Advances in Bioresearch
Adv. Biores., Vol 11 (3) May 2020: 143-149

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.11.3.143149

Advances in Bioresearch

ORIGINAL ARTICLE

Risk factors associated with Alzheimer's disease in Saudi Arabia: a descriptive study (Alzheimer's disease in Saudi Arabia)

Hemat E. El-Horany[1, 4*], Ahmed Hamed Aljadani[2], Razan S. Alsubhi[3], Maymonah S. Alshammari[3], Shouq N. Alruwaili[3], Asrar F. Alfaiqiri[3]
[1]Department of Biochemistry, College of Medicine, University of Hai'l, Hai'l, Saudi Arabia.
[2]Department of Internal Medicine, College of Medicine, University of Hai'l, Hai'l, Saudi Arabia.
[3]College of Medicine, University of Hai'l, Hai'l, Saudi Arabia
[4]Department of Medical Biochemistry, Faculty of Medicine, Tanta University, Tanta, Egypt.
*Corresponding author: hematelhorany@yahoo.com

ABSTRACT
To assess the risk factors associated with Alzheimer's disease (AD) in Saudi Arabia and to raise the awareness of healthcare providers about AD underlying neuropathological mechanisms and the differences in lifestyle risk factors, thus ensuring a better life quality for the Saudi population. A cross-sectional study, a questionnaire was designed, including inquiries on socio-demographic data and vascular risk factors including type 2 diabetes mellitus then sent to the health education administration of Saudi Alzheimer's Disease Association to collect data. A total sample of 309 patients were selected by systematic random sample. The prevalence of main risk factors in our sample were urban residence (77.35%), unemployment (69.9%), illiteracy (60.8%), hypertension (60%), being female (59.2%), low economic status (49.84%), diabetes (36.6%), followed by history of stroke (30.1%) and dyslipidemia (28.2%). The current analysis highlights the main risk factors for AD in Saudi Arabia to be taken into consideration when searching for solutions to control AD. This study highlights the urgent need for implementing a national program to address the modifiable risk factors at the community level, strengthening the role of geriatric medicine to support these high-risk groups and evaluate them regularly to impact their life quality positively.
Keywords*: Alzheimer, Alzheimer's disease, risk factors, Dementia, Saudi Arabia*.
Abbreviations: AD: Alzheimer's disease; T2DM: type 2 diabetes mellitus.

Received 11.05.2020 Revised 24.05.2020 Accepted 04.06.2020

How to cite this article:
H E. El-Horany, A H Aljadani, R S. Alsubhi, M S. Alshammari, S N. Alruwaili, A F. Alfaiqiri. Risk factors associated with Alzheimer's disease in Saudi Arabia: a descriptive study (Alzheimer's disease in Saudi Arabia). Adv. Biores., Vol 11 (3) May 2020: 143-149

INTRODUCTION

In recent years, the elderly population has grown at an accelerated pace due to increased life expectancy. This is often linked to the increase in the number of age-related diseases and increasing the need for healthcare services and social security [1]. In Saudi Arabia, the age of the population is shifting toward the elderly. In 2016, the number of people over 60 years of age was 1.3 million (6.5 %), and by 2050, this age group will exceed 10 million, representing 25% of the total population [2].

Alzheimer's disease is a progressive neurodegenerative age-related disease and the most dominant form of dementia, accounting for 60–80% of dementia cases, and ranking as the 6th highest cause of death. AD is characterized by amyloid-β peptide (Aβ) accumulation, produced through an altered cleavage of amyloid precursor protein (APP), the formation of neurofibrillary tangles, and synaptic and neuronal loss [3].

AD presents with the characteristic features of memory problems, challenges with learning and problem solving, language, swallowing, and walking difficulties, which often leads to interference with activities of daily living and other cognitive impairments. [4].

The latest World Alzheimer Report estimated that 46.8 million people worldwide are having dementia in 2015, and this number will double every 2 decades, reaching 74.7 million in 2030 and 131.5 million in

2050. These new estimates are 12-13% higher than those made for the World Alzheimer Report 2009. The regional estimates of dementia prevalence in people aged 60 years and over a range from 4.6% in Central Europe to 8.7% in North Africa and the Middle East [5].

AD has multi-factorial etiology. Many risk factors are involved in its incidence and progression, some of these are modifiable, and others are not. Numerous studies have reported a range of individual and environmental factors such as age, sex, education, socio-economic status, family history, and chronic disease (hypertension, diabetes mellitus, and depression) might be related to the risk of AD [6].

Alzheimer's disease has a relevant social and economic impact according to the evolutionary phase of the pathology, corresponding to medical costs, attention provided, training of caregivers, among others, placing a tremendous medical and fiscal burden on society [7].

The rising number of persons with AD and the lack of effective treatments highlight the urgency for risk factors to be better understood, while the studies conducted to investigate the risk factors of Alzheimer's disease in Arab countries and the Gulf region are still lacking. This issue is relevant for the implementation of preventive services at the population level, as even modest decreases in the prevalence of cognitive impairment in older populations might yield relevant reductions of the considerable healthcare and social costs. Indeed, it has been reported that careful control of vascular risk factors can postpone the onset or even reverse disease progression [8].

Therefore, a crucial step in the effective management of AD is to raise the awareness of healthcare providers about AD underlying neuropathological mechanisms and the differences in lifestyle risk factors and thus to ensure a better life quality for the Saudi population. To this aim, this cross-sectional study has been undertaken to investigate risk factors associated with AD in Saudi Arabia.

MATERIAL AND METHODS

Ethical considerations

Study protocols and instruments were institutionally approved bythe institutional review board at Hai'l University medical college.

Study area, design and population

A descriptive cross-sectional study was conducted from January 2019 to February 2019 among Alzheimer's disease patients registered at Saudi Alzheimer's Disease Association.

Sampling method & sample size

Systematic random sampling was proposed for this study. The estimated sample size for this study was 323 participants using Raosoft online sample size calculator at C.I. of 95%.

Data collection and study instrument

An electronic questionnaire was used to collect the data from the patients' fileselected by systematic random sample. The first section of the questionnaire captured socio-demographic characteristics of Alzheimer patients, including age, gender, residence, marital status, level of education, occupation, and economic status. The second section captured risk factors, including diabetes mellitus, hypertension, dyslipidemia, history of stroke, smoking, and family history of AD.

Statistical analysis

Data were represented in terms of frequencies (number of patients) and valid percentages for categorical variables. IBM Statistical Package for the Social Science (SPSS version 21) for Microsoft Windows was used to perform all statistical calculations. During data collection, Confidentiality of information was maintained. Moreover, their identity was not collected, so their information could never be matched to their responses.

RESULTS

The study included 309 Alzheimer's disease. There were 18 patients (5.83%) aged less than 60, 85 patients (27.51%) aged 60-74, 109 patients (32.28%) aged 75-84, and 97 patients (31.39%) aged 85 or over. There were more slightly female (59.22%) than male. More than two-thirds of the patients (77.35%) were from urban areas. One hundred sixty-one patients (52.1%) were married, while 14 patients (40.78%), 18 patients (40.78%), and 116 patients (37.54%) were single, divorced, and widowed, respectively. More than half of the patients (60.84%) were illiterate, and only 15 patients (4.85%) went to college. While 50 (16.18%), 25 (8.09%), and 31 (10.03%) of the patients had attended primary, preparatory, and secondary school, respectively. Approximately two-thirds of the patients were unemployed, while 75 patients (24.27%) were retired, and only 18 (5.83%) were employed. About half of the patients (49.84%) had low economic status, while only 4.21% of patients had excellent status. (Table 1)

Around one-third of the patients (36.57%) had diabetes mellitus, mostly type 2. Only 16 patients (5.18%) were smokers. Approximately half of the patients had been diagnosed with hypertension. 87 (28.16%) patients had dyslipidemia. About one-third of the patients (30.1%) had a history of stroke, either ischemic or hemorrhagic. Around one-third (9.1%) of the patients had a family history of AD. Tables 2.

Table 1: Socio-demographic characteristics of the patients

Characteristics	**N (%)**
Age (years)	
<60	18 (5.83%)
65-74	85 (27.51%)
75-84	109 (35.28%)
> 85	97 (31.39%)
Gender	
Male	126 (40.78%)
Female	183 (59.22%)
Residence	
Urban	239 (77.35%)
Rural	70 (22.65%)
Marital status	
Married	161 (52.10%)
Widowed	116 (37.54%)
Divorced	18 (5.83%)
Single	14 (4.53%)
Level of Education	
Illiterate	188 (60.84%)
Primary School	50 (16.18%)
Preparatory School	25 (8.09%)
Secondary School	31(10.03%)
College Completed	15 (4.85%)
Occupation	
Employed	18 (5.83%)
Retired	75 (24.27%)
Unemployed	216 (69.90%)
Economic status	
Excellent	13 (4.21%)
Average	142 (45.95%)
Low	154 (49.84%)

Table 2: Prevalence of relevant AD risk factors

Factor	N (%)
Hypertension	
Yes	173 (55.99%)
No	136 (44.01%)
Diabetes	
Yes	113 (36.57%)
No	196 (63.43%)
Type of diabetes	
Type 1	13 (11.50%)
Type 2	100 (88.50%)
Duration of diabetes	
<5 years	5(4.42%)
6-10 years	54 (47.79%)
>10 years	54 (47.79%)
Treatment for diabetes	
Insulin	54 (47.79%)
Oral hypoglycemic drugs	52 (46.02%)
Diet	7 (6.19%)
Glycemic control	
Yes	64 (20.71%)
No	245 (79.29%)
Dyslipidemia	

Yes	87 (28.16%)
No	222 (71.84%)
History of Stroke	
Yes	93 (30.10%)
No	216 (69.90%)
Smoking	
Yes	16 (5.18%)
No	293 (94.82%)
Family history of AD	
Yes	28 (9.06%)
No	281 (90.94%)
Duration of AD	
<1 Years	81 (26.21%)
1-3 Years	107 (34.63%)
4-6 Years	89 (28.80%)
>6 Years	32 (10.36%)

DISCUSSION

Emerging evidence has reported that several medical, environmental, and lifestyle risk factors implicated in AD development are modifiable. So, increasing attention is directed to the interplay of AD with comorbidities such as diabetes and hypertension, as well as socio-behavioral risk factors as educational attainment [9]. Until disease-modifying treatment becomes available, risk reduction interventions could drastically reduce the future burden of AD at the population level.

In the light of scarce data regarding AD risk factors in medical literature for the gulf area and Arab region, we aimed in our current study to throw light on risk factors associated with AD in Saudi Arabia.

Older age is strongly associated with AD in all studies, and similar associations have been reported globally, with the vast majority of people with Alzheimer's dementia being age 65 or older, as well disease probability is doubled every five years over the age of 65 [10]. In agreement, the present study revealed that the highest prevalence, about two-thirds of the patients, were among those aged 75 and over.

The current study demonstrated that women were more likely to have AD compared with their male counterparts in this sample, as 59.2% of the patients were female. Consistently, it was reported that dementia and AD frequencies were higher in women in Lebanon and Turkey [11, 12]. This could be related to various factors, including menopause transition, differences in cognitive reserve, resilience, as well as genetics (apolipoprotein Ɛ4), and functional and structural brain changes. It is also pointed out that women have a higher risk of having comorbidities due to a longer lifespan, like coronary heart disease, depression, and myocardial infarction, which are all risk factors for cognitive decline or impairment [13, 14].

The current study found that 77.4% of the patients were urban residents. In the published literature, the association between urbanization levels and AD risk is still inconclusive. The presence of green, environmental layout and complexity, levels of traffic and noise can act as a source of brain training and possibly contribute to cognitive resilience in older age; however, environmental stimulation can cause cognitive overload depending on the relationship between levels of stimulation and the individuals' cognitive and physical functionality [15].

There is an independent and substantial association between marital status in mid-life and cognitive function later in life, it was reported that the risk of developing Alzheimer's disease is twice in people without a partner compared with people living with a partner [16]. In parallel, the present report revealed that 47.9% of patients had disturbed marital life or singles.

Of note, certain protective behavioral factors may promote resiliency against the development of age-related neuropathological changes in the brain. A wealth of epidemiologic studies suggested that lifetime exposures, including educational and occupational attainment, and leisure activities in late life, can increase cognitive reserve and protect against AD [17].

It is widely documented that having a lower level of education was also recognized as one of the most established risks for dementia and AD [18]. Similarly, the current study reported that 60.8% and 69.9% of the investigated AD patients were illiterate and unemployed, respectively.

These observations could be based on two primary possible explanations. Firstly, the cognitive reserve hypothesis postulates that people with a higher cognitive reserve can tolerate more neurodegenerative pathology and maintain brain function for longer than people with a low reserve before the damage manifests clinically as dementia. Secondly, people with higher education have a more favorable environment, including a healthier lifestyle, better compliance to treatment and better access to healthcare leading to less cognitive decline and dementia [17, 19].

Therefore, lifestyle interventions at all stages, even in late life, are highly appreciated, in order to impart cognitive reserve and slow age-related cognitive decline for prolonged healthy aging.

As indicated by the current study, AD was more prevalent among those of lower income (49.8%). In parallel, the association between low socio-economic status and AD is widely documented in the literature. They attributed this finding to poor access to health care services, unhealthy diet or lifestyle, low education, and increased physiological stress that can contribute to higher blood pressure and depression [20].

Hypertension is a significant global and national health challenge due to its high prevalence. At the national, the prevalence of hypertension and prehypertension is significantly increased due to economic development, acceleration of population aging, as well as modifications in lifestyle and traditional dietary habits. According to 2010 estimates, hypertension was classified as the leading risk factor for death in Saudi Arabia. The most recent report presented a prevalence of 31.4% for hypertension among the Saudi population [21].

Growing evidence has demonstrated that hypertension is a significant contributor to the pathogenesis of AD. Multiple mechanisms have been explained. Hypertension alters the structure and molecular composition of cerebral blood vessels and disrupts the homeostatic mechanisms that ensure adequate blood supply to the brain. Thus, damage to the cerebral vasculature compromises oxygen and glucose delivery for proper neuronal function, as well as the removal of metabolic waste and toxic proteins, rendering the brain more vulnerable to ischemic injury, white matter disease, and to the development of neurodegenerative pathologies [22].

The present study revealed an alarming finding; hypertension was a highly notable risk factor in this study as it found in 60% of our patients, which is compatible with the findings of another study underscored on the Arab population living in Wadi Ara and reported higher odds of AD associated with hypertension [23].

DM is a metabolic disease characterized by elevated level of blood glucose as a result of insulin secretion defect, insulin action defect or possibly both. T2DM accounts for up to 90% of total diabetes incidence and has become a significant health problem globally. Saudi Arabia was reported to rank the second in the Middle East and the seventh worldwide in terms of diabetes rate. It is estimated that around 7 million of the population are diabetic and almost around three million have pre-diabetes [24].

Like AD, T2DM is also considered as a degenerative metabolic disease that occurs in later age and is associated with the gradual loss of insulin-secreting pancreatic beta-cells. The deposition of islet amyloid polypeptide (known as amylin) within beta-cells of the pancreas is considered as a major contributor in pathogenesis of T2DM. Also, it has been envisaged that AD may be a type of 'brain diabetes' or 'type 3 diabetes' resulting from both insulin deficiency and insulin resistance in the brain. Moreover, T2DM results in chronic cerebral hypoperfusion leading to neuro-glial dysfunction and degeneration, as well, individuals with T2DM are at increased risk of suffering transient ischemic attacks that, although often silent, can lead to severe consequences in the long-term, including dementia.; posing the question as to whether one leads to the other in aged individuals [25].

A notable portion of the AD patients investigated in our analysis (36.6%) were T2DM. These findings should not be surprising given that a growing health issue of T2DM among the Saudi population.

Several meta-analysis studies from published literature have estimated an aggregated relative risk of approximately 1.5 linking T2DM with AD, and the relative risk increases considerably by the presence of hypertension, smoking and APOE4 positivity [26, 27]. On the other hand, there is a clear discrepancy between epidemiological results and neuropathological autopsy findings in linking AD with type 2 diabetes and concluded that type 2 diabetes does not promote AD pathology in the brain and instead vascular pathologies in the brain are more commonly associated with type 2 diabetes [26, 28].

T2DM is a preventable disease that is influenced by several modifiable risk factors such as obesity, active smoking, physical inactivity, and unhealthy diet. Therefore, there is an urgent need for an effective public health multidisciplinary approach to reduce and control the modifiable risk factors for T2DM.

As hypertension and diabetes mellitus are huge clinical and public health burden in the Kingdom of Saudi Arabia, healthcare professionals must be aware of these risk factor associated with AD, and direct community awareness campaigns for increasing individual's knowledge of risk factors for AD among the Saudi population.

Herein, 30.1% of the patients had a history of stroke. In line with our observation, stroke was recorded as a relevant contributor to cognitive decline and the development of dementia [19].

The relationship between hyperlipidemia and cognition is very complex, controversial, and still need more elucidate [29]. In the current report, 28.2% of our patients had dyslipidemia.

A meta-analysis study stated that smoking is a significant risk factor for AD [30]. However, as smoking is less of an issue in KSA than in other parts of the world, herein, only 5.2% of AD patients were smokers.
Only 9.1% of the patients had a family history of AD. It was reported that a family history of Alzheimer's is not necessary for an individual to develop the disease. However, individuals who have a first-degree relative with AD are more likely to develop the disease than those who do not have [10].

CONCLUSION

In sum, the current work provides novel findings about the prevalence of primary risk factors in Saudi AD patients. It is undoubtedly vital for health caregivers to reconsider the role of cardiovascular and socio-economic risk factors in the oldest subjects. Since there is no effective treatment for this disease today, prevention and lifestyle modification are critical. A multidisciplinary approach is required with great emphasis laid on advocating a healthy diet, exercise, multiple mental activities, active lifestyles, and weight control.
Also, it is recommended to regularly review and follow up older patients with cardiovascular risk factors, like hypertension and diabetes, especially those with low socio-economic status, through an organized system of healthcare delivery.

AUTHOR CONTRIBUTIONS

All authors provided significant input into the manuscript and have read and approved the final version.

ACKNOWLEDGMENTS

The authors are grateful for the support provided by health education administration of Saudi Alzheimer's Disease Association, especially the health educator, Lujain Abdullah Bin Amer until this research paper has been completed.

COMPETING INTERESTS

The authors have no conflicts of interest.

REFERENCES

1. Aly, H.Y., Hamed, A.F., and Mohammed, N.A. (2018). Depression among the elderly population in Sohag governorate. Saudi Med J, 39(2): p. 185-190 DOI: 10.15537/smj.2018.2.21353.
2. Alkhunizan, M., A. Alkhenizan, and Basudan, L. (2018).Prevalence of Mild CognitiveImpairment and Dementia in Saudi Arabia: A Community-Based Study. Dement Geriatr Cogn Dis Extra, 8(1): p. 98-103 DOI: 10.1159/000487231.
3. Yoshida, K., Moein, A., Bittner, T., et al., (2020).Pharmacokinetics and pharmacodynamic effect of crenezumab on plasma and cerebrospinal fluid beta-amyloid in patients with mild-to-moderate Alzheimer's disease. Alzheimer's research & therapy, 12(1): p. 16-16 DOI: 10.1186/s13195-020-0580-2.
4. Ali, M.M., Ghouri, R.G., Ans, A.H., et al., (2019).Recommendations for Anti-inflammatory Treatments in Alzheimer's Disease: AComprehensive Review of the Literature. Cureus, 11(5): p. e4620-e4620 DOI: 10.7759/cureus.4620.
5. Prince, M.J., World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. 2015: Alzheimer's Disease International.
6. [6]. Bhatti, G.K., Reddy, A.P., Reddy, P.H., et al., (2020). Lifestyle Modifications and Nutritional Interventions in Aging-Associated Cognitive Decline and Alzheimer's Disease. Frontiers in aging neuroscience,11: p. 369-369 DOI: 10.3389/fnagi.2019.00369.
7. Alacreu, M., Pardo, J., Azorín, M., et al., (2019). Importance of Increasing Modifiable Risk Factors Knowledge on Alzheimer's Disease Among Community Pharmacists and General Practitioners in Spain. Front Pharmacol, 10: p. 860 DOI: 10.3389/fphar.2019.00860.
8. Morovic, S., Budincevic, H., Govori, V., et al., (2019).Possibilities of Dementia Prevention - It is Never Too Early to Start. J Med Life, 12(4): p. 332-337 DOI: 10.25122/jml-2019-0088.
9. Ivanova, N., Liu, Q., Agca, C., et al., (2020). White matter inflammation and cognitive function in a co-morbid metabolic syndrome and prodromal Alzheimer's disease rat model. Journal of neuroinflammation, 17(1): p. 29-29 DOI: 10.1186/s12974-020-1698-7.
10. Alzheimer's disease facts and figures. Alzheimer's & Dementia, 2018. 14(3): p. 367-429 DOI:10.1016/j.jalz.2018.02.001.
11. Ertekin, A., Demir R., Özdemir, G., et al., (2015). An Investigation of the Risk Factors and Prevalence of Alzheimer's Disease in the Eastern Region of Turkey. European Journal of General Medicine, DOI.10.15197/sabad.1.12.29
12. Chaaya, M., Phung, K., Atweh, S., et al., (2017).Socio-demographic and cardiovascular disease risk factors associated with dementia: Results of a cross-sectional study from Lebanon. Preventive medicine reports, 9: p. 1-5 DOI: 10.1016/j.pmedr.2017.11.006.

13. Rahman, A., Jackson, H., Hristov, H., et al., (2019).Sex and Gender Driven Modifiers of Alzheimer's: The Role for Estrogenic Control Across Age, Race, Medical, and Lifestyle Risks. Frontiers in aging neuroscience, 11: p. 315-315 DOI: 10.3389/fnagi.2019.00315.
14. Laws, K.R., Irvine, K., and Gale, T.M., (2018).Sex differences in Alzheimer's disease. Current opinion in psychiatry, 31(2): p. 133-139 DOI: 10.5498/wjp.v6.i1.54.
15. Cassarino, M. and A. Setti, (2015). Environment as 'Brain Training': A review of geographical and physical environmental influences on cognitive ageing. Ageing Res Rev, 23(Pt B): p. 167-82 DOI: 10.1016/j.arr.2015.06.003.
16. Håkansson, K., Rovio, S., Helkala, E., et al., (2009).Association between mid-life marital status and cognitive function in later life: population based cohort study. BMJ (Clinical research ed.), 339: p. b2462-b2462 DOI: 10.1136/bmj.b2462.
17. DuBose, L.E., Moser, D. J., Harlynn, E., et al., (2019).Education moderates the effects of large central artery aging on cognitive performance in middle-aged and older adults. Physiological reports, 7(23): p. e14291-e14291 DOI: 10.14814/phy2.14291.
18. Elshahidi, M.H., Elhadidi, M. A., Sharaqi, A. A.,et al., (2017). Prevalence of dementia in Egypt: asystematic review. Neuropsychiatric disease and treatment, 13: p. 715-720 DOI: 10.2147/NDT.S127605
19. Srithumsuk, W., Kabayama, M., Gondo, Y., et al.,(2020).The importance of stroke as a risk factor of cognitive decline in community dwelling older and oldest peoples: the SONIC study. BMC geriatrics, 22;20(1):24. DOI: 10.1186/s12877-020-1423-5.
20. Camacho-Mercado, C.L., Figueroa, A., Acosta, H., et al., (2016). Profiling of Alzheimer's disease patients in Puerto Rico: A comparison of two distinct socioeconomic areas. SAGE Open Med, 4: p. 2050312115627826 DOI: 10.1177/2050312115627826.
21. Aldiab, A., Shubair, M.M., Al-Zahrani J.M.,et al., (2018). Prevalence of hypertension and prehypertension and its associated cardioembolic risk factors; a population based cross-sectional study in Alkharj, Saudi Arabia. BMC public health, 18(1): p. 1327-1327 DOI: 10.1186/s12889-018-6216-9.
22. Iulita, M.F. and H. Girouard, (2017).Treating Hypertension to Prevent Cognitive Decline and Dementia: Re-Opening the Debate. Adv Exp Med Biol, 956: p. 447-473 DOI: 10.1007/5584_2016_98.
23. Israeli-Korn, S.D., Masarwa, M., Schechtman, E., et al., (2010). Hypertensionincreases the probability of Alzheimer's disease and of mild cognitive impairment in an Arab community in northern Israel. Neuroepidemiology, 34(2): p. 99-105 DOI: 10.1159/000264828.
24. Alqahtani, M., Almutairi, F.E., Albasseet, A.O., et al., (2020).Knowledge, Attitude, and Practice of Diabetes Mellitus Among the Saudi Population in Riyadh, Saudi Arabia: A Quantitative Study. Cureus,12(1): p. e6601-e6601 DOI: 10.7759/cureus.6601.
25. Ashraf, G.M., Greig, N.H., Khan, T.A., et al., (2014). Protein misfolding and aggregation in Alzheimer's disease and type 2 diabetes mellitus. CNS & neurological disorders drug targets, 13(7): p. 1280-1293 DOI: 10.2174/18715273136661409170955 14.
26. Vagelatos, N.T. and Eslick, G.D. (2013).Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol Rev, 35: p. 152-60 DOI: 10.1093/epirev/mxs012.
27. Exalto, L.G., Whitmer, R.A., Kappele, L.J., et al., (2012).An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol, 47(11): p. 858-64 DOI: 10.1016/j.exger.2012.07.014.
28. Ahtiluoto, S., Polvikoski, T., Peltonen, M., et al., (2010).Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology, 75(13): p. 1195-202 DOI: 10.1212/WNL.0 b013e3181f4d7f8.
29. Laudisio, A., Marzetti, E., Pagano, F., et al., (2008).Associationof metabolic syndrome with cognitive function: the role of sex and age. Clin Nutr, 27(5): p. 747-54 DOI: 0.1016/j.clnu.2008.07.001.
30. Cataldo, J.K., J.J. Prochaska, and S.A. Glantz, 2010. Cigarette smoking is a risk factor for Alzheimer's Disease: ananalysis controlling for tobacco industry affiliation. Journal of Alzheimer's disease, 19(2): p. 465-480 DOI: 10.3233/JAD-2010-1240.

Advances in Bioresearch
Adv. Biores., Vol 11 (3) May 2020: 143-149

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.11.3.143149

Advances in Bioresearch

ORIGINAL ARTICLE

Risk factors associated with Alzheimer's disease in Saudi Arabia: a descriptive study (Alzheimer's disease in Saudi Arabia)

Hemat E. El-Horany[1, 4*], Ahmed Hamed Aljadani[2], Razan S. Alsubhi[3], Maymonah S. Alshammari[3], Shouq N. Alruwaili[3], Asrar F. Alfaiqiri[3]
[1]Department of Biochemistry, College of Medicine, University of Hai'l, Hai'l, Saudi Arabia.
[2]Department of Internal Medicine, College of Medicine, University of Hai'l, Hai'l, Saudi Arabia.
[3]College of Medicine, University of Hai'l, Hai'l, Saudi Arabia
[4]Department of Medical Biochemistry, Faculty of Medicine, Tanta University, Tanta, Egypt.
*Corresponding author: hematelhorany@yahoo.com

ABSTRACT
To assess the risk factors associated with Alzheimer's disease (AD) in Saudi Arabia and to raise the awareness of healthcare providers about AD underlying neuropathological mechanisms and the differences in lifestyle risk factors, thus ensuring a better life quality for the Saudi population. A cross-sectional study, a questionnaire was designed, including inquiries on socio-demographic data and vascular risk factors including type 2 diabetes mellitus then sent to the health education administration of Saudi Alzheimer's Disease Association to collect data. A total sample of 309 patients were selected by systematic random sample. The prevalence of main risk factors in our sample were urban residence (77.35%), unemployment (69.9%), illiteracy (60.8%), hypertension (60%), being female (59.2%), low economic status (49.84%), diabetes (36.6%), followed by history of stroke (30.1%) and dyslipidemia (28.2%). The current analysis highlights the main risk factors for AD in Saudi Arabia to be taken into consideration when searching for solutions to control AD. This study highlights the urgent need for implementing a national program to address the modifiable risk factors at the community level, strengthening the role of geriatric medicine to support these high-risk groups and evaluate them regularly to impact their life quality positively.
Keywords*: Alzheimer, Alzheimer's disease, risk factors, Dementia, Saudi Arabia*.
Abbreviations: AD: Alzheimer's disease; T2DM: type 2 diabetes mellitus.

Received 11.05.2020 Revised 24.05.2020 Accepted 04.06.2020

How to cite this article:
H E. El-Horany, A H Aljadani, R S. Alsubhi, M S. Alshammari, S N. Alruwaili, A F. Alfaiqiri. Risk factors associated with Alzheimer's disease in Saudi Arabia: a descriptive study (Alzheimer's disease in Saudi Arabia). Adv. Biores., Vol 11 (3) May 2020: 143-149

INTRODUCTION

In recent years, the elderly population has grown at an accelerated pace due to increased life expectancy. This is often linked to the increase in the number of age-related diseases and increasing the need for healthcare services and social security [1]. In Saudi Arabia, the age of the population is shifting toward the elderly. In 2016, the number of people over 60 years of age was 1.3 million (6.5 %), and by 2050, this age group will exceed 10 million, representing 25% of the total population [2].

Alzheimer's disease is a progressive neurodegenerative age-related disease and the most dominant form of dementia, accounting for 60–80% of dementia cases, and ranking as the 6th highest cause of death. AD is characterized by amyloid-β peptide (Aβ) accumulation, produced through an altered cleavage of amyloid precursor protein (APP), the formation of neurofibrillary tangles, and synaptic and neuronal loss [3].

AD presents with the characteristic features of memory problems, challenges with learning and problem solving, language, swallowing, and walking difficulties, which often leads to interference with activities of daily living and other cognitive impairments. [4].

The latest World Alzheimer Report estimated that 46.8 million people worldwide are having dementia in 2015, and this number will double every 2 decades, reaching 74.7 million in 2030 and 131.5 million in

2050. These new estimates are 12-13% higher than those made for the World Alzheimer Report 2009. The regional estimates of dementia prevalence in people aged 60 years and over a range from 4.6% in Central Europe to 8.7% in North Africa and the Middle East [5].

AD has multi-factorial etiology. Many risk factors are involved in its incidence and progression, some of these are modifiable, and others are not. Numerous studies have reported a range of individual and environmental factors such as age, sex, education, socio-economic status, family history, and chronic disease (hypertension, diabetes mellitus, and depression) might be related to the risk of AD [6].

Alzheimer's disease has a relevant social and economic impact according to the evolutionary phase of the pathology, corresponding to medical costs, attention provided, training of caregivers, among others, placing a tremendous medical and fiscal burden on society [7].

The rising number of persons with AD and the lack of effective treatments highlight the urgency for risk factors to be better understood, while the studies conducted to investigate the risk factors of Alzheimer's disease in Arab countries and the Gulf region are still lacking. This issue is relevant for the implementation of preventive services at the population level, as even modest decreases in the prevalence of cognitive impairment in older populations might yield relevant reductions of the considerable healthcare and social costs. Indeed, it has been reported that careful control of vascular risk factors can postpone the onset or even reverse disease progression [8].

Therefore, a crucial step in the effective management of AD is to raise the awareness of healthcare providers about AD underlying neuropathological mechanisms and the differences in lifestyle risk factors and thus to ensure a better life quality for the Saudi population. To this aim, this cross-sectional study has been undertaken to investigate risk factors associated with AD in Saudi Arabia.

MATERIAL AND METHODS

Ethical considerations

Study protocols and instruments were institutionally approved bythe institutional review board at Hai'l University medical college.

Study area, design and population

A descriptive cross-sectional study was conducted from January 2019 to February 2019 among Alzheimer's disease patients registered at Saudi Alzheimer's Disease Association.

Sampling method & sample size

Systematic random sampling was proposed for this study. The estimated sample size for this study was 323 participants using Raosoft online sample size calculator at C.I. of 95%.

Data collection and study instrument

An electronic questionnaire was used to collect the data from the patients' fileselected by systematic random sample. The first section of the questionnaire captured socio-demographic characteristics of Alzheimer patients, including age, gender, residence, marital status, level of education, occupation, and economic status. The second section captured risk factors, including diabetes mellitus, hypertension, dyslipidemia, history of stroke, smoking, and family history of AD.

Statistical analysis

Data were represented in terms of frequencies (number of patients) and valid percentages for categorical variables. IBM Statistical Package for the Social Science (SPSS version 21) for Microsoft Windows was used to perform all statistical calculations. During data collection, Confidentiality of information was maintained. Moreover, their identity was not collected, so their information could never be matched to their responses.

RESULTS

The study included 309 Alzheimer's disease. There were 18 patients (5.83%) aged less than 60, 85 patients (27.51%) aged 60-74, 109 patients (32.28%) aged 75-84, and 97 patients (31.39%) aged 85 or over. There were more slightly female (59.22%) than male. More than two-thirds of the patients (77.35%) were from urban areas. One hundred sixty-one patients (52.1%) were married, while 14 patients (40.78%), 18 patients (40.78%), and 116 patients (37.54%) were single, divorced, and widowed, respectively. More than half of the patients (60.84%) were illiterate, and only 15 patients (4.85%) went to college. While 50 (16.18%), 25 (8.09%), and 31 (10.03%) of the patients had attended primary, preparatory, and secondary school, respectively. Approximately two-thirds of the patients were unemployed, while 75 patients (24.27%) were retired, and only 18 (5.83%) were employed. About half of the patients (49.84%) had low economic status, while only 4.21% of patients had excellent status. (Table 1)

Around one-third of the patients (36.57%) had diabetes mellitus, mostly type 2. Only 16 patients (5.18%) were smokers. Approximately half of the patients had been diagnosed with hypertension. 87 (28.16%) patients had dyslipidemia. About one-third of the patients (30.1%) had a history of stroke, either ischemic or hemorrhagic. Around one-third (9.1%) of the patients had a family history of AD. Tables 2.

Table 1: Socio-demographic characteristics of the patients

Characteristics	**N (%)**
Age (years)	
<60	18 (5.83%)
65-74	85 (27.51%)
75-84	109 (35.28%)
> 85	97 (31.39%)
Gender	
Male	126 (40.78%)
Female	183 (59.22%)
Residence	
Urban	239 (77.35%)
Rural	70 (22.65%)
Marital status	
Married	161 (52.10%)
Widowed	116 (37.54%)
Divorced	18 (5.83%)
Single	14 (4.53%)
Level of Education	
Illiterate	188 (60.84%)
Primary School	50 (16.18%)
Preparatory School	25 (8.09%)
Secondary School	31(10.03%)
College Completed	15 (4.85%)
Occupation	
Employed	18 (5.83%)
Retired	75 (24.27%)
Unemployed	216 (69.90%)
Economic status	
Excellent	13 (4.21%)
Average	142 (45.95%)
Low	154 (49.84%)

Table 2: Prevalence of relevant AD risk factors

Factor	N (%)
Hypertension	
Yes	173 (55.99%)
No	136 (44.01%)
Diabetes	
Yes	113 (36.57%)
No	196 (63.43%)
Type of diabetes	
Type 1	13 (11.50%)
Type 2	100 (88.50%)
Duration of diabetes	
<5 years	5(4.42%)
6-10 years	54 (47.79%)
>10 years	54 (47.79%)
Treatment for diabetes	
Insulin	54 (47.79%)
Oral hypoglycemic drugs	52 (46.02%)
Diet	7 (6.19%)
Glycemic control	
Yes	64 (20.71%)
No	245 (79.29%)
Dyslipidemia	

Yes	87 (28.16%)
No	222 (71.84%)
History of Stroke	
Yes	93 (30.10%)
No	216 (69.90%)
Smoking	
Yes	16 (5.18%)
No	293 (94.82%)
Family history of AD	
Yes	28 (9.06%)
No	281 (90.94%)
Duration of AD	
<1 Years	81 (26.21%)
1-3 Years	107 (34.63%)
4-6 Years	89 (28.80%)
>6 Years	32 (10.36%)

DISCUSSION

Emerging evidence has reported that several medical, environmental, and lifestyle risk factors implicated in AD development are modifiable. So, increasing attention is directed to the interplay of AD with comorbidities such as diabetes and hypertension, as well as socio-behavioral risk factors as educational attainment [9]. Until disease-modifying treatment becomes available, risk reduction interventions could drastically reduce the future burden of AD at the population level.

In the light of scarce data regarding AD risk factors in medical literature for the gulf area and Arab region, we aimed in our current study to throw light on risk factors associated with AD in Saudi Arabia.

Older age is strongly associated with AD in all studies, and similar associations have been reported globally, with the vast majority of people with Alzheimer's dementia being age 65 or older, as well disease probability is doubled every five years over the age of 65 [10]. In agreement, the present study revealed that the highest prevalence, about two-thirds of the patients, were among those aged 75 and over.

The current study demonstrated that women were more likely to have AD compared with their male counterparts in this sample, as 59.2% of the patients were female. Consistently, it was reported that dementia and AD frequencies were higher in women in Lebanon and Turkey [11, 12]. This could be related to various factors, including menopause transition, differences in cognitive reserve, resilience, as well as genetics (apolipoprotein Ɛ4), and functional and structural brain changes. It is also pointed out that women have a higher risk of having comorbidities due to a longer lifespan, like coronary heart disease, depression, and myocardial infarction, which are all risk factors for cognitive decline or impairment [13, 14].

The current study found that 77.4% of the patients were urban residents. In the published literature, the association between urbanization levels and AD risk is still inconclusive. The presence of green, environmental layout and complexity, levels of traffic and noise can act as a source of brain training and possibly contribute to cognitive resilience in older age; however, environmental stimulation can cause cognitive overload depending on the relationship between levels of stimulation and the individuals' cognitive and physical functionality [15].

There is an independent and substantial association between marital status in mid-life and cognitive function later in life, it was reported that the risk of developing Alzheimer's disease is twice in people without a partner compared with people living with a partner [16]. In parallel, the present report revealed that 47.9% of patients had disturbed marital life or singles.

Of note, certain protective behavioral factors may promote resiliency against the development of age-related neuropathological changes in the brain. A wealth of epidemiologic studies suggested that lifetime exposures, including educational and occupational attainment, and leisure activities in late life, can increase cognitive reserve and protect against AD [17].

It is widely documented that having a lower level of education was also recognized as one of the most established risks for dementia and AD [18]. Similarly, the current study reported that 60.8% and 69.9% of the investigated AD patients were illiterate and unemployed, respectively.

These observations could be based on two primary possible explanations. Firstly, the cognitive reserve hypothesis postulates that people with a higher cognitive reserve can tolerate more neurodegenerative pathology and maintain brain function for longer than people with a low reserve before the damage manifests clinically as dementia. Secondly, people with higher education have a more favorable environment, including a healthier lifestyle, better compliance to treatment and better access to healthcare leading to less cognitive decline and dementia [17, 19].

Therefore, lifestyle interventions at all stages, even in late life, are highly appreciated, in order to impart cognitive reserve and slow age-related cognitive decline for prolonged healthy aging.

As indicated by the current study, AD was more prevalent among those of lower income (49.8%). In parallel, the association between low socio-economic status and AD is widely documented in the literature. They attributed this finding to poor access to health care services, unhealthy diet or lifestyle, low education, and increased physiological stress that can contribute to higher blood pressure and depression [20].

Hypertension is a significant global and national health challenge due to its high prevalence. At the national, the prevalence of hypertension and prehypertension is significantly increased due to economic development, acceleration of population aging, as well as modifications in lifestyle and traditional dietary habits. According to 2010 estimates, hypertension was classified as the leading risk factor for death in Saudi Arabia. The most recent report presented a prevalence of 31.4% for hypertension among the Saudi population [21].

Growing evidence has demonstrated that hypertension is a significant contributor to the pathogenesis of AD. Multiple mechanisms have been explained. Hypertension alters the structure and molecular composition of cerebral blood vessels and disrupts the homeostatic mechanisms that ensure adequate blood supply to the brain. Thus, damage to the cerebral vasculature compromises oxygen and glucose delivery for proper neuronal function, as well as the removal of metabolic waste and toxic proteins, rendering the brain more vulnerable to ischemic injury, white matter disease, and to the development of neurodegenerative pathologies [22].

The present study revealed an alarming finding; hypertension was a highly notable risk factor in this study as it found in 60% of our patients, which is compatible with the findings of another study underscored on the Arab population living in Wadi Ara and reported higher odds of AD associated with hypertension [23].

DM is a metabolic disease characterized by elevated level of blood glucose as a result of insulin secretion defect, insulin action defect or possibly both. T2DM accounts for up to 90% of total diabetes incidence and has become a significant health problem globally. Saudi Arabia was reported to rank the second in the Middle East and the seventh worldwide in terms of diabetes rate. It is estimated that around 7 million of the population are diabetic and almost around three million have pre-diabetes [24].

Like AD, T2DM is also considered as a degenerative metabolic disease that occurs in later age and is associated with the gradual loss of insulin-secreting pancreatic beta-cells. The deposition of islet amyloid polypeptide (known as amylin) within beta-cells of the pancreas is considered as a major contributor in pathogenesis of T2DM. Also, it has been envisaged that AD may be a type of 'brain diabetes' or 'type 3 diabetes' resulting from both insulin deficiency and insulin resistance in the brain. Moreover, T2DM results in chronic cerebral hypoperfusion leading to neuro-glial dysfunction and degeneration, as well, individuals with T2DM are at increased risk of suffering transient ischemic attacks that, although often silent, can lead to severe consequences in the long-term, including dementia.; posing the question as to whether one leads to the other in aged individuals [25].

A notable portion of the AD patients investigated in our analysis (36.6%) were T2DM. These findings should not be surprising given that a growing health issue of T2DM among the Saudi population.

Several meta-analysis studies from published literature have estimated an aggregated relative risk of approximately 1.5 linking T2DM with AD, and the relative risk increases considerably by the presence of hypertension, smoking and APOE4 positivity [26, 27]. On the other hand, there is a clear discrepancy between epidemiological results and neuropathological autopsy findings in linking AD with type 2 diabetes and concluded that type 2 diabetes does not promote AD pathology in the brain and instead vascular pathologies in the brain are more commonly associated with type 2 diabetes [26, 28].

T2DM is a preventable disease that is influenced by several modifiable risk factors such as obesity, active smoking, physical inactivity, and unhealthy diet. Therefore, there is an urgent need for an effective public health multidisciplinary approach to reduce and control the modifiable risk factors for T2DM.

As hypertension and diabetes mellitus are huge clinical and public health burden in the Kingdom of Saudi Arabia, healthcare professionals must be aware of these risk factor associated with AD, and direct community awareness campaigns for increasing individual's knowledge of risk factors for AD among the Saudi population.

Herein, 30.1% of the patients had a history of stroke. In line with our observation, stroke was recorded as a relevant contributor to cognitive decline and the development of dementia [19].

The relationship between hyperlipidemia and cognition is very complex, controversial, and still need more elucidate [29]. In the current report, 28.2% of our patients had dyslipidemia.

A meta-analysis study stated that smoking is a significant risk factor for AD [30]. However, as smoking is less of an issue in KSA than in other parts of the world, herein, only 5.2% of AD patients were smokers.
Only 9.1% of the patients had a family history of AD. It was reported that a family history of Alzheimer's is not necessary for an individual to develop the disease. However, individuals who have a first-degree relative with AD are more likely to develop the disease than those who do not have [10].

CONCLUSION

In sum, the current work provides novel findings about the prevalence of primary risk factors in Saudi AD patients. It is undoubtedly vital for health caregivers to reconsider the role of cardiovascular and socio-economic risk factors in the oldest subjects. Since there is no effective treatment for this disease today, prevention and lifestyle modification are critical. A multidisciplinary approach is required with great emphasis laid on advocating a healthy diet, exercise, multiple mental activities, active lifestyles, and weight control.
Also, it is recommended to regularly review and follow up older patients with cardiovascular risk factors, like hypertension and diabetes, especially those with low socio-economic status, through an organized system of healthcare delivery.

AUTHOR CONTRIBUTIONS

All authors provided significant input into the manuscript and have read and approved the final version.

ACKNOWLEDGMENTS

The authors are grateful for the support provided by health education administration of Saudi Alzheimer's Disease Association, especially the health educator, Lujain Abdullah Bin Amer until this research paper has been completed.

COMPETING INTERESTS

The authors have no conflicts of interest.

REFERENCES

1. Aly, H.Y., Hamed, A.F., and Mohammed, N.A. (2018). Depression among the elderly population in Sohag governorate. Saudi Med J, 39(2): p. 185-190 DOI: 10.15537/smj.2018.2.21353.
2. Alkhunizan, M., A. Alkhenizan, and Basudan, L. (2018).Prevalence of Mild CognitiveImpairment and Dementia in Saudi Arabia: A Community-Based Study. Dement Geriatr Cogn Dis Extra, 8(1): p. 98-103 DOI: 10.1159/000487231.
3. Yoshida, K., Moein, A., Bittner, T., et al., (2020).Pharmacokinetics and pharmacodynamic effect of crenezumab on plasma and cerebrospinal fluid beta-amyloid in patients with mild-to-moderate Alzheimer's disease. Alzheimer's research & therapy, 12(1): p. 16-16 DOI: 10.1186/s13195-020-0580-2.
4. Ali, M.M., Ghouri, R.G., Ans, A.H., et al., (2019).Recommendations for Anti-inflammatory Treatments in Alzheimer's Disease: AComprehensive Review of the Literature. Cureus, 11(5): p. e4620-e4620 DOI: 10.7759/cureus.4620.
5. Prince, M.J., World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. 2015: Alzheimer's Disease International.
6. [6]. Bhatti, G.K., Reddy, A.P., Reddy, P.H., et al., (2020). Lifestyle Modifications and Nutritional Interventions in Aging-Associated Cognitive Decline and Alzheimer's Disease. Frontiers in aging neuroscience,11: p. 369-369 DOI: 10.3389/fnagi.2019.00369.
7. Alacreu, M., Pardo, J., Azorín, M., et al., (2019). Importance of Increasing Modifiable Risk Factors Knowledge on Alzheimer's Disease Among Community Pharmacists and General Practitioners in Spain. Front Pharmacol, 10: p. 860 DOI: 10.3389/fphar.2019.00860.
8. Morovic, S., Budincevic, H., Govori, V., et al., (2019).Possibilities of Dementia Prevention - It is Never Too Early to Start. J Med Life, 12(4): p. 332-337 DOI: 10.25122/jml-2019-0088.
9. Ivanova, N., Liu, Q., Agca, C., et al., (2020). White matter inflammation and cognitive function in a co-morbid metabolic syndrome and prodromal Alzheimer's disease rat model. Journal of neuroinflammation, 17(1): p. 29-29 DOI: 10.1186/s12974-020-1698-7.
10. Alzheimer's disease facts and figures. Alzheimer's & Dementia, 2018. 14(3): p. 367-429 DOI:10.1016/j.jalz.2018.02.001.
11. Ertekin, A., Demir R., Özdemir, G., et al., (2015). An Investigation of the Risk Factors and Prevalence of Alzheimer's Disease in the Eastern Region of Turkey. European Journal of General Medicine, DOI.10.15197/sabad.1.12.29
12. Chaaya, M., Phung, K., Atweh, S., et al., (2017).Socio-demographic and cardiovascular disease risk factors associated with dementia: Results of a cross-sectional study from Lebanon. Preventive medicine reports, 9: p. 1-5 DOI: 10.1016/j.pmedr.2017.11.006.

13. Rahman, A., Jackson, H., Hristov, H., et al., (2019).Sex and Gender Driven Modifiers of Alzheimer's: The Role for Estrogenic Control Across Age, Race, Medical, and Lifestyle Risks. Frontiers in aging neuroscience, 11: p. 315-315 DOI: 10.3389/fnagi.2019.00315.
14. Laws, K.R., Irvine, K., and Gale, T.M., (2018).Sex differences in Alzheimer's disease. Current opinion in psychiatry, 31(2): p. 133-139 DOI: 10.5498/wjp.v6.i1.54.
15. Cassarino, M. and A. Setti, (2015). Environment as 'Brain Training': A review of geographical and physical environmental influences on cognitive ageing. Ageing Res Rev, 23(Pt B): p. 167-82 DOI: 10.1016/j.arr.2015.06.003.
16. Håkansson, K., Rovio, S., Helkala, E., et al., (2009).Association between mid-life marital status and cognitive function in later life: population based cohort study. BMJ (Clinical research ed.), 339: p. b2462-b2462 DOI: 10.1136/bmj.b2462.
17. DuBose, L.E., Moser, D. J., Harlynn, E., et al., (2019).Education moderates the effects of large central artery aging on cognitive performance in middle-aged and older adults. Physiological reports, 7(23): p. e14291-e14291 DOI: 10.14814/phy2.14291.
18. Elshahidi, M.H., Elhadidi, M. A., Sharaqi, A. A.,et al., (2017). Prevalence of dementia in Egypt: asystematic review. Neuropsychiatric disease and treatment, 13: p. 715-720 DOI: 10.2147/NDT.S127605
19. Srithumsuk, W., Kabayama, M., Gondo, Y., et al.,(2020).The importance of stroke as a risk factor of cognitive decline in community dwelling older and oldest peoples: the SONIC study. BMC geriatrics, 22;20(1):24. DOI: 10.1186/s12877-020-1423-5.
20. Camacho-Mercado, C.L., Figueroa, A., Acosta, H., et al., (2016). Profiling of Alzheimer's disease patients in Puerto Rico: A comparison of two distinct socioeconomic areas. SAGE Open Med, 4: p. 2050312115627826 DOI: 10.1177/2050312115627826.
21. Aldiab, A., Shubair, M.M., Al-Zahrani J.M.,et al., (2018). Prevalence of hypertension and prehypertension and its associated cardioembolic risk factors; a population based cross-sectional study in Alkharj, Saudi Arabia. BMC public health, 18(1): p. 1327-1327 DOI: 10.1186/s12889-018-6216-9.
22. Iulita, M.F. and H. Girouard, (2017).Treating Hypertension to Prevent Cognitive Decline and Dementia: Re-Opening the Debate. Adv Exp Med Biol, 956: p. 447-473 DOI: 10.1007/5584_2016_98.
23. Israeli-Korn, S.D., Masarwa, M., Schechtman, E., et al., (2010). Hypertensionincreases the probability of Alzheimer's disease and of mild cognitive impairment in an Arab community in northern Israel. Neuroepidemiology, 34(2): p. 99-105 DOI: 10.1159/000264828.
24. Alqahtani, M., Almutairi, F.E., Albasseet, A.O., et al., (2020).Knowledge, Attitude, and Practice of Diabetes Mellitus Among the Saudi Population in Riyadh, Saudi Arabia: A Quantitative Study. Cureus,12(1): p. e6601-e6601 DOI: 10.7759/cureus.6601.
25. Ashraf, G.M., Greig, N.H., Khan, T.A., et al., (2014). Protein misfolding and aggregation in Alzheimer's disease and type 2 diabetes mellitus. CNS & neurological disorders drug targets, 13(7): p. 1280-1293 DOI: 10.2174/18715273136661409170955 14.
26. Vagelatos, N.T. and Eslick, G.D. (2013).Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. Epidemiol Rev, 35: p. 152-60 DOI: 10.1093/epirev/mxs012.
27. Exalto, L.G., Whitmer, R.A., Kappele, L.J., et al., (2012).An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol, 47(11): p. 858-64 DOI: 10.1016/j.exger.2012.07.014.
28. Ahtiluoto, S., Polvikoski, T., Peltonen, M., et al., (2010).Diabetes, Alzheimer disease, and vascular dementia: a population-based neuropathologic study. Neurology, 75(13): p. 1195-202 DOI: 10.1212/WNL.0 b013e3181f4d7f8.
29. Laudisio, A., Marzetti, E., Pagano, F., et al., (2008).Associationof metabolic syndrome with cognitive function: the role of sex and age. Clin Nutr, 27(5): p. 747-54 DOI: 0.1016/j.clnu.2008.07.001.
30. Cataldo, J.K., J.J. Prochaska, and S.A. Glantz, 2010. Cigarette smoking is a risk factor for Alzheimer's Disease: ananalysis controlling for tobacco industry affiliation. Journal of Alzheimer's disease, 19(2): p. 465-480 DOI: 10.3233/JAD-2010-1240.