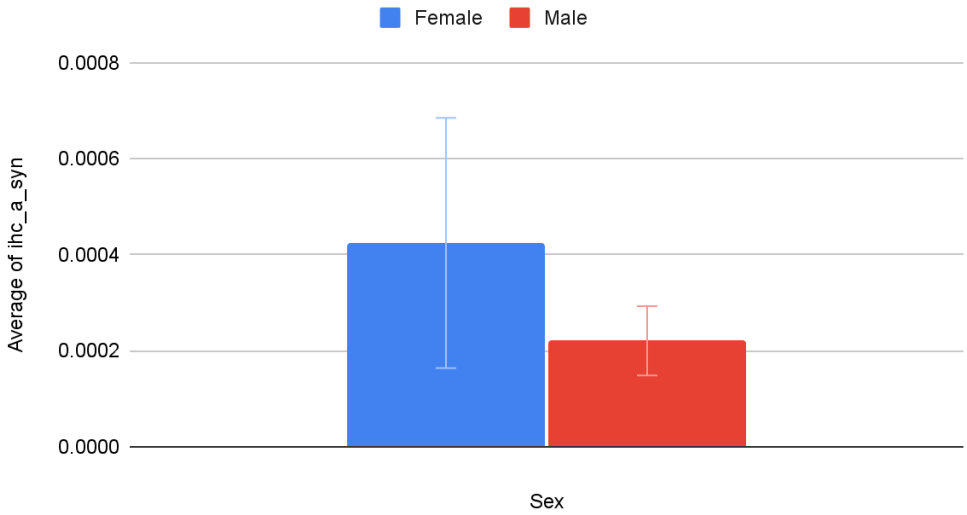
Figure 1 An unpaired-sample t-test was conducted to compare the means of Braak stage values between the two sex groups. Regarding the Braak staging method, females had higher averages than males, averaging stage 3.909, while males averaged 3.079. The standard error for females was 0.280, while males was 0.224. The p-value calculated was 0.013, below our predetermined alpha = 0.05 criterion for statistical significance. Females having a higher Braak stage suggest that, on average, they have a higher amount of neurofibrillary tangles in the brain than males do.

Figure 2



An unpaired-sample t-test was conducted to compare the means of NIA-Reagan values between the two sex groups. The average NIA-Reagan criteria values for females were higher than for males, averaging 1.68, while males averaged 1.54. The standard error for females was 0.129, while the standard error for males was 0.108. The p-value calculated was 0.40, which indicated that the difference between means was not statistically significant.

Figure 3



The average percent of alpha-synuclein proteins in females was higher than in males, at 0.000424%, while in males, it was 0.000221%. The standard error for females was 0.000260%, and for males it was 0.0000721%. The p-value calculated was 0.38, which indicated that the difference between the means was not statistically significant.

DISCUSSION

Females have greater amounts of neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are accumulations of a protein called tau in neurons [12]. Tau collects together and creates tangles in the neurons, which hinder the neuron's functions and cause malfunctions in brain areas [12]. Females averaged at a higher Braak stage, which implies they have more neurofibrillary tangles in the brain, causing them to have dementia. On the other hand, males, on average, do not have as many neurofibrillary tangles, meaning they have a lower chance of getting dementia. The second method used is the NIA-Reagan criteria. Females, on average, also have a higher value. Neuritic plaques consist of deteriorating neuronal material [12]. A higher value in the NIA-Reagan criteria suggests females have greater neurofibrillary tangles and neuritic plaques in the brain, which hinder brain function. Conversely, males have lower amounts of neuritic plaques and neurofibrillary tangles, meaning they have lower amounts of non-functioning proteins, causing them to have a lower chance of getting dementia. Lewy bodies and Lewy neurites are abnormal protein deposits, including alpha-synuclein proteins, which positively correlate to neurological degeneration [13]. The average Braak stage graph's p-value was 0.013. This suggests a significant difference in the means of female and male Braak stages, which suggests a biological difference in the development of dementia between the sexes.

Previously, researchers had found that females were at a greater risk of developing dementia than males. It has been attributed to biological differences between females and males, such as menstruation, pregnancies, and menopause [7]. Still, it has also been attributed

to traditional societal roles, specifically differences in work life and lifestyle [7]. The Braak stage difference between both sexes supports the idea that females have a greater risk of developing dementia. With females averaging a Braak stage of 3.909, while males with a 3.079, there is a clear disparity between the two. Females have a higher average Braak stage, meaning they are at a greater risk of developing dementia. The causes for this are still unknown and will have to be advanced by further research.

The neurological differences between sexes regarding dementia have a greater impact on treatments and how doctors diagnose patients. Doctors should prescribe medication and treatment accordingly and even take preventative measures, especially for biological females. Further, considering these biological and neurological differences between males and females will enhance knowledge and development of treatments, as well as future studies. Diagnosis will also change with this knowledge. It is important to note these different methods were used to diagnose dementia, and knowing that they differ between sexes can further inform scientists and doctors about advancing diagnosis. Knowing females have a higher chance of developing dementia, doctors should encourage screening females for dementia earlier in their lives to be proactive. Analyzing test results for females should also change; the scale of the tests should differ between sexes, with females having a lower value to be diagnosed with dementia, as they have a greater risk of developing it. Doctors should also curate specific tests between sexes, testing for sex-specific neurological dysfunction. Management of the disease will also be impacted, as there is a greater risk for females, which should be made known to the public to help prevent the disease.

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