

## Evaluation of Different Factors Leading to the Genesis of Alzheimer's Disease: Research Proposal on Dementia

Yifei Pei\*

Keck School of Medicine, University of Southern California, Los Angeles, USA

\*Corresponding author: Yifei Pei, Research Assistant, Keck School of Medicine, University of Southern California, Los Angeles, USA, Tel: 12132907906; E-mail: yifeipei@usc.edu; yifeipeter@gmail.com; 1595132339@qq.com

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### Abstract

Alzheimer's disease is a neurodegenerative disorder that is featured by the momentary loss of memory and forgetfulness. Alzheimer's disease and dementia affect millions of individuals all over the globe. Individuals suffering from Alzheimer's or dementia are prone to accidental falls and are at increased risk of life-threatening injuries. Identification of the predisposing risk factors would help to reduce the prevalence and complications of both these diseases in the near future. The present article portrayed a research proposal for evaluating the role of probable factors leading to the genesis of Alzheimer's disease. The present study would be conducted as a cohort and cross-sectional study. The study would be based on quantitative analysis and end-points would be reflected through quantitative data. The study would be conducted on 5000 participants belonging to 4 cities. The cities selected for the present study would be Shanghai, Beijing, Guangzhou, and Wuhan. MMSE would be used to classify different grades of dementia. However, it could not be used to portray the presence of Alzheimer's disease amongst the study participants. Therefore, plasma A $\beta$ -42/A $\beta$ -40 ratio and plasma TNF-alpha/IL-1 $\beta$ -40 ratio would be implemented for confirming the presence of Alzheimer's disease. Regression analysis would be conducted for dementia and Alzheimer's with the individual risk factors. Based on the evaluation of risk factors, a public health model would be planned and implemented. The public health model would involve the family members of affected individuals. Implementation of a public health model is speculated to reduce the progression of Alzheimer's or dementia.

**Keywords:** Alzheimer's disease; Dementia; Detection; Predisposing factors

### Introduction

#### Background

Alzheimer's disease is a neurodegenerative disorder that is featured by the momentary loss of memory and forgetfulness [1-3]. Different studies have indicated that around 5% of individuals suffering from Alzheimer's disease develop symptoms of the disease, before the age of 65 years [1,4]. Dementia is a marker of Alzheimer's disease. Dementia is an age-related disease and is usually prevalent in individuals over the age of 85 years [4-6]. Life expectancy with dementia is higher in women compared to their control counterparts [4-7]. The severity of dementia implicates the genesis of Alzheimer's disease [2]. Alzheimer's disease leads to negative health outcomes in geriatric patients [8]. Alzheimer's disease increases the prevalence of accidental falls and cognitive defects [1-3]. The pathophysiology of the disease stems from the degeneration of neurons in the memory pathway [9,10].

The neuronal loss is more pronounced in the Nucleus Basalis of Meynert. Alzheimer's disease results from the loss of cholinergic neurons in the Nucleus Basalis of Meynert. Nucleus Basalis of Meynert is an important link for connecting the hypothalamus and hippocampus [7,11]. Hence, formation and retrieval of short-term memory are impaired in individuals suffering from Alzheimer's disease [12,13]. Aging-related cognitive impairments are due to loss of cholinergic function [14]. The loss of cholinergic neurons results from

the deposition of amyloid plaques around such neurons. Various factors are related with the genesis of Alzheimer's disease [7,11,15,16]. Out of these factors, genetics and environmental factors play a major role in the development of Alzheimer's disease [13]. Alzheimer's and dementia has a significant socioeconomic impact on the affected individual and their family members [9,10,17].

Alzheimer's and dementia may predispose an individual towards accidental falls and may increase the risk of injuries. Hence, the predisposing risk factors for Alzheimer's and dementia should be appropriately identified. Identification of the predisposing risk factors would help to reduce the prevalence and complications of both these diseases [13,18].

#### Problem statement/purpose of research

Alzheimer's disease is a neurodegenerative disorder and affects geriatric individuals all over the world. The prevalence of Alzheimer's is also high in middle age group adults. Alzheimer's and dementia have a significant socioeconomic impact. The burden of these diseases affects the concerned individual and their family members. Individuals suffering from Alzheimer's or dementia are prone to accidental falls and are at increased risk of life-threatening injuries. Hence, the predisposing risk factors for Alzheimer's and dementia should be appropriately identified. The present study would try to evaluate the role of different factors leading to the genesis of Alzheimer's disease. The present article portrays a research proposal for evaluating the role of probable factors leading to the genesis of

Alzheimer's disease. Identification of the predisposing risk factors would help to reduce the prevalence and complications of both these diseases. Based on the evaluation of risk factors, a public health model would be planned and implemented. The public health model would involve the family members of affected individuals. Implementation of a public health model is speculated to reduce the progression of Alzheimer's or dementia.

### Research questions

The study would aim to address the following research questions:

- a. What are the predisposing risk factors for Alzheimer's disease and Dementia?
- b. Do the predisposing risk factors significantly vary in individuals suffering from normal cognitive impairment, Alzheimer's disease and Dementia?
- c. Could the prevalence of Alzheimer's/Dementia be predicted from the individual risk factors?
- d. Whether the predisposing risk factors are independently related or holistically related to the development of Alzheimer's disease and Dementia?
- e. Whether implementation of a public health model would reduce the progression of Alzheimer's disease and Dementia?

### Review of Literature

Although dementia and Alzheimer's are interchangeably used in practice settings, the two conditions are clinically different. These words are interchangeably used due to the number of similarities associated with these conditions. The main similarity for both these diseases is momentary forgetfulness and loss of cognitive control. However, dementia is usually an age-related disease and mainly affects geriatric individuals. On the other hand, Alzheimer's may occur during the middle ages [19]. Therefore, dementia is an age-related condition. On the other hand, Alzheimer's signifies an organic disease. Dementia might be caused due to various factors. Alzheimer's disease is one of the predisposing risk factors for dementia. Hence, neurodegenerative diseases may lead to dementia. On the other hand, all forms of dementia are not neurodegenerative diseases [13,18].

Alzheimer's disease is one of the major causes of dementia, which affects millions of individuals all over the globe. Alzheimer's disease is prevalent across the geriatric population and is caused due to multifactorial etiology. Air pollution is one of the major risk factors for Alzheimer's disease. Environmental pollutants and toxicants are some of the predisposing risk factors for Alzheimer's. Environmental pollutants lead to the generation of free radicals. Free radicals and reactive oxygen species lead to oxidative stress [19]. Air pollutants like suspended particulate matter, carbon monoxide, ozone, sulfur dioxide and lead have been implicated in Alzheimer's disease. On the other hand, advanced age, the presence of Down's syndrome, the presence of APOE-4 alleles and presence of cardiovascular diseases, increase the risk of Alzheimer's disease [20].

Oxidative stress leads to the destruction of neurons, associated with the formation and retrieval of memory [21,22]. Neurons have a high content of lipids and fatty acids. Reactive oxygen species contains unpaired electrons in their outermost electron shells. ROS accepts positive charges from neighboring compounds and gets neutralized. However, such reactions lead to the formation of new reactive oxygen

species. ROS mainly affects tissues, which have a high content of lipids and fatty acids. ROS withdraws H<sup>+</sup> ions from the fatty acids and converts them into fatty acid peroxy radical. Formation of one fatty acid peroxy radical leads to the sequential genesis of fatty acid peroxy radicals [21-23]. As a result, the respective neuron degenerates. The neurons that are most affected include the neurons that are present in the brain. The brain is an organ where oxygen consumption is one of the highest in the body. Therefore, ROS formation is expedited in the brain and other neuronal tissue [24].

Lipid profile is strongly associated with the genesis of Alzheimer's disease. Studies indicated that Alzheimer's disease is strongly linked to high HDL levels, low serum triglycerides, and lower total cholesterol/HDL ratio [25]. The association of lipids with Alzheimer's is associated with the formation of apolipoproteins. However, there was a significant correlation with cognitive aspects of Alzheimer's [25,26].

Based on the theoretical framework of air pollution and ROS; lipid content and increased body mass index may also increase the risk of Alzheimer's disease [20,27,28]. However, it is often difficult to isolate dementia due to Alzheimer's disease and dementia due to other factors. Analysis of cerebrospinal fluid and assay of blood-based biomarkers are often used as confirmatory tests for Alzheimer's [29].

The biomarkers that have been strongly associated with the diagnosis of Alzheimer's are A $\beta$ -40, A $\beta$ -42 and tau proteins [30-35]. All these biomarkers have been isolated from the cerebrospinal fluid and provide a fair estimation of Alzheimer's disease. However, lumbar puncture needs to be performed for assaying the cerebrospinal fluid [29]. Lumbar puncture is associated with different complications. One of the major complications of lumbar puncture is the development of neuropathic pain in the concerned individual. Hence, the focus for diagnosis of Alzheimer's has been shifted towards less invasive procedures. Assay of blood-based biomarkers has received great attention for the diagnosis and detection of Alzheimer's [30-32]. Studies have indicated that the plasma concentrations of A $\beta$ -40 and A $\beta$ -42 are high in individuals suffering from Alzheimer's.

Increased plasma concentrations of A $\beta$ -40 and A $\beta$ -42 increase the risk of Alzheimer's disease in an individual. Urinary concentrations of these proteins are also high in individuals suffering from Alzheimer's. The blood-based biomarkers and urine-based biomarkers were significantly correlated with the Clinical Dementia Rating Scale. Other blood-based biomarkers have also been implicated in Alzheimer's diseases. These biomarkers include conformational alterations in p53 protein, IL-1 receptor antagonist, C-reactive protein, alpha-1 chymotrypsin and tumor necrosis factor-alpha [31,32]. Studies have suggested that the etiology Alzheimer's is extremely complex and diagnosis should not be based on any one specific biomarker [30-35]. Single marker assays are either ineffective or inappropriate for diagnosing the presence of Alzheimer's disease in an individual. Therefore, different studies have necessitated the use of multiple biomarkers for diagnosing the presence of Alzheimer's disease in an individual. Finehout et al indicated that assay of amyloid proteins, inflammatory proteins, and neuronal membrane proteins could effectively diagnose Alzheimer's in 90% of the target population.

The same authors also indicated that evaluation of proteolytic inhibition is strongly associated with the detection and diagnosis of Alzheimer's in a concerned individual [36]. These assays were carried out in the cerebrospinal fluid. Simonsen et al also confirmed the

findings of Finehout et al and implicated different sets of biomarkers from the CSF [37].

Studies have also implicated the assay of biomarkers from the serum and plasma of the target population. Graff-Radford et al have implicated that plasma A $\beta$ -42/A $\beta$ -40 ratio is an effective diagnostic measure for Alzheimer's disease [38]. This measure is effective in diagnosing Alzheimer's disease and cognitive deficits in elderly individuals. On the other hand, Paganelli et al indicated that plasma TNF-alpha/IL-1 $\beta$ -40 ratio is also an effective diagnostic measure for Alzheimer's disease. The authors reported that plasma TNF-alpha/IL-1 $\beta$ -40 ratio was significantly lower in individuals who suffered from Alzheimer's, compared to their control counterparts ( $p < 0.0001$ ) [39]. Ray et al indicated that 18 proteins could be used as biomarkers for diagnosing the presence of Alzheimer's disease in an individual. However, the biomarker assays should be clinically correlated with the symptoms of Alzheimer's disease [40]. Different factors are related with the genesis of Alzheimer's disease and dementia. Hence, the biochemical diagnosis should be appropriately correlated with the physical symptoms.

Studies indicate that it is difficult to conduct research with older adults, especially those who suffer from delirium and Alzheimer's. The difficulties arise due to non-cooperation and cognitive impairments in study participants. Moreover, the stigma associated with Alzheimer's disease imposes a challenge to researchers [41,42]. Public health model could be used to identify the barriers in recruiting study participants and implementation of healthcare recommendations. Studies indicated that involvement of family members in planning therapeutic interventions leads to positive health outcomes in patients [43-45]. Longitudinal multidisciplinary studies have been conducted to evaluate the risk factors for Alzheimer's disease [46,47]. Such studies have generated a wealth of clinical, neurological, genetic and biomarker-based information [48,49].

The prevalence of Alzheimer's disease and dementia in China is fairly high. The predominant forms of dementia that are noted in the Chinese population are Lewy body dementia, frontotemporal dementia, and vascular dementia. The prevalence of dementia is high in Shanghai, Beijing, Guangzhou, and Wuhan. Earlier studies have not significantly portrayed the burden of dementia in China [50-54]. The major disadvantages of such studies were the small sample size [55-58].

## Methodology

### Study design and site of study

The present study would be conducted as a longitudinal, cohort, cross-sectional study. The study would be based on quantitative analysis and end-points would be reflected through quantitative data. The study would be conducted on 5000 participants belonging to 4 cities. The cities selected for the present study would be Shanghai, Beijing, Guangzhou, and Wuhan.

The inclusion criteria for the study participants would be (1) registered residents of the selected cities; (2) study participants should be more than 60 years old; (3) the participants should not exhibit symptoms of schizophrenia or mental retardation; (4) they should be able to communicate and respond to the Mini-mental state exam; and (5) Participants should be willing to participate in the study. The exclusion criteria for the study include failure to receive ethical approval, lack of willingness for participating in the study and presence of cognitive deficits that are not features of Dementia/Alzheimer's.

The prospective participants would be identified through a government maintained 'residents list', which includes the name, sex, age address, and telephone number of every resident. The confidence interval for the present study would be fixed at 95%. The study participants would be initially screened through the Mini-mental state examination (MMSE) scores. After the initial screening, the blood-based biomarker assay would be conducted on the study participants. Individuals exhibiting a high plasma A $\beta$ -42/A $\beta$ -40 ratio and a low plasma TNF-alpha/IL-1 $\beta$ -40 ratio would be considered to suffer from Alzheimer's disease. Hence, the study participants would be segregated into two groups. One group would comprise of dementia individuals without the presence of Alzheimer's disease. The other group would comprise of dementia individuals with the presence of Alzheimer's disease. Both the groups would be compared on the presence of individual risk factors or the individual predisposing factors.

Based on the evaluation of possible risk factors, a public health model would be implemented in study participants. The public health model would engage the family members of study participants in implementing therapeutic interventions. The success of the public health model would be evaluated through specific endpoints. The specific endpoints would include evaluating the prevalence of accidental falls, evaluating the prevalence of life-threatening injuries and evaluation of MMSE scores.

### Instruments

**Mini-mental state examination (MMSE):** MMSE would be used to classify different grades of dementia. During the MMSE, a health professional asks a patient a series of questions designed to test a range of everyday mental skills. The maximum MMSE score is 30 points. A score of 20 to 24 suggests mild dementia, 13 to 20 suggest moderate dementia, and less than 12 indicates severe dementia [59].

**Assessment of Air Quality Indexes:** Air Quality Indexes would be measured by the average of the Real-Time Air Quality Index of the four cities over 1 year. Air Quality Indexes would include assessment of the suspended particulate matter, carbon monoxide, ozone, sulfur dioxide and lead concentrations in the ambient air.

**Physical Measurements:** Participants would be assessed fasting glucose, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG). The blood pressure and BMI of the study participants would also be assessed.

**Demographic and Lifestyle Characteristics:** The personal characteristics that would be measured include the age of the participants, sex, marital status, employment, education level, smoking status and economic status of the participants. The cognitive status of relatives and family history of dementia would also be assessed.

**Differentiating Criteria for Dementia and Alzheimer's disease:** The MMSE instrument would be used to assess the prevalence of dementia. However, it could not be used to portray the presence of Alzheimer's disease amongst the study participants. Therefore, two measures would be implemented for confirming the presence of Alzheimer's disease. The confirmatory test would be based on the biomarker assay for Alzheimer's. Blood-based biomarker assay would be performed for confirming the presence of Alzheimer's disease. The blood-based biomarkers that would be considered in this study are plasma A $\beta$ -42/A $\beta$ -40 ratio and plasma TNF-alpha/IL-1 $\beta$ -40 ratio. This is because both these assays have been supported by the evidence-based literature.

Specific Endpoints: Prevalence of life-threatening injuries and evaluation of MMSE scores would be measured after 1-year engagement of the family members of study participants in therapeutic interventions.

### Statistical tests and plan of analysis

Continuous variables are expressed as mean (SD), or median (25%, 75%), and categorical variables are frequencies (%). The Student t-test or One-way analysis of variances was used for comparisons for continuous variables. The  $\chi^2$  test would be used for comparisons for categorical variables. The prevalence and 95% confidence intervals for dementia and AD are calculated. The Student t-test, One-way analysis of variances and  $\chi^2$  test would be used for comparison analysis. The comparisons would be based on the MMSE scores. The MMSE scores would be evaluated based on the individual determinants. The individual determinants would include the different Air Quality Indexes, physical/physiological parameters, and demographic/lifestyle characteristics of the study participants. The MMSE scores would be categorized into three classes of dementia. The individual determinants would be compared across three classes of MMSE scores. Such evaluation would help to speculate the causal relationship between the individual determinants of dementia. The statistical tests of comparison compare the mean of two or more groups. These tests help to signify whether the mean of one group is significantly different from another.

The causal relationships would be confirmed through correlation analysis. For this purpose, Pearson's correlation coefficient would be estimated. Pearson's correlation coefficient estimates the relation between two variables. The correlation coefficient could be positive or negative. A positive correlation indicates that increasing the magnitude of one variable would increase the magnitude of another variable. On the other hand, negative correlation indicates that increasing the magnitude of one variable would decrease the magnitude of another variable. If the correlation coefficients are statistically significant, they would be considered for regression analysis.

Regression analysis would be conducted to evaluate the relation of different independent variables with the dependent variable. The dependent variable for the present study would be MMSE score. The independent variables would include the different Air Quality Indexes, physical and physiological parameters and demographic and lifestyle characteristics of the study participants. The analysis would be based on a multiple logistic regression model. The regression model would holistically evaluate the impact of independent variables on the dependent variable.

### Hypothesis testing

These analyses would be repeated in both the experimental groups that are considered for the present study.

For Comparative Analysis: The null hypothesis contends that there is no significant difference in mean MMSE (Mini-mental state examination) scores between patients with respect to different independent variables. Any observed difference would be attributed to chance factors of random sampling. The null hypothesis would be accepted if the p-value for the statistical test of significance is greater than 0.05 ( $p > 0.05$ ). The alternative hypothesis contends that there is a significant difference in mean MMSE (Mini-mental state examination) scores between patients with respect to different independent variables. Any observed difference would not be attributed to chance

factors of random sampling. The alternate hypothesis would be accepted if the p-value for the statistical test of significance is lesser than 0.05 ( $p < 0.05$ ).

For Correlation Analysis: The null hypothesis contends that there is no significant relation between MMSE (Mini-mental state examination) score and the different independent variables predicted to cause dementia. Any observed correlation would be attributed to chance factors of random sampling. The null hypothesis would be accepted if the p-value for the Pearson's correlation coefficient is greater than 0.05 ( $p > 0.05$ ). The alternative hypothesis contends that there is a significant relation between MMSE (Mini-mental state examination) score and the different independent variables predicted to cause dementia. Any observed correlation would not be attributed to chance factors of random sampling. The alternate hypothesis would be accepted if the p-value for the Pearson's correlation coefficient is lesser than 0.05 ( $p < 0.05$ ).

For Regression Analysis: The null hypothesis contends that MMSE scores could not be holistically and significantly predicted from the independent variables, which are predicted to cause dementia. Any observed prediction would be attributed to chance factors of random sampling. The null hypothesis would be accepted if the p-value for the regression analysis (based on ANOVA) is greater than 0.05 ( $p > 0.05$ ). The alternative hypothesis contends that MMSE scores could be holistically and significantly predicted from the independent variables, which are predicted to cause dementia. Any observed prediction would not be attributed to chance factors of random sampling. The alternate hypothesis would be accepted if the p-value for the statistical test of significance is lesser than 0.05 ( $p < 0.05$ ).

Evaluation of the Public Health Model: The null hypothesis contends that there would be no significant reduction in the prevalence of accidental falls/life-threatening injuries/MMSE scores in study participants after implementation of the public health model. Any observed reduction would be attributed to chance factors of random sampling. The null hypothesis would be accepted if the p-value for the students-t test is greater than 0.05 ( $p > 0.05$ ). The alternative hypothesis contends that there would be a significant reduction in the prevalence of accidental falls/life-threatening injuries/MMSE scores in study participants after implementation of the public health model. Any observed reduction would not be attributed to chance factors of random sampling. The null hypothesis would be accepted if the p-value for the students-t test is less than 0.05 ( $p < 0.05$ ).

### Prospective Outcomes of the Study

The present study would help to identify the risk factors for dementia and Alzheimer's disease. Moreover, the study would also help to segregate the individual risk factors/predisposing factors for both these diseases. The chances of developing dementia and Alzheimer's may be extrapolated from this study. Such extrapolations would be only feasible if the regression analysis is significant. Alzheimer's disease and dementia affect millions of individuals all over the globe. Individuals suffering from Alzheimer's or dementia are prone to accidental falls and are at increased risk of life-threatening injuries. Identification of the predisposing risk factors would help to reduce the prevalence and complications of both these diseases in the near future.

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