PROBING THE LINK BETWEEN DEMENTIA AND DIABETES: A META-ANALYSIS

A Thesis

Submitted for Partial Fulfillment of Masters Degree

To [Name of University]

By

[Name of Student]

[Name of University]

[Date]

Declaration by Student

I, [Name of Student], hereby declare that the work presented here is original work done by me and has not been published or submitted elsewhere for the requirement of a degree program. Any literature or work done by others and cited within this thesis has been given due acknowledgement and listed in the Reference section.

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Acknowledgements

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Abstract

Dementia and diabetes are globally prevalent conditions deeply interconnected at the metabolic level. Several mechanisms have been proposed that present diabetes as an important risk factor for dementia; however, the complexities of the mechanisms remain unclear. **Aim:** The objective of the present study was to perform a meta-analysis of population-based studies to investigate diabetes as a risk factor for Alzheimer's disease, vascular dementia, and mixed dementia. **Methods:** Population-based observational studies that described the incidence of dementia in people with and without diabetes were extracted from the databases, PubMed and Science Direct, between the years 2000 and 2020. Pooled odds ratio estimates and 95% confidence intervals were calculated using the random-effects model and forest plots were generated. **Results:** A total of 15 studies were used in the meta-analysis to identify the differences in risk of developing dementia in diabetics and non-diabetics. Additional risk factors such as age, gender, and anti-diabetic therapy were also evaluated. The odds ratio for developing dementia in patients with diabetes was 1.04, the odds ratio when comparing the incidence of early-onset and late-onset dementia in diabetics and non-diabetics was 1.71 and 1.12 respectively, and the odds ratio when comparing the incidence of dementia in diabetic males and diabetic females was 1.05 and 1.01 respectively. **Conclusions:** People with diabetes have only a slightly higher risk of acquiring dementia. People with diabetes have a 71% higher risk of developing early-onset dementia and men have a higher risk of developing dementia as compared to women.

Chapter 1: Introduction

1.1 Dementia

According to the ICD-10 Classification of Mental and Behavioural Disorders published by the World Health Organization (1992), dementia is a condition of the brain where higher cortical functions such as memory, comprehension, judgement, thinking, language, learning, and calculation are impaired. It is a chronic syndrome that leads to loss of emotional and social behavioural control. Dementia is not a single condition; rather it is a collection of several features and symptoms that co-exist in a person forming a specific recognizable pattern (Thomas and Dening, 2013).

People belonging to the age group of 65 to 85 years are most susceptible to developing this condition, with the chances doubling every 5 years after the age of 65 (Poon et al., 2012). Other risk factors of dementia include gender, lifestyle, smoking and drinking, and prevalence of cardiovascular conditions, high blood sugar, and a family history of dementia. Of all cases of dementia, Alzheimer's disease alone contributes to 60% to 80% and cerebrovascular disease contributes to 5% to 10% of all dementia cases. Apart from Alzheimer's disease and vascular dementia, 5% to 10% of people with dementia show the presence of Lewy bodies that are abnormal aggregates of the protein α-synuclein in the neurons. People who develop dementia due to the presence of Lewy bodies experience disturbances in sleep cycles, hallucinations, visuospatial impairment, and movement-related impairment such as gait imbalance (Alzheimer's Association, 2019).

1.1.1 Alzheimer's Disease

This is the most common type of dementia and one of the earliest symptoms of this condition is memory loss relating to events in the near past, followed by language-related difficulties (Taylor and Thomas, 2013). If left unchecked, the memory loss worsens and the language difficulties become more pronounced. This leads to problems in day-to-day activities such as handling money and shopping. Other symptoms that appear to a lesser extent include lack of motivation and anxiety. Eventually, the person is unable to perform tasks independently and requires constant supervision (Steinberg et al., 2008).

The physiological changes in the brain that contribute to Alzheimer's disease include the formation of insoluble plaques made from the protein, amyloid, in the brain. The abnormal deposition of these plaques along with the formation of neurofibrillary tangles in the form of twisted fibres hinders the normal functioning of the brain leading to specific brain-related symptoms. Another finding in Alzheimer's disease is a deficiency of acetylcholine, which is a neurotransmitter, leading to problems with memory and learning (Piggott, 2013).

1.1.2 Vascular Dementia

This is the second most common type of dementia after Alzheimer's disease which usually develops after a stroke. Apart from the clinical features that develop in Alzheimer's disease, people with this type of dementia also have problems with thinking processes, apathy, depression, and anxiety. It usually occurs due to a decrease in blood supply to the brain resulting from arterial disease and is characterized by compromised neuronal function due to death of brain cells (Jackson et al., 2013).

1.1.3 Dementia – A Global Health Burden

According to a report by Alzheimer's Disease International (2019), the number of dementia cases worldwide are over 50 million currently, and this number is believed to increase to over 150 million in the next 30 years. In the United States alone, people living with dementia occurring due to Alzheimer's disease is 5.8 million currently, out of which 81% are over 75 years old (Alzheimer's Association, 2019). In the United Kingdom, around 0.88 million people were diagnosed with dementia in 2019, which forms 7.1% of the older population in the region. This number is thought to reach the 1 million mark by 2024 and jump to 1.6 million by 2040 (Wittenberg et al., 2019). In Australia, dementia is the third most common cause of death in males and the first most common cause of death in females, with an estimated 0.44 million affected people throughout the country. The number of people diagnosed with dementia in Australia is thought to reach the 1 million mark by 2058 (Dementia Australia, 2019).

Around 50 million people around the world are living with dementia currently and the number will increase to 131 million by 2050. Annually, the care and treatment of patients with dementia costs around 818 billion US dollars (Dementia Australia, 2019). As the lifespan of people keep increasing due to breakthroughs in medical technology, the number of people likely to get dementia is also on the rise. The expenses of care of dementia patients combined with an absence of definitive treatment for dementia has made this syndrome a huge health burden for most countries around the world (Ricci, 2019).

1.2 Diabetes

Diabetes is a group of metabolic disorders characterized by the presence of high levels of sugar in the blood due to defects in the production of insulin or action of insulin or both. Some of the classic symptoms of diabetes include excessive thirst, frequent urination, weight loss, and blurring of vision. In extreme cases, it may lead to ketoacidosis that may eventually cause dehydration, and even death. Although diabetes is, to a large extent, manageable, people suffering from diabetes are at an increased risk for developing cardiovascular and cerebrovascular disorders, nonalcoholic fatty liver disease, erectile dysfunction, retinopathy, neuropathy, and nephropathy (World Health Organization, 2019).

1.2.1 Types of Diabetes

Diabetes is largely divided into two major types based on the extent to which pancreatic β-cell function is disrupted, the extent to which a patient shows insulin resistance, age of onset, and progression of symptoms. People having type 1 diabetes completely lack insulin secretion due to a combination of genetic factors and autoimmune pathologic processes in the pancreas. Compared to type 1 diabetes, type 2 diabetes is more common and dependent on lifestyle factors such as unhealthy diet and lack of sufficient exercise. Type 2 diabetes occurs due to insufficient secretion of insulin combined with a marked resistance to insulin function. Type 1 diabetes accounts for 5% to 10% of all diabetes cases whereas type 2 diabetes accounts for 90% to 95% of diabetes cases (American Diabetes Association, 2014).

1.2.2 Diabetes – A Global Health Burden

As per statistical data from 2019, the current number of people living with diabetes worldwide is 463 million, and the number is thought to reach 700 million by 2045. In North America alone, the number of affected people is 48 million, whereas the number is 32 million in South America and 19 million in Africa. Given the population size, Asia and Australia together have 163 million people affected with diabetes whereas 59 million people are living with diabetes in Europe. Being one of the fastest growing health conditions today, not only does it claim millions of lives annually, but it is also estimated that over 50% of people with diabetes are undiagnosed. This presents an alarming health issue with the numbers of caregivers and expenses of treatment being constantly on the rise (International Diabetes Federation, 2019).

Diabetes has been reported to affect a larger population of low-income and middle-income countries in comparison to that of high-income countries. Among the affected population, at least 1.1 million are reported to belong to the age group of 0 to 19 years and 352 million affected people belong to the working age group (20 to 64 years). This disease not only affects individuals, but also the socio-economic status of countries, bringing down the economy and productivity of young adults. The annual expense of prevention and treatment-oriented diabetes programs is 850 billion US dollars, putting a heavy economic toll on countries that can barely afford good healthcare (World Health Organization, 2019).

1.3 Link between Dementia and Diabetes

Several studies have contemplated a strong connection between dementia and diabetes, especially because the continual presence of high amounts of sugar in the blood can harm several major organs, particularly the brain (Alzheimer's Association, 2007). Type 2 diabetes has been linked to both vascular dementia (Ahtiluoto et al., 2010) and Alzheimer's disease (Peila et al., 2002). Even people having prediabetes are at an increased risk of undergoing cognitive decline and brain atrophy, both of which can in turn lead to dementia (Rasgon et al., 2010). Studies conducted in this regard have given mixed results with some studies showing a strong connection between diabetes and cognitive decline (Gregg et al., 2000), some studies showing a negative relationship between diabetes and cognitive decline (Sanz et al., 2009), and some studies showing that diabetes and cognitive decline are independent of each other (Kanaya et al., 2004).

Differences in the results have been attributed to use of different tools for assessment and different demographics of the populations surveyed.

Type 1 diabetes primarily occurs due to underlying genetic and autoimmune aetiologies, whereas type 2 diabetes is, to a larger extent, influenced by environmental factors such as age, ethnicity, and lifestyle. In type 2 diabetes, the decline in function of pancreatic β-cells and resistance to the insulin hormone develops gradually, and this chronic presence of glucose in the blood can, over time, damage the brain affecting cognition. If not treated, chronic hyperglycemia can lead to the production of Advanced Glycation End products (AGE), and this along with free radicals can lead to oxidative stress and neuronal injury (Umegaki et al., 2013).

Another explanation of the link between dementia and diabetes is the inter-relatedness of several pathways in the body. For example, the hormone insulin plays an important role in cerebral energy metabolism by increasing the movement of Glucose Transporter in the brain. When insulin secretion is affected in diabetes, the transport of glucose in the brain is disrupted leading to glucose dysregulation (Cholerton et al., 2011). Type 2 diabetes has also been reported to affect the metabolism of the amyloid-β protein in the brain, increasing the risk for developing cerebrovascular conditions (Carlsson, 2010).

The link between diabetes and dementia is significant for several reasons. Most factors leading to type 2 diabetes can be prevented by taking certain precautionary measures, and this in turn can reduce the risk of several other conditions, including dementia. The diagnosis and treatment for dementia may not be well documented yet, but diabetes is quite well understood in terms of diagnostic criteria and treatment strategies. Hence, the effective management of diabetes can prevent or delay the onset of dementia (Ravona-Springer and Schnaider-Beeri, 2011).

1.3.1 Type-3 Diabetes

Some of the earliest symptoms of dementia-related cognitive decline include problems with utilization of cerebral glucose and impairment of energy metabolism (Hoyer, 2004). Due to the strong connections made between disruption of insulin signaling pathways in the brain and development of Alzheimer’s disease, several researchers have proposed that Alzheimer’s disease may be considered ‘type 3 diabetes’ (Steen et al., 2005). Just like the other two types of diabetes, Alzheimer’s disease or type 3 diabetes is also characterized by insulin deficiency and insulin resistance which is limited to the brain, unless the individual also has one of the other two types of diabetes (Rivera et al., 2005).

Several studies have established that the insulin gene is expressed in the brain and the development of Alzheimer's disease is linked to the impairment of insulin signaling pathways in the brain. Insulin deficiency in the brain has been strongly linked to neurodegeneration pathways and the abnormalities observed in the brain of Alzheimer's disease patients is markedly similar to those identified in patients with the other two types of diabetes. Based on this observation, it has been hypothesized that Alzheimer's disease may be diabetes of the brain categorizing it as 'type 3 diabetes' (de la Monte and Wands, 2008).

1.4 Aims and Objectives

The purpose of the present study is to explore the links between diabetes mellitus and dementia, especially Alzheimer's disease and vascular dementia, and to find irrefutable evidence for the theory that Alzheimer's disease is actually type 3 diabetes. In order to accomplish this, a meta-analysis will be performed to understand the significance of the connection between diabetes and dementia by taking into account published scientific data.

The objectives of this meta-analysis are two-fold:

i. To understand if there is a statistically significant relationship between diabetes mellitus and dementia, especially Alzheimer's disease and vascular dementia
ii. To look for and identify scientific evidence to support the claim that Alzheimer's disease is type 3 diabetes

The results of this meta-analysis are significant in terms of providing appropriate management and prevention strategies to people with diabetes in order to lower the possibility of developing Alzheimer's disease. Given the immense numbers of people affected with both these conditions, any strategy for preventing or delaying either of these will go a long way in reducing the economic burden of these conditions. Not only will this study be beneficial at an international and national level, but it will also mark a beginning in an attempt to alter patients' quality of life by providing them the necessary information and guidance for managing these conditions at their early stages.

Chapter 2: Methods and Materials

2.1 Study Selection for Meta-Analysis

The flowchart shown in Figure 1 outlines the procedure employed for selection of studies for the meta-analysis. The PubMed and Science Direct databases were used to search for relevant articles and the inclusion and exclusion criteria were applied to finalize 12 studies for the meta-analysis.

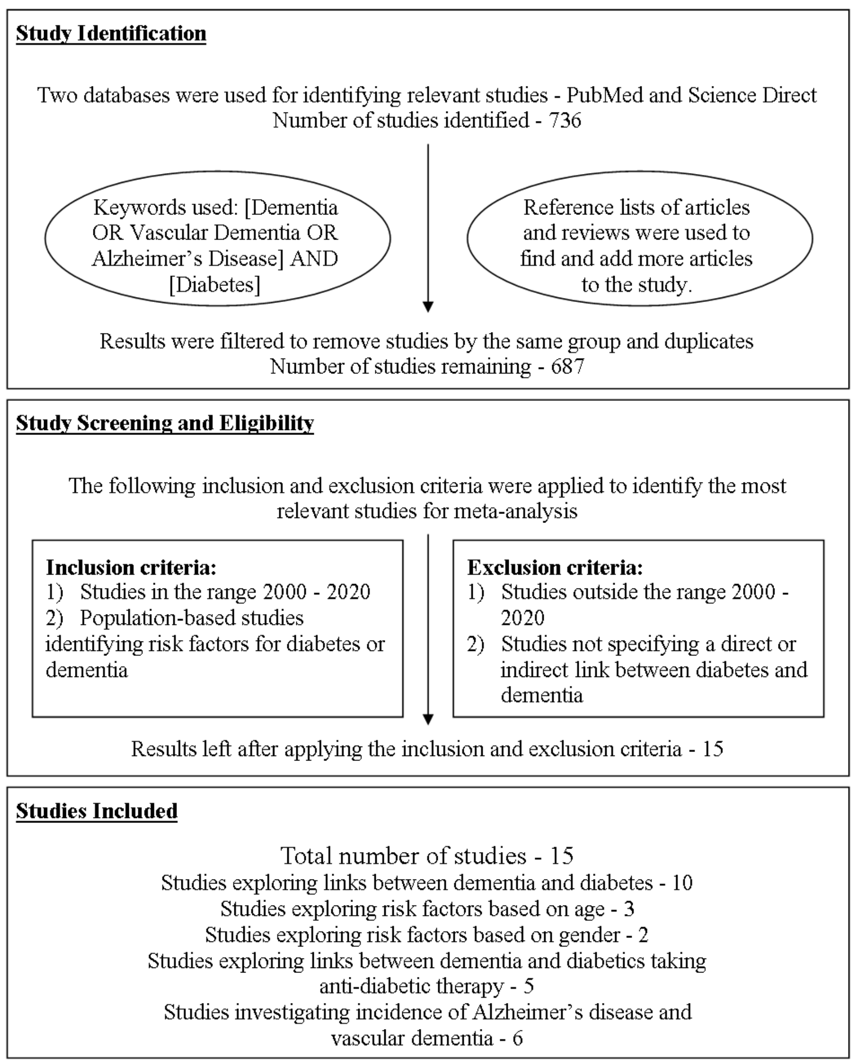

Figure 1: A flowchart showing the steps using which relevant studies for the meta-analysis were identified and screened

2.2 Meta-Analysis

The studies that were identified following the rigorous screening process were entered into Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, 2014) for meta-analysis. Based on the type of data available in the studies, the method of entering data used was dichotomous data. The inverse variance statistical method and the fixed effects model were used for calculation of the odds ratio and generation of forest plots.

Chapter 3: Results

3.1 Features of Studies Included in the Meta-Analysis

Using the databases PubMed and Science Direct, 736 studies were identified initially which were then carefully screened to remove multiple studies by the same group and duplicates. Further, the studies were subjected to a rigorous screening process based on the inclusion and exclusion criteria given in Figure 1. Studies that were population-based and analyzed the risk of developing dementia in diabetic and non-diabetic groups were included. Studies that considered the effect of anti-diabetic medications on the incidence of dementia were also considered. Finally, studies that investigated the difference in incidence between Alzheimer's disease and vascular dementia were also included in the meta-analysis. Studies that were merely qualitative and those that did not analyze dementia risk between diabetic and control groups were eliminated from the meta-analysis. Studies that considered other factors such as presence of co-morbidities in relation to dementia risk were also eliminated. Finally, 15 studies remained, all of which came from PubMed, and the features of these studies are given in Table 1.

Out of the 15 studies, 10 studies were used to compare dementia risk between diabetic and non-diabetic cohorts. The remaining studies were included in the meta-analysis because they measured the differences in risks between early-onset and late-onset dementia, risk of developing dementia between males and females, differences in the incidence of types of dementia, and differences in the risk of developing dementia in diabetics who were either taking or not taking anti-diabetic medications. The studies were conducted in the year range of 2006 to 2019, and most of them involved 5 to 15 years of follow-up with patients to assess cognitive decline in the subjects. The heterogeneity in the studies was due to the sample size, tools used to assess diabetes and dementia, and study design. Considering the study design, 14 studies were prospective population-based or cohort-based studies whereas 1 was a retrospective study. The sample sizes varied from as low as 174 to as high as 6,68,070.

Study	Aim of Study	Population Studied	Age at Baseline (years)	Follow-up Time (years)	Male Gender (%)	Type of Diabetes	Type of Dementia	Sample Size Diabetic/ Control	Number of Events Diabetic/ Control	Result of the Study
Akomolafe et al., 2006	To compare the risk of developing Alzheimer's disease in people with and without diabetes	Framingham Study Cohort, Boston	70	12.7	51	Diabetes Mellitus	Alzheimer's Disease	202/2008	17/220	Diabetes did not increase the incidence of Alzheimer's disease
Chang et al., 2016	To evaluate if the use of aspirin in diabetics affects the risk of developing dementia	National Health Insurance Research Database Cohort, Taiwan	>50	4.5 to 5	51.4	Type 2 Diabetes Mellitus	Alzheimer's Disease and non-Alzheimer's Dementia	2876/ 10720	117/360	Daily use of aspirin in diabetics may lower the risk of developing dementia
Chen et al., 2014	To evaluate if the use of statin in diabetics lowers the risk of developing dementia	National Health Insurance Research Database Cohort, Taiwan	>50	8	53.7	Type 2 Diabetes Mellitus	Alzheimer's Disease and non-Alzheimer's Dementia	2400/ 15770	53/824	Regular use of statins may lower the risk of Alzheimer's disease in diabetics
Davis et al., 2016	To analyze if patients with diabetes	Fremantle Diabetes Study Cohort,	>64	13.8±5.8	48.7	Type 2 Diabetes Mellitus	Alzheimer's Disease, Vascular Dementia,	1286/ 5132	179/636	Patients with diabetes have a higher risk of developing dementia

	had a higher risk of developing dementia	Australia					All-cause Dementia, Unspecified Dementia			
Fan et al., 2017	To evaluate the risk of developing dementia in patients with and without diabetes	National Health Insurance Research Database Cohort, Taiwan	53	10	53	Type 1 and Type 2 Diabetes Mellitus	Dementia	10316/ 41264	333/981	Diabetes is a significant risk factor for developing dementia
Haroon et al., 2015	To study is diabetes onset in old age is a risk factor for dementia	Provincial Health Data Cohort, Canada	73	7.2	49.2	Diabetes	Dementia	225045/ 668070	43029/ 126085	Diabetes onset in late life is an important risk factor for development of dementia
Heneka et al., 2015	To evaluate if pioglitaz-one lowered the risk of dementia in diabetics	United States	>60	10	-	Diabetes	Dementia	67822/ 122036	1478/ 3854	Pioglitazone is associated with lower risk of dementia in people with non-insulin dependent diabetes
Hsu et al., 2011	To evaluate if use of oral agents lowered the risk of	National Health Insurance Research Database Cohort,	>50	8	-	Type 2 Diabetes Mellitus	Dementia	1864/ 10519	66/434	The combined use of sulfonylurea and metformin lowers the risk of dementia in diabetics

	dementia in diabetics	Taiwan								
Huang et al., 2014	To evaluate the relation between diabetes and Alzheimer's disease	National Health Insurance Research Database Cohort, Taiwan	58.74±14.02	11	51.8	Diabetes Mellitus	Alzheimer's Disease	71433/ 71311	346/266	Newly diagnosed diabetes is associated with increased dementia risk
Imfeld et al., 2012	To study the effects of anti-diabetic therapy on developm-ent of dementia	General Practice Research Database (GPRD), United Kingdom	>60	10	-	Diabetes Mellitus	Alzheimer's Disease	791/ 13538	356/6802	Anti-diabetic therapy did not lower the risk of Alzheimer's disease in diabetics
Katon et al., 2015	To study the effect of diabetes on risk of all-cause dementia	Denmark	>50	7	39	Type 2 Diabetes	All-cause Dementia	318865/ 477133	10488/ 15729	Presence of diabetes increases the risk of developing dementia
Mayeda et al., 2013	To study the link between diabetes and dementia in Mexican Americans	Sacramento Area Latino Study Cohort, California	60 to 98	10	44.4	Type 2 Diabetes	Dementia and Cognitive Impairment without Dementia	677/940	84/75	Diabetes and dementia are strongly associated in the Mexican American population
Secnik et	Effect of	Swedish	78±7.3	-	48.5	Diabetes	Alzheimer's	4881/	3471/	People with diabetes

al., 2017	diabetes treatment on risk of dementia	Dementia Registry Cohort, Sweden					Disease, Vascular Dementia, Mixed Dementia, Dementia with Lewy Bodies, Parkinson Disease Dementia	24749	17246	have less optimal treatment for dementia
Wang et al., 2012	To study age and gender-specific relation between diabetes and dementia	Taiwan	60.1±12.7	9	48.1	Diabetes	Alzheimer's Disease	615532/ 614871	4615/ 3873	Diabetes increases the risk of dementia in both sexes and all age groups
Wium-Andersen et al., 2019	To evaluate risk of dementia in patients with type 1 and type 2 diabetes	National Diabetes Registry Cohort, Glostrup Cohort, ADDITION Study Cohort, Copenhagen Aging and Midlife Biobank, Denmark	60.2	6.7	56	Type 1 and Type 2 Diabetes	Dementia	145781/ 144807	7283/ 6257	Both diabetes types are associated with increased dementia risk

Table 1: Characteristics of studies included in the meta-analysis

3.2 Risk of developing dementia for diabetics

Initially, data from the included studies was subjected to meta-analysis to identify the risk of developing dementia between diabetic and non-diabetic groups. Out of the 23 selected studies, 10 studies were included for this meta-analysis comprising of a total control population of 20,50,285 individuals and a total diabetic population of 13,94,018 individuals. The number of individuals who developed dementia were 1,71,368 and 69,845 respectively.

The raw data from the studies was used to generate a forest plot (Figure 2) which indicated that people with diabetes had a slightly higher risk of acquiring dementia as compared to people without diabetes. The odds ratio was found to be 1.04, 95% CI [1.03, 1.05], P < 0.00001, indicating that the risk of developing dementia in the diabetic population is 4% higher as compared to the non-diabetic population.

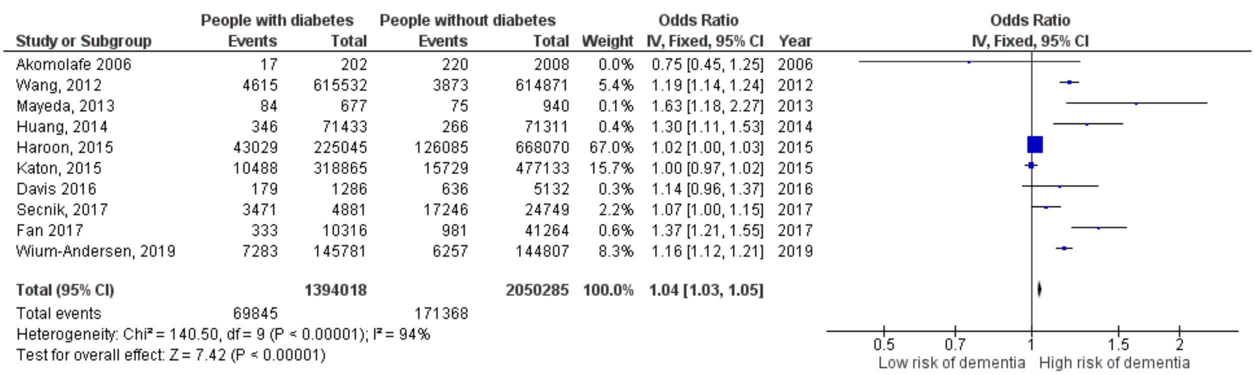

Figure 2: Forest plot showing the relative risk of developing dementia between diabetics and non-diabetics

3.3 Risk of developing Alzheimer's disease in the diabetic population

Six studies were included in this meta-analysis which compared the risk of developing Alzheimer's disease between diabetics and non-diabetics. The diabetic population comprised of 7,81,391 individuals and the non-diabetic population comprised of 8,16,756 individuals. Out of the included population, 7,703 diabetics and 14,890 non-diabetics developed Alzheimer's disease.

The raw data from the studies was used to generate a forest plot (Figure 3) which indicated that there was no significant difference in the risk of developing Alzheimer's disease between the diabetic and non-diabetic population. The odds ratio was found to be 0.99, 95% CI [0.96, 1.02], P < 0.00001, indicating that both diabetics and non-diabetics had a similar risk of developing Alzheimer's disease.

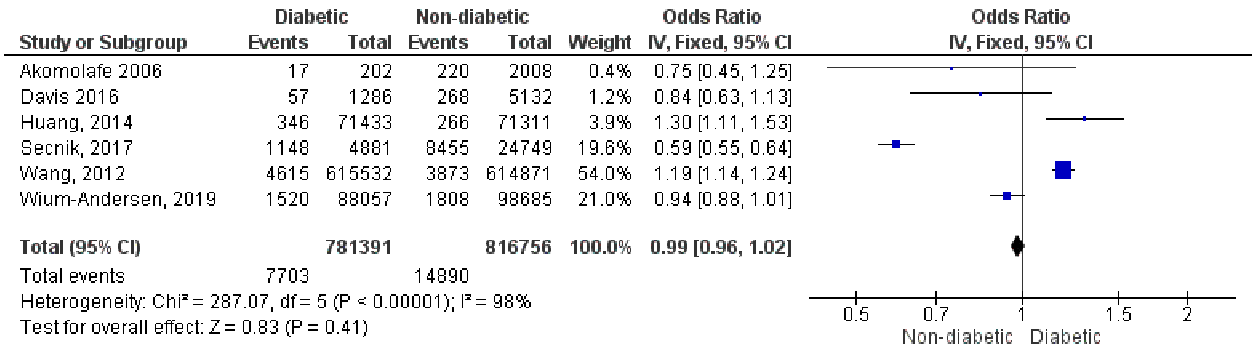

Figure 3: Forest plot showing the relative risk of developing Alzheimer's disease between diabetics and non-diabetics

3.4 Risk of developing vascular dementia in the diabetic population

Three studies were included in this meta-analysis which compared the risk of developing vascular dementia between diabetics and non-diabetics. The diabetic population comprised of 94,224 individuals and the non-diabetic population comprised of 1,28,566 individuals. Out of the included population, 1,907 diabetics and 4,819 non-diabetics developed vascular dementia.

The raw data from the studies was used to generate a forest plot (Figure 4) which indicated that diabetics had a significantly higher risk of developing vascular dementia as compared to non-diabetics. The odds ratio was found to be 1.58, 95% CI [1.49, 1.68], P < 0.00001, indicating that diabetics had a 58% higher risk of developing vascular dementia as compared to non-diabetics.

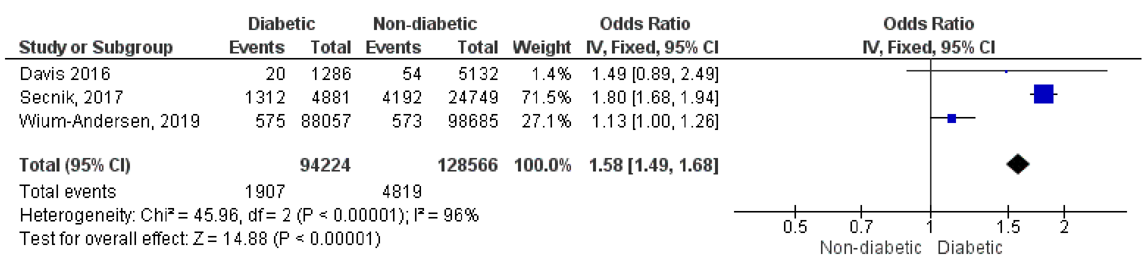

Figure 4: Forest plot showing the relative risk of developing vascular dementia between diabetics and non-diabetics

3.5 Risk of developing early-onset dementia in the diabetic population

Three studies were included in this meta-analysis which compared the risk of developing dementia between diabetics and non-diabetics below the age of 65. The diabetic population comprised of 5,13,493 individuals and the non-diabetic population comprised of 5,16,366 individuals. Out of the included population, 1,584 diabetics and 931 non-diabetics developed early-onset dementia.

The raw data from the studies was used to generate a forest plot (Figure 5) which indicated that the diabetic group had a significantly higher risk of acquiring early-onset dementia as compared to the non-diabetic group. The odds ratio was found to be 1.71, 95% CI [1.58, 1.85], $P < 0.00001$, indicating that diabetics had a 71% higher chance of developing early-onset dementia as compared to the non-diabetic population.

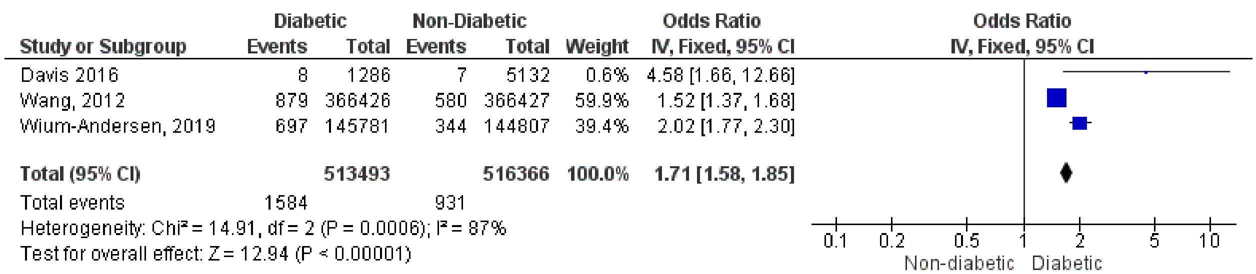

Figure 5: Forest plot showing the relative risk of developing early-onset dementia between diabetics and non-diabetics

3.6 Risk of developing late-onset dementia in the diabetic population

Three studies were included in this meta-analysis which compared the risk of developing dementia between diabetics and non-diabetics above the age of 65. The diabetic population comprised of 3,95,514 individuals and the non-diabetic population comprised of 3,98,383 individuals. Out of the included population, 10,655 diabetics and 10,403 non-diabetics developed late-onset dementia.

The raw data from the studies was used to generate a forest plot (Figure 6) which indicated that the diabetic group had a slightly higher risk of acquiring late-onset dementia as compared to the non-diabetic group. The odds ratio was found to be 1.12, 95% CI [1.09, 1.15], P

< 0.00001, indicating that diabetics had a 12% higher chance of developing late-onset dementia as compared to the non-diabetic population.

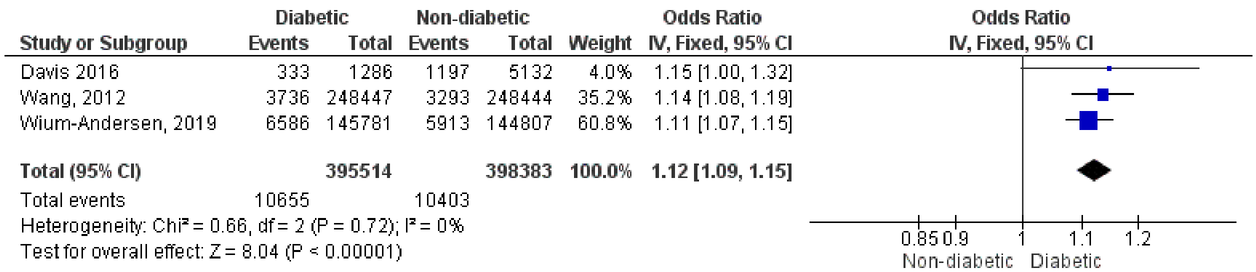

Figure 6: Forest plot showing the relative risk of developing late-onset dementia between diabetics and non-diabetics

3.7 Risk of developing dementia in males between diabetics and non-diabetics

Two studies were included for this meta-analysis as only these studies reported the difference in dementia risk between male diabetics and non-diabetics. The male diabetic population comprised of 4,06,408 individuals and the male non-diabetic population comprised of 6,22,076 individuals. Out of the included population, 20,663 diabetics and 55,322 non-diabetics developed dementia.

The raw data from the studies was used to generate a forest plot (Figure 7) which indicated that the male diabetics had a slightly higher risk of acquiring dementia as compared to male non-diabetics. The odds ratio was found to be 1.05, 95% CI [1.03, 1.07], P < 0.00001, indicating that the risk of developing dementia in male diabetics was only 5% higher as compared to that of male non-diabetics.

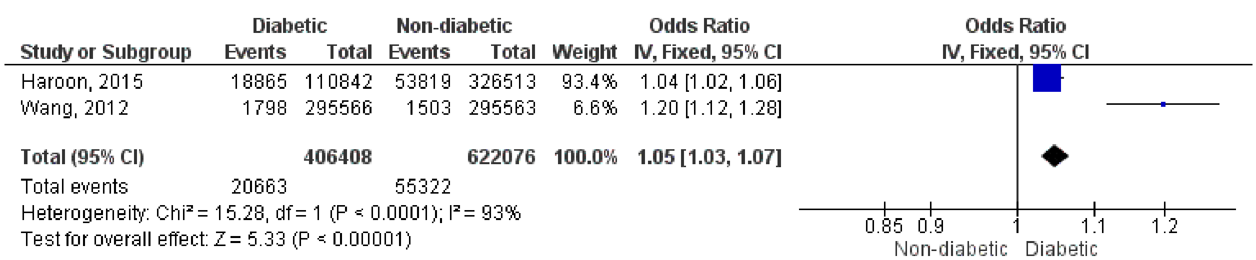

Figure 7: Forest plot showing the relative risk of developing dementia between male diabetics and non-diabetics

3.8 Risk of developing dementia in females between diabetics and non-diabetics

Two studies were included for this meta-analysis as only these studies reported the difference in dementia risk between female diabetics and non-diabetics. The female diabetic population comprised of 4,33,513 individuals and the female non-diabetic population comprised of 6,60,865 individuals. Out of the included population, 26,981 diabetics and 74,636 non-diabetics developed dementia.

The raw data from the studies was used to generate a forest plot (Figure 8) which indicated that the female diabetics had a negligibly higher risk of acquiring dementia as compared to female non-diabetics. The odds ratio was found to be 1.01, 95% CI [1.00, 1.03], $P < 0.00001$, indicating that the risk of developing dementia in female diabetics was only 1% higher as compared to that of female non-diabetics.

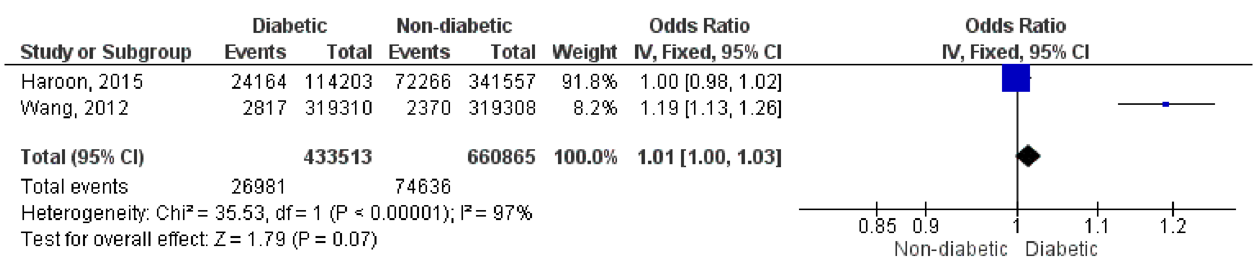

Figure 8: Forest plot showing the relative risk of developing dementia between female diabetics and non-diabetics

3.9 Risk of developing dementia in diabetics taking anti-diabetic therapy as compared to diabetics not taking any medications

Five studies were included for this meta-analysis that reported the difference in dementia risk between diabetics taking some form of anti-diabetic treatment and diabetics not taking any anti-diabetic medications. The number of people taking anti-diabetic medications was 75,753 and the number of people not taking anti-diabetic medications was 1,72,583. Out of the included population, 2,070 people in the first group and 12,274 people in the second group developed dementia respectively.

The raw data from the studies was used to generate a forest plot (Figure 9) which indicated that people not taking anti-diabetic treatment had a higher risk of developing dementia as compared to people who were on anti-diabetic medications. The odds ratio was found to be 0.72, 95% CI [0.68, 0.76], P < 0.00001, indicating that the risk of developing dementia in people not taking anti-diabetic therapy was 28% higher as compared to those that were taking anti-diabetic medications. This indicates that taking anti-diabetic medication to control diabetes may have an effect on controlling the risk of acquiring dementia in the diabetic population.

	Anti-diabetic therapy		No anti-diabetic therapy			Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Chang 2016	117	2876	360	10720	6.0%	1.22 [0.99, 1.51]
Chen 2014	53	2400	824	15770	3.4%	0.41 [0.31, 0.54]
Heneka 2015	1478	67822	3854	122036	73.6%	0.68 [0.64, 0.73]
Hsu 2011	66	1864	434	10519	3.9%	0.85 [0.66, 1.11]
Imfeld 2012	356	791	6802	13538	13.1%	0.81 [0.70, 0.94]
Total (95% CI)		**75753**		**172583**	**100.0%**	**0.72 [0.68, 0.76]**
Total events	2070		12274			

Heterogeneity: Chi² = 46.12, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 12.52 (P < 0.00001)

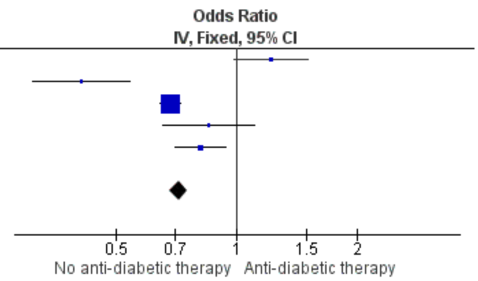

Figure 9: Forest plot showing the relative risk of developing dementia between people taking anti-diabetic medication and people not taking anti-diabetic medication

Chapter 4: Discussion

A meta-analysis of 15 studies was performed in order to study the associations between diabetes mellitus and dementia, keeping in mind factors such as age, gender, and whether the diabetic population was on anti-diabetic treatment. Initially, 10 studies were subjected to meta-analysis to study the differences in the risk of developing dementia between people with and without diabetes. It was found that people with diabetes had only a 4% higher risk of developing dementia compared to people without diabetes. All the studies used for the meta-analysis showed an increased risk of developing dementia in diabetics except one study (Akomolafe et al., 2006) which showed a negative association between risk of dementia and diabetes. The reason for this may be their predominantly white study sample and classification of diabetics based on non-fasting blood glucose levels rather than fasting blood sugar. Their sample size was also small, which included 2008 non-diabetics and 202 diabetics, as compared to other studies with a relatively large sample size. These factors may have influenced the results of the study. All the other studies showed varying risks of developing dementia in the diabetic population as compared to the non-diabetic population ranging from 2% to 63%. The reason for this wide range may be attributed to several factors such as age, gender, and presence of other co-morbidities in the population tested.

Further analyses were carried out to understand the risk of developing Alzheimer's disease and vascular dementia between the diabetic and non-diabetic populations. The analysis showed that there was no significant association between the risk of developing Alzheimer's disease and diabetes as evidenced by an odds ratio of 0.99. However, the risk of developing vascular dementia was 58% higher in diabetics as compared to non-diabetics. This shows that there is a significant association between the underlying physiological mechanisms that lead to the development of vascular dementia and diabetes. On the other hand, having diabetes does not significantly increase the chances of developing Alzheimer's disease in people.

These results are similar to other reports of meta-analyses in the literature which show close associations between diabetes and dementia to varying extents. A meta-analysis of 28 prospective observational studies conducted by Gudala et al. (2013) found that people with diabetes had a 73% higher chance of developing all-type dementia, a 56% higher chance of developing Alzheimer's disease, and a 127% higher chance of developing vascular dementia (Gudala et al., 2013). Another study has found that not only diabetes, but also prediabetes, can increase the risk of developing dementia (Xue et al., 2019). A meta-analysis on 19 longitudinal studies found that the relative risk of developing Alzheimer's disease and vascular dementia in people with diabetes was 1.46 and 2.48 when compared to people without diabetes. This shows that people with diabetes have a much higher chance of developing dementia, specifically vascular dementia as compared to Alzheimer's disease (Cheng et al., 2012).

The reason that our meta-analysis did not find any significant association between diabetes and Alzheimer's disease could be attributable to several factors such as diagnostic criteria for diabetes and Alzheimer's disease, categorization of dementia, differences in follow-up times, small samples sizes, and specific groups of populations. Among the six studies that were included in our meta-analysis, only two studies showed a significant risk of developing Alzheimer's disease in the diabetic cohort. Secnik et al. (2017) gave an odds ratio of 0.59 for the development of Alzheimer's disease in the diabetic population. This was a reverse longitudinal study which recruited the study sample from the Swedish Dementia Registry and then tested the study population for diabetes. The study did not eliminate people who were on anti-diabetic medication which might have resulted in bias in identifying patients with diabetes. The study by Akomolafe et al. (2006) gave an odds ratio of 0.75 which could be attributed to its very small sample size (202 diabetics and 2008 non-diabetics). Davis et al. (2016) studied the incidence of dementia and death in diabetics and proposed that the negative relationship between diabetes and risk of developing Alzheimer's disease could be because people with type 2 diabetes may die before they are diagnosed with Alzheimer's disease.

Subsequent meta-analyses were carried out to understand if there were any differences in the risk of developing dementia between diabetics and non-diabetics based on two important risk factors, age and gender. Separate meta-analyses were carried out for early-onset dementia and late-onset dementia in order to investigate if there was any difference in the risk of developing these two types of dementia in the diabetic and non-diabetic cohorts. Interestingly, it was seen that diabetics had a 71% higher risk of developing early-onset dementia and a 12% higher risk of developing late-onset dementia as compared to the non-diabetic population. This result indicates a significant association between dementia and diabetes. It is well-known that the chance of acquiring dementia increases with age and so, the risk of developing dementia in people over the age of 65 was only 12% in the diabetic population. However, when we considered the diagnosis of early-onset dementia between the diabetics and non-diabetics, we found that diabetics had a 71% higher risk of developing dementia in the diabetic population. This result indicates that diabetes is an important risk factor for the development of dementia.

We performed a similar meta-analysis between males and females comparing the risk of developing dementia in the diabetic and non-diabetic populations. Our findings suggest that males are at a greater risk of acquiring dementia than females in the diabetic population. Diabetic males had a 5% higher chance of acquiring dementia and diabetic females had a 1% higher risk of developing dementia as compared to their non-diabetic counterparts. Comparing the results of this meta-analysis with current literature, the results found here fall in the middle of the spectrum with one end showing a heavy association between diabetes and dementia and the other end showing no correlation between the two conditions on the basis of risk factors such as age and gender. This discrepancy is attributable to the complex underlying mechanisms that connect diabetes with cognitive decline and dementia, along with several other mechanisms that contribute to the progress of cognitive impairment towards dementia.

Chatterjee et al. (2016) studied the link between diabetes and dementia comparing the risk differences between men and women. Their meta-analyses of 14 studies found that people with diabetes had a 60% higher risk of developing dementia regardless of their gender. However, they also reported that women had a 19% higher risk than men of acquiring vascular dementia (Chatterjee et al., 2016). Despite the fact that the risk of developing dementia is higher in diabetics who are older in age as confirmed by our meta-analysis results, studies have found that people who have diabetes are often diagnosed with dementia at an earlier age as compared to the non-diabetic population (Secnik et al., 2017). This may be because the presence of diabetes leads to an earlier manifestation and faster progression of cognitive decline leading to an earlier diagnosis of dementia.

In order to further understand the link between diabetes and dementia, and if other co-morbid conditions too increase the risk of dementia, several studies have analyzed patients diagnosed with hypertension and hyperlipidemia. A study conducted by Fan et al. (2017) has found that although co-morbidites contribute to enhancing the risk of acquiring dementia in diabetic patients, they don't play a very important role in dementia progression in non-diabetic people. Another study analyzed the impact of chronic liver disease along with diabetes in the progression of dementia. This report found that when compared to chronic liver disease, people with diabetes had a significantly higher risk of developing dementia. Additionally, the presence of chronic liver disease and diabetes together did not significantly increase the risk of developing dementia when compared to people who had diabetes alone (Kim et al., 2017). These studies are indicative of the fact that diabetes mellitus is the most important metabolic disorder that contributes to an increased risk of developing dementia.

Several studies have also attempted to analyze the differences in risk of developing dementia in diabetics belonging to different ethnicities. A study conducted by Mayeda et al. (2014) has found that the risk of developing dementia for people with diabetes was highest for Native Americans, closely followed by African Americans, non-Hispanic Whites, and Latinos. Hence, diabetic Native Americans and African Americans had an approximately 50% higher chance of developing dementia as compared to diabetic Asians. However, their study only included older patients and did not analyze disease trends in the younger population (Mayeda et al., 2014). This result is inconsistent with another study that found that diabetic Whites had a 17% higher risk of acquiring dementia, whereas diabetic Blacks had a 33% chance and diabetic Hispanics had a 36% chance of acquiring dementia (Luchsinger et al., 2001).

As our meta-analysis found a strong association between diabetes and dementia, we hypothesized that diabetics taking anti-diabetic medications should have a lower incidence of dementia as compared to a diabetic cohort that is not on any anti-diabetic therapy. In order to test this hypothesis, we performed a meta-analysis of 5 studies where we found that diabetics who were not taking any anti-diabetic medications had a 28% higher risk of developing dementia as compared to diabetics who were on anti-diabetic therapy. This result points towards a clear link between the physiological mechanisms involved in diabetes with the development of dementia.

Hayden (2019) has shown that there are at least 18 risk factors that are common for both diabetes mellitus and Alzheimer's disease including insulin resistance, hyperglycemia, dysregulation of kinases, and neuroinflammation. As both the conditions worsen with age and have multifactorial risk profiles, the chances that intersecting risks might lead to intense cognitive abnormalities are quite high (Hayden, 2019). Despite different studies that point to a clear association between diabetes and dementia, the exact underlying physiological mechanisms remain unclear. One study has reported that insulin resistance in type 2 diabetes mellitus might increase the risk of cognitive impairment in patients, thereby increasing the risk of developing dementia (Kim and Feldman, 2015). Insulin resistance affects different parts of the body in different ways, but in the brain, it can lead to impairment of insulin signaling that plays an important role in learning, memory, and regulation of food intake and reproduction. As impairment of insulin signaling is an important mechanism in the development and progression of Alzheimer's disease, insulin resistance that develops due to diabetes has been proposed as a plausible link between diabetes and dementia (De Felice and Ferreira, 2014). Disruption in insulin signaling in the brain can lead to the phosphorylation of the soluble protein tau, normally present in neuronal cells. Phosphorylation of the tau protein leads to the formation of aggregates, which results in the formation of neurofibrillary tangles and beta-amyloid plaques in the brain (Tokutake et al., 2012). As these are physiological changes that are directly linked to the diagnosis of Alzheimer's disease in patients, insulin resistance that develops due to diabetes plays an important role in the development of dementia.

As diabetes has been more consistently linked to the development of vascular dementia, this can be attributed to cerebrovascular disease and vasculopathy as the common complications of diabetes. Cerebrovascular disease independently increases the risk of cognitive impairment and in combination with impaired insulin signaling in case of diabetics, this risk becomes more pronounced (Ravona-Springer and Schnaider-Beeri, 2011). Prolonged exposure to high glucose levels can lead to the formation of Advanced Glycation End products (AGEs) through reactions between molecules of sugars and amino acids. Some amount of AGE is found in all people which gets deposited as they age; however, the deposition of AGE takes place at a more rapid pace in diabetic patients. Some of the consequences of AGE deposition include development of rigidity in the protein matrix, resistance to proteolysis, thickening of basement capillary membrane, endothelial dysfunction, and atherosclerosis (Singh et al., 2001). It also leads to the formation of covalent crosslinks with proteins, that leads to tissue destruction, vascular pathologies, and Alzheimer's disease (Jerums et al., 2003).

As impairment of insulin signaling in the brain has been increasingly demonstrated in early stages of cognitive decline and dementia, it has been proposed that Alzheimer's disease be considered 'type 3 diabetes' (Steen et al., 2005). Independent studies of neurodegeneration in Alzheimer's disease patients have shown significant reduction in the levels of insulin and its receptors in the brain. Additionally, all signaling pathways related to insulin and its roles in neuronal survival, mitochondrial function, and energy metabolism are largely disrupted. These studies proved that even in the absence of diabetes and its related risk factors such as hypertension and hyperlipidemia, insulin deficiency in the brain can lead to neurodegenerative pathologies ultimately leading to dementia. These pathologies involved a marked reduction in the levels of insulin and insulin growth factors in the brain followed by the withdrawal of these growth factors that ultimately leads to death of neurons. These neurodegenerative pathologies were quite similar to the pathologies observed in the case of type 1 and type 2 diabetes, and as all the three share common insulin deficiency and resistance patterns, Alzheimer's disease has been proposed to be a brain-specific type of diabetes known as type 3 diabetes (de la Monte and Wands, 2008).

Contrary to the large number of studies that have identified links between diabetes and dementia, there are several reports that state otherwise. Ahtiluoto et al. (2010) has found that people with diabetes are less likely to develop neurofibrillary tangles and beta-amyloid plaques, which are the hallmarks of Alzheimer's disease, and more likely to develop cerebral infarctions. Other studies have also confirmed that although diabetes leads to severe cerebrovascular complications in patients, it does not contribute to the development of pathologies specifically associated with Alzheimer's disease and vascular dementia (Beeri et al., 2005; Nelson et al., 2011). Neuroimaging studies have shown that vascular pathology due to diabetes may not be directly linked to cognitive decline and progression to dementia, and that there may be other underlying mechanisms involved (Van Harten et al., 2006).

A population-based retrospective study conducted by Matioli et al. (2017) found no link between diabetes and dementia. They conducted an autopsy study where they acquired data from the Brain Bank of the Brazilian Aging Brain Study Group between the years 2004 and 2015. People with diabetes had a 29% prevalence rate of dementia whereas people without diabetes had a 27% prevalence rate indicating that the occurrence of dementia was not radically different in people with and without diabetes. However, they did report that vascular dementia was more common in diabetic patients and mixed-dementia was more common in non-diabetic patients indicating that there may be some pathophysiological changes common to both diabetes and vascular dementia (Matioli et al., 2017).

Other studies have confirmed these results by showing that there is very little difference in the prevalence of dementia in people with and without diabetes. Arvanitakis et al. (2006) found that the prevalence of dementia in diabetics was 50% whereas in non-diabetics, it was 44.2%. In a study by Ahtiluoto et al. (2010), the prevalence rate of dementia was 60% for diabetics and 65.9% for non-diabetics. Another study by Abner et al. (2016) found that the rate of prevalence of dementia was 39.1% for diabetics and 38.2% for non-diabetics. A study by Alafuzoff et al. (2009) showed that the prevalence of dementia was more in the non-diabetic group (31%) as compared to the diabetic group (21%). It should be noted that in all these studies, the population that was analyzed had a majority of patients over the age of 80 years.

A possible explanation for these discrepancies may be differences in the ages of patients whose brain lesion samples were analyzed for understanding the pathophysiology of cognitive impairment. As people age, the disruption of several systems may manifest at once leading to a misinterpretation of co-existence of two or more conditions. Another proposed explanation is that the vascular pathologies that lead to the development of dementia in diabetic and non-diabetic people may be different. Diabetic people undergoing regular anti-diabetic therapy may also show reduced vascular lesions in the brain in neuroimaging studies that can be attributed to their treatment. However, the risk between diabetes and dementia that has emerged through observational population-based studies, even if to a small extent, cannot be ignored and/or attributed to chance factors.

It has been argued that cognitive decline in a person is gradual and in several cases, it is diagnosed at a later stage or, sometimes, not diagnosed at all. This may also be a factor in studies which does not show a difference in prevalence rates of dementia between diabetic and non-diabetic groups of people. It is possible that many people may develop dementia or other degrees of cognitive decline after the study period leading to variations in the initially determined prevalence rates. It has been reported that up to 12% of diabetic patients are not aware that they have diabetes (Pineda et al., 2004) and dementia may also go undiagnosed due to early deaths, inaccurate diagnosis, or underestimation. All these factors may lead to a misrepresentation of the actual prevalence rates of dementia in diabetic and non-diabetic populations.

This study has several limitations. The risk profiles for different types of dementia other than Alzheimer's disease and vascular dementia were not analyzed; rather the numbers obtained covered one or more types of dementia including Alzheimer's disease, vascular dementia, mixed-dementia, and all-type dementia. The link between diabetes and a single type of dementia may provide insights into the complex pathophysiological changes that lead to dementia in diabetic patients. The second limitation was that it was a meta-analysis of observational population-based studies where several patients had self-reported diagnoses of diabetes and dementia. The dropout rates for the studies were as high as 20% introducing a bias in the reported dementia prevalence rates in diabetic and non-diabetic cohorts. The third limitation was that the studies did not report any neuroimaging studies on the patients to see if there was actually a physiological connection between diabetes and dementia or if the observed risk was merely a chance event.

Chapter 5: Conclusions

As per our meta-analysis of 15 studies, the risk of developing dementia for people with diabetes was found to be slightly higher than for people without diabetes. There was a significant risk for the development of vascular dementia in the diabetic population; however, no significant link was found between diabetes and Alzheimer's disease. Comparisons between the risk of developing early-onset dementia and late-onset dementia showed that diabetics had a significantly higher risk of developing dementia at an earlier age as compared to the non-diabetics. Also, males had a slightly higher chance of developing dementia as compared to females as per our analysis. Among the diabetic population, people who were on anti-diabetic therapy had a lower risk of developing dementia as compared to people who were not on anti-diabetic medications.

A majority of published reports have shown different degrees of association between diabetes and dementia, while a few have shown no link between these two conditions. There is controversial evidence in the literature aimed at analyzing the underlying association between diabetes and dementia. While some studies have found such a strong connection between the pathologies observed in diabetes mellitus and Alzheimer's disease that they have coined the term 'type 3 diabetes' for this condition, others have found absolutely no link between the two disorders. Future studies should focus on understanding the pathophysiological mechanisms that connect insulin resistance with cognitive impairment in patients, so that undertaking the necessary precautions at an early age can reduce the global burden of diabetes complications and dementia.

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