Supplement for
"Risk Factors and Identifiers for Alzheimer's Disease: A Data Mining Analysis"

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Review of Literature on Factors that Affect Alzheimer's Disease

Neuroscience is the field of science that studies the human nervous system, the brain, and the biological basis of consciousness, perception, memory and learning. Neuroscience investigates brain activities of humans and associates the psychological state and physical behavior of humans with their brain activities. According to Sylwester (1993), "the nervous system and the brain are the physical foundation of the human learning process; neuroscience links our observations about cognitive behavior with the actual physical processes that support such behavior". Neuroscience interacts and collaborates with other fields of sciences, including chemistry, engineering, psychology, and medicine.

AD has a significant impact over a large proportion of the society, especially after the age of 60. The lack of a certain treatment method for AD makes the situation more critical and increases the importance of the prediagnosis of this disease. The significance of the disease is reported by National Academy on an Aging Society (NAAS,2000) through several statistics. NAAS (2000) reports that 90% of Alzheimer's patients are older than 65. AD affects white females the most. 85% of the population with the AD is white and 68% of the population with the disease is women. It is shown that behavioral problems are one of the common symptoms of dementia and that the chance of having the disease is higher if a person has poor physical health. In 2000 there were 4 million people with the disease, and this number is projected to increase to 6.8 million in 2020 and to 14.3 million in 2050 in the US alone.

In the light of the projections about AD, the importance of prediagnosis methodologies for AD is increasing. Radiological Society of North America (RSNA) reports that with the help of MRI scans and neuropsychological assessment, it is possible to gather information about AD and relatedly obtain a pre-diagnosis of the disease (RSNA,2011). Chiang et al. (2011) analyze not only the medieval temporal lobe of the brain but also multiple regions of the brain. In the frame of this new contribution, Chiang et al. (2011) observe that the volume loss in multiple regions of the brain signal future memory loss (RSNA, 2011).

In a study that is similar to Chiang et. al. (2011), Deweer et al. (1995) report the effects of hippocampal volume formation, amygdala (A), caudate nucleus (CN), normalized for total intracranial volume (TIV) on the AD prediagnosis. The analyses are done in terms of making comparisons between each factors. According to the results for these comparisons, there does not exist any clear relation between CN and TIV, nor between A and TIV. However, it is concluded that the volume change of hippocampal part of the brain is related to the probability of being an Alzheimer's patient.

Other than the volume changes of multiple regions of the brain, prediagnosis of AD can be facilitated by observing other factors. Davatzikos *et al.* (2008) emphasize the significance of early diagnosis of AD and suggest that by detecting complex patterns of brain abnormality in very early stages, the disease can be diagnosed. 30 subjects participated in the study of Davatzikos *et al.* (2008) and the pattern of each person composed of measurements of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). In terms of making the segmentation according to the variables, the stereotaxic space organization method is used. In other words, the brain structures are examined independent of the personal differences. According to the results of the analysis, Davatzikos *et al.* (2008) claimed that the early diagnosis of AD is possible through the analysis of brain images.

Similarly, De Jong *et al.* (2008) investigate the effect of the deep grey matter structure in AD. The authors compare the brain images of the subjects and cognitive test results. The brain volumes of the different regions are correlated with cognitive test results and FMRIB's Integrated Registration and Segmentation Tool (FIRST) methodology is used to calculate the brain volumes. According to the results, the decrease in the volumes of putamen and thalamus regions of the brain is linked to increasing probability of having AD. The existence of deep gray matter tissues is also linked to AD. At this point, within the scope of the studies mentioned above, it is appropriate to say that Grey Matter (GM) and White Matter (WM) diffusions in the brain are associated with the AD in a considerable way.

The effect of GM and WM densities can be examined through the classification analysis of MRI images (sMRI). Casanova *et al.* (2011) analyze MRI data using classification methods. In the scope of the obtained results of sMRI classification, the authors report that Gray matter (GM) and White matter (WM) densities are highly indicative in terms of differentiating patients and normal subjects. In addition to this study, Grydeland *et al.* (2012) analyze the effect of White matter (WM) vs. Grey matter (GM) composition on the diagnosis of the AD. The analysis has been done with the help of a contrast between white matter/gray matter (WM/GM) signal intensity obtained from MRI scans. As a result, the authors suggest that the WM/GM intensity contrast is a distinctive factor to validate the accuracy of morphometric measures and it is one of the significant biomarkers of brain degeneration in AD.

Grey and white matter densities are not the only markers/indicators that can be analyzed with the help of MRI scans. Medial temporal lobe atrophy (MTA) can also be analyzed on plain MRI films to distinguish patients with AD. Scheltens *et al.* (1992), who performed such a study, report that in Alzheimer patients, the degree of MTA is correlated significantly with scores on the mini-mental state examination (MMSE) and memory tests, but poorly with mental speed tests. The conclusion is that MMSE and memory test scores could be identifiers of AD. Additionally, the study shows that MTA can be analyzed easily with the help of MRI scans.

As mentioned earlier, volume changes of multiple regions of the brain could be signals of AD. In addition to that, volume changes of some brain regions can be related to other factors such as apolipoprotein ε4, which is a protein type that binds to fat, and carries it.

Apolipoprotein ε4 is a factor that is closely associated with AD. Lehtovirta *et al.* (1996) investigate the risk of the ε4 allele of apolipoprotein E (ApoE) with regards to AD. They report that the patients of AD have smaller volumes of hippocampal and amygdala compared to the normal subjects. More significantly, the people who have double ε4 allele gene structure, in other words, who have homozygous ε4 allele, are more likely to have AD: The

risk of medial temporal lobe degeneration for people who have double genes of ε4 allele is considerably higher than the people who have one ε4 allele or none.

In a more recent study, Schuff *et al.* (2009) investigate the effects of Hippocampal volume changes over time. The authors compare the MRI scans of different subjects and come up with insights on correlations. The study interconnects the presence of AD to the increased apolipoprotein ε4 and decreased cerebrospinal fluid CSF.

In the frame of the studies involving apolipoprotein ε4, it is appropriate to conclude that the genetics of the patients play a role in having AD. Woordward et al. (2007) report that the most likely risk factors of AD are age, genetic mutations that affect apolipoprotein ε status, and the Down syndrome. Whether having the Down syndrome or giving birth to a child who has Down syndrome both increase the risk of AD. Schupf et al. (2001) study the population of mothers who give birth to a child with Down's syndrome before the age of 35. The study reports that there is an increase in AD ratio for the mothers who give birth to a child with Down's syndrome and who are below the age of 35.

Flirski & Sobow (2005) present an examination of other biological markers of AD. Some of the biological markers studied by the authors are beta-amyloid, tau protein, and phosphorylated tau-protein. Other than the biological markers of AD, some other markers such as oxidative stress markers and inflammatory markers, which could have a place in the prediction of AD, are examined as well. It is seen that further studies are required for oxidative stress markers examination. Some biological markers, such as low levels of CSF Ab42 and high levels of CSF tau and Ptau, are significant factors for predicting AD.

Other than genetic factors, age is one of the biggest risk factors for AD. Lallanilla (2009) presents the effects of age, ethnic, life style, and depression on AD. The author suggests that the biggest risk factor is age, and that females are under a greater risk when combined with age. Also, it is observed from the subjects that the risk is increasing further after the age of 71. In the study, Japanese, Americans, and African-Americans are taken as independent groups. It is seen that Japanese and Americans are more likely to have AD than African-Americans. As a last analysis, Lallanilla (2009) focuses on the people with depression history and concludes that they are more likely to have AD in latter periods of their lives. Genova (2012) also shows that after the age 65, the risk of AD nearly doubles. Genova (2012) also emphasizes the importance of the genetic mutations, especially ApoE4 mutation. On the other hand, the author concludes that education level can be also a factor for AD. Van Oijen *et al.* (2007) also examine and show the existence of the positive relation between higher education levels and increasing risk of AD. The subjects' ages are above 55 and nearly 8000 subjects are questioned in Van Oijen *et al.* (2007). At the end of a period of examinations 568 of them appeared to be Alzheimer's patients. According to the results of the study, "the subjective memory complaints might be a crucial sign of AD especially in high educated segment" (Van Oijen *et al.*, 2007).

Genetics factors, age, education are only some of the risk factors that could play a significant role in AD. Patterson *et al.* (2007) report that estrogen level is associated with high risk of AD, while testosterone level is associated with low risk. Furthermore, diabetes, stroke, hyperthyroidism, and smoking are associated with increased risk of AD. On the contrary, regular physical activity is associated with decreased risk of AD. Meanwhile, the risks of the type 2 diabetes, fatty diet and head trauma are found to be associated with having the risk of AD (Genova, 2012). Kloppenborg *et al.* (2008) study the effects of diabetes, hypertension,

obesity and dyslipidaemia on AD. According to the results, all these four factors are associated with the existence of AD. Additionally, the results of the subjects with diabetes or obesity seemed more consistent. In detail, while for middle age hypertension matters most, for later life years diabetes seems the highest risk factor for AD.

Other than the most known risk factors of AD, there are several ones such as the effect of migraine, loneliness, and other factors. For instance, Tyas *et al.* (2001) suggest risk factors for AD such as effect of migraine and occupational exposure to defoliants. History of migraine has been found associated with the existence of AD at the latter stages and this association risk is higher among women. Finally, it is reported by Tyas *et al.* (2001) that occupational exposure to fumigants increases the risk of AD.

Wilson *et al.* (2007) aim to find out whether the loneliness of a person is associated with increasing in AD. To achieve this aim, Cox proportional methods adjusted for age, sex, and years of formal education are used. In the initial model a unique term for loneliness is added and then this model is modified for different analyses (for social network, cognitive activity etc.). As a conclusion, the authors report that loneliness is associated with an increased late-life dementia, while the relation between AD and loneliness is not clear.

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