ANALYSIS OF A POSSIBLE ASSOCIATION BETWEEN PARKINSON'S DISEASE AND DIABETES: A META-ANALYSIS

A Thesis

Submitted for Partial Fulfillment of Masters Degree

To [Name of University]

By

[Name of Student]

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[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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I hereby certify that the thesis entitled “ANALYSIS OF A POSSIBLE ASSOCIATION BETWEEN PARKINSON’S DISEASE AND DIABETES: A META-ANALYSIS” submitted by [Name of Student] towards the partial fulfillment of the Masters degree is based on the investigation carried out under my guidance. The thesis has not been submitted to any other University or institution for the award of any academic degree.

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Acknowledgements

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Abstract

Parkinson's disease and diabetes are both globally prevalent diseases that share several common metabolic pathways. Diabetes is considered an important risk factor for Parkinson's disease; however, there are mixed findings in the literature and the mechanism of this association is still unclear. **Aim:** The objective of the present investigation was to perform a meta-analysis of studies that have analyzed the prevalence of Parkinson's disease in diabetic and non-diabetic cohorts at the population level. **Methods:** Population-based studies, cohort studies, and case-control studies that described the incidence of Parkinson's disease in diabetic and non-diabetic participants between the years 2005 and 2021 were extracted from PubMed and Science Direct. Pooled odds ratio estimates and 95% confidence intervals were calculated using the fixed-effects model and inverse variance method, and forest plots were generated. **Results:** A total of 20 studies were used in the meta-analysis to identify the risk of developing Parkinson's disease in diabetic patients and non-diabetic controls. Age-related analysis was also done to identify if the risk of developing Parkinson's disease was higher in older or younger diabetics. Meta-analysis to investigate the potential therapeutic effect of anti-diabetic medication on the risk of developing Parkinson's disease was also carried out in medication users and non-users in the diabetic population. The odds ratio for developing Parkinson's disease in diabetics was 2.08, the odds ratio for risk of Parkinson's disease in older diabetics as compared to younger diabetics was 5.95, and the odds ratio for risk of Parkinson's disease in users of anti-diabetic medication as compared to non-users was 0.65. **Conclusions:** People with diabetes have a considerably higher risk of developing Parkinson's disease. This risk is highly pronounced in older diabetics as compared to younger diabetics, and use of anti-diabetic medication has a potentially protective effect on the development of Parkinson's disease.

Chapter 1: Introduction

1.1 Parkinson's Disease

Parkinson's disease was first described as a 'shaking palsy' by Dr. James Parkinson, an English surgeon, in 1817. It is a progressive, chronic neurodegenerative disease that has characteristics of both motor as well as non-motor features. Its progressive degenerative effects manifest itself on muscle control as well as mobility (DeMaagd and Philip, 2015). Parkinson's disease is characterised by the loss of striatal dopaminergic neurons that contribute to motor symptoms and loss of non-dopaminergic neurons that contribute to non-motor symptoms. The motor symptoms of this condition form a complex known as Parkinsonism, and they comprise of muscular rigidity, resting tremors, and bradykinesia or slowness in movement. Non-motor symptoms of this condition include cognitive changes, depression, and sleep disorders (Kalia and Lang, 2015).

1.1.1 Epidemiology

Parkinson's disease is one of the most common disorders of the nervous system known to affect as many as 1 million Americans according to the Parkinson's Disease Foundation report (Parkinson's Disease Foundation Statistics on Parkinson's, n.d.). The incidence of this condition is approximately 60,000 new cases annually at the rate of 20 cases per 100,000 in the United States. The prevalence of this condition is 1% in people aged 60 and above, and up to 3% in people aged 80 and above. However, these percentages may be misleading because of a considerable number of undiagnosed cases in the elderly (Radhakrishnan and Goyal, 2018). In the United Kingdom, the number of people living with Parkinson's disease is roughly 121,927, or one in 460 people. The lifetime risk of acquiring Parkinson's disease in the UK population is 2.7% (CPPE, 2021). Gender differences also affect the prevalence of Parkinson's disease and the male to female ratio of this condition is 3:2 (Miller and Cronin-Golomb, 2010). The age of onset on average is also found to be 2.2 years later for women as compared to men (Georgiev et al., 2017).

1.1.2 Causes

The most important risk factors for acquiring Parkinson's disease include exposure to environmental toxins such as herbicides, pesticides, and cyanide, high cholesterol and increased BMI, inflammation due to microglia activation, nitric oxide toxicity, oxidative stress, and amphetamine abuse (Spatola and Wider, 2014). A few genetic mutations have also been identified that increase a person's susceptibility to Parkinson's disease (Santiago et al., 2014). Tobacco smoking and high caffeine intake has been found to have a protective effect on the risk of acquiring Parkinson's disease through the inhibition of the monoamine oxidase enzyme and adenosine antagonist activity respectively (Liu et al., 2012). Apart from this, ethnic differences also play a role in modifying the risk associated with developing Parkinson's disease (van der Merwe et al., 2012).

Table 1: Association between Parkinson's disease and different variables (Tufail, 2020)

Variables	Cases	Controls	OR (95% CI)	*p* value
Use of pesticides	222 (37.0%)	138 (11.5%)	4.52 (2.49–8.19)	0.0001
Exposure to chemicals	180 (30%)	318 (26.5%)	1.18 (0.69–2.02)	0.523
Smoking cigarettes	114 (19.0%)	576 (48.0%)	0.25 (0.14–0.45)	0.0001
Close contact with smokers	114 (19.0%)	354 (29.5%)	0.56 (0.31–1.01)	0.052
Smoking pipe	18 (3.0%)	3 (2.50%)	1.21 (0.28–5.15)	0.800
Use of snuff	174 (29.0%)	576 (48.0%)	0.44 (0.26–0.79)	0.002
Worked in places of tobacco	30 (5.00%)	102 (8.50%)	0.56 (0.20–1.58)	0.273
Taking tea	576 (96.0%)	1,140 (95.0%)	1.26 (0.38–4.13)	0.699
Taking coffee	36 (6.00%)	84 (7.00%)	0.84 (0.31–2.27)	0.743
Number of family members				
1–5	186 (31.0%)	480 (40.0%)	0.67 (0.405–1.12)	0.163
6–10	162 (27.0%)	384 (32.0%)	0.78 (0.462–1.33)	0.425
11–15	162 (27.0%)	384 (32.0%)	0.78 (0.462–1.33)	0.425
15 and above	102 (17.0%)	126 (10.5%)	1.74 (0.87–3.48)	0.140

1.1.3 Pathophysiology

In the human body, there are two types of motor tracts that control movement – the pyramidal system that is responsible for voluntary movement and the extrapyramidal system that is responsible for involuntary movement. Parkinson's disease affects the extrapyramidal system comprising of the motor segments of the basal ganglia subsequently causing loss of dopaminergic action and decreased motor function. The major cause of the clinical manifestations of this disease is the depletion of dopaminergic neurons of the substantia nigra compacta that project to motor areas like the striatum. The non-motor manifestations of

Parkinson's disease are attributed to the dysregulation of other neurotransmitters such as glutamine, choline, and serotonin, with or without the presence of dopamine deficiency (Chen and Swope, 2014).

This condition is characterised by progressive neuronal degeneration of the dopamine neurons in the substantia nigra pars compacta, which then proceeds to the striatum. Once 50 to 80% of dopaminergic neurons have been destroyed, the clinical presentation begins. Neuronal loss also leads to increased activity of the internal globus pallidal segment (GPi) / pars reticulata portion of the substantia nigra (SNpr) circuit and dysfunction of gamma aminobutyric acid (GABA) in the thalamus. This dysfunction in the activity of the thalamus leads to the failure of activation of the primary motor cortex present in the frontal cortex, which results in decreased motor activity, both voluntary and involuntary, in Parkinson's disease patients (Beaulieu and Gainetdinov, 2011).

One of the hallmark findings of Parkinson's disease is the presence of Lewy bodies which are intracellular aggregates made up of lipids, proteins, and other materials. The Lewy bodies in Parkinson's disease are located in the substantia nigra in dopaminergic neurons, and they appear as circular bodies with radiating fibrils. They draw in mitochondria from neuronal cells causing the cells to lose mitochondrial integrity resulting in cytotoxicity and eventually, cell death. One reason for the formation of these aggregates is mutations in the α-synuclein protein which results in insoluble fibrils of the protein (Rohn, 2012). Another protein involved in the formation of Lewy bodies is the ubiquitin protein, where mutations result in the formation of cytoplasmic aggregates. The presence of Lewy bodies in Parkinson's disease is a characteristic feature of neurodegeneration and its various lesion patterns mark various stages of the disease. Therefore, neuronal lesions first appear in the non-dopaminergic neurons located in the brainstem in pons and medulla, and they later develop in the dopaminergic neurons of the nigrostriatal region connecting the midbrain with the forebrain. However, they are not limited to Parkinson's disease and are also found in other neurodegenerative disorders such as dementia (Del Tredici and Braak, 2012). Also, there are several cases of Parkinson's disease where obvious genetic abnormalities are not found and these are referred to as idiopathic Parkinson's disease (Jankovic and Tan, 2020).

1.1.4 Idiopathic Parkinson's Disease (IPD)

As mentioned above, Parkinson's disease without any identifiable cause or characteristic features is known as Idiopathic Parkinson's Disease (IPD) and it accounts for a large majority of patients, up to 85%, suffering from parkinsonism. IPD is considered to be a multi-system neurodegenerative disorder with major non-motor manifestations, disability, and poor quality of life for patients. IPD occurs due to disturbances in the muscle control of the locomotor system and may lead to olfactory dysfunction, depression, constipation, and sleep disorders. This spectrum of non-motor symptoms forms a major part of IPD, even in the early stages of the disease. As IPD progresses, autonomic, cognitive, and neuropsychiatric symptoms may occur along with increase in strength of the non-motor symptoms (Erro et al., 2016).

As no specific cause has been attributed to IPD, it is assumed that a number of individual as well as environmental factors work together for the development of IPD. Pathologically, IPD is characterized by a loss of neurons and gliosis in substantia nigra compacta along with other pigmented nuclei, and the presence of abnormal levels of Lewy bodies in the neurons. In certain cases of IPD, Lewy bodies are found to be diffusely distributed and it is also known as diffuse Lewy body disease. IPD may also occur in the absence of Lewy bodies, in which case the disease is characterized by nigral neurofibrillary tangles, neuronal loss, and gliosis. Dopamine levels are found to be reduced by about 70 – 90% along with a 50 – 85% loss of neurons and considerable decrease in levels of norepinephrine in the substantia nigra (Kouli et al., 2018).

1.2 Diabetes

It has recently come to light that people diagnosed with diabetes have an increased risk of Parkinson's disease with increase in age. Diabetes is a complex and heterogeneous disorder that is characterised by glucose intolerance and hyperglycemia due to inadequate insulin or defects in insulin function or both. The major system affected is the regulatory system that is responsible for storage and transport of metabolic fuels, involving anabolism and catabolism of fats, proteins, and carbohydrates (Piero et al., 2015). Diabetes is a major concern for all populations worldwide because it has adverse effects on every vital organ of the body. It can lead to failure of one or more organs and other metabolic complications such as nephropathy, retinopathy, and

neuropathy. People suffering from diabetes also have a high risk of cardiovascular and cerebrovascular diseases (Abutaleb, 2016).

1.2.1 Types of Diabetes

Based on the etiology and clinical presentation of diabetes, it may be classified into several types. Type 1 diabetes accounts for relatively few cases of diabetes and is primarily found in the younger age group and people living in developed countries. Over 90% of all diabetes cases belong to Type 2, and it is mainly characterised by dysfunction of insulin in the target cells of the body. This type of diabetes is a growing health concern all over the world especially in the elderly and people who follow unhealthy lifestyle practices. Apart from this, there is gestational diabetes that occurs only during pregnancy, and other specific types of insulin impairment in the body (Baynest, 2015).

1.2.2 Epidemiology

Currently, type 2 diabetes is considered to be one of the most common diseases affecting around 422 million people worldwide, which is around 8.5% of the total population. An additional 175 million people are considered to be undiagnosed. The total number of diagnosed cases is projected to increase to 592 million by 2035 (WHO, 2016). These statistics are comparatively much higher than previous estimates, and this disease is proving to be a major health and economic burden for all countries around the world. Although the mean age of onset of diabetes is around 40 to 60 years, its incidence in younger age groups is on the rise. According to a WHO report, since 2000, the incidence of diabetes has risen by 114% globally. Therefore, diabetes is a growing concern and demands attention with respect to prevention and management (Hsia et al., 2009).

1.2.3 Pathophysiology

The pathophysiology of diabetes is thought to result from a combination of genetic and environmental factors which manifest as either inadequate insulin production or defects in insulin action. The characteristic features of this disease are insulin resistance, impaired glucose regulation, and reduced function of pancreatic β cells. As the secretion and function of insulin decreases, the ability of β cells to manage hyperglycemia also decreases resulting in impaired

metabolic regulation in target cells and tissues. Complex genetic abnormalities may result in defects in the receptor binding sites of insulin or in its signal transduction pathway, both of which contribute to the clinical presentation of diabetes. In order to achieve metabolic balance within the body, the β cells start secreting extra insulin resulting in hyperinsulinemia. This, in turn, increases the production of endogenous glucose contributing to hyperglycemia, which is the primary driver of diabetes complications in the body (Balaji et al., 2018).

1.3 Link between Parkinson's Disease and Diabetes

In recent years, several underlying pathophysiological links between diabetes and neurodegenerative disorders have become apparent. Several similarities have been identified between diabetes and Parkinson's disease in terms of etiology and presentation. In its most basic state, both diseases arise from the destruction of specific cells in the body – β-pancreatic cells in diabetes and dopaminergic neuronal cells in Parkinson's disease. This destruction eventually results in reduced insulin and dopamine in the two diseases respectively (Hassan et al., 2020). The pathways that are similar for both the diseases are insulin resistance, mitochondrial dysfunction, oxidative stress, neuroinflammation, and presence of misfolded proteins. In both cases, apoptotic pathways in pancreatic beta cells are activated as a result of underlying misregulations leading to cell death and further complications (Fiory et al., 2019). For instance, amylin is co-secreted with insulin by the pancreatic beta cells and it has important functions in the central nervous system. However, formation of amylin aggregates can lead to mitochondrial damage and membrane disruption, which can ultimately lead to diabetes (Kiriyama and Nochi, 2018). Mitochondrial dysfunction is also a consequence of mutations in genes responsible for Parkinson's disease such as PARK2 and PARK6, which can lead to mitophagy and hyperglycemia. Treatment with hypoglycemic agents have been shown to reverse alterations due to these mutations and restore the lost dopaminergic neurons indicating that mitochondrial dysregulation may be a shared mechanism between diabetes and Parkinson's disease (Cheng et al., 2020).

An imbalance between antioxidants and reactive oxygen species (ROS) in the body results in oxidative stress. This may be a consequence of stress, diseases, and other environmental factors, and may lead to cell death. Oxidative stress is an important underlying mechanism for both diabetes and Parkinson's disease and it has been implicated in causing

central nervous system damage in people with diabetes. ROS is majorly produced by the mitochondria, and mitochondrial dysregulation has also been implicated in both diseases (Yan et al., 2013). Further, it has been found that diabetes affects the function of the PGC1α protein, a transcription coactivator which is important for the stimulation of mitochondrial biogenesis and regulation of cellular energy metabolism. Therefore, mitochondrial dysregulation as a consequence of diabetes is linked to several other disorders in the body, including Parkinson's disease (Das and Unger, 2018).

Both diabetes and Parkinson's disease form a part of protein misfolding disorders (PMD) where specific proteins are misfolded, aggregated, and accumulated in specific body tissues. PMDs may either be metabolic, neurodegenerative, or systemic, and the disease manifestations depend on the protein that is misregulated. In case of diabetes, aggregates of the protein amylin in the pancreas and brain tissues have been linked to the underlying pathophysiology (Martinez-Valbuena et al., 2019). In case of Parkinson's disease, aggregates of the α-synuclein protein in the neurological tissues contribute to the pathology. Studies have shown that similar consequences of both these protein aggregates may increase the risk of Parkinson's disease in diabetics (Horvath and Wittung-Stafshede, 2016).

A study conducted by Horvath et al. (2016) has reported the occurrence of cross-talk between amyloidogenic proteins in Parkinson's disease and diabetes where an increased level of the amyloid protein in diabetics leads to the formation of abnormal aggregates of α-synuclein protein, a characteristic feature of Parkinson's disease. Prolonged hyperglycemia has also been linked to dysfunction and aggregation of proteins, contributing to an increased risk of Parkinson's disease (Vicente Miranda et al., 2016). Another study conducted by Hong et al. (2020) reported that insulin resistance is one of the factors that promote the progression of Parkinson's disease in individuals diagnosed with diabetes. A possible mechanism that has been proposed for this correlation is that insulin resistance contributes to mitochondrial dysfunction, leads to oxidative stress, and causes misfolding of the α-synuclein protein, therefore directly contributing to the progression and aggravation of Parkinson's disease in diabetics (Yang et al., 2017).

Epidemiological studies conducted to study the link between diabetes and Parkinson's disease have found varying degrees of correlation between the two conditions. Pablo-Fernandez

et al. (2018) analysed a large group of 8 million individuals and found that people diagnosed with diabetes had a much higher risk of developing Parkinson's disease. On the other hand, studies have also shown that there is no significant link between the two diseases (Lu et al., 2014; Savica et al., 2012). A few studies have also disproved a link between diabetes and Parkinson's disease or have uncovered an inverse relationship (Miyake et al., 2010; Palacios et al., 2011). It has been hypothesized that these studies may not have considered undiagnosed diabetes cases or may have small sample sizes (Maluf et al., 2019).

1.4 Aims and Objectives

The aim of the present study is to explore the possible link between diabetes mellitus and Parkinson's disease, analyse this link in different age groups, and to find out if there is any effect of taking anti-diabetic therapy on the risk of acquiring Parkinson's disease. In order to achieve this, a systematic review and meta-analysis will be performed to uncover the relationship between diabetes and Parkinson's disease by using data from published studies.

The objectives of this meta-analysis are:

- To find out if there is a statistically significant relationship between diabetes mellitus and Parkinson's disease
- To find out if the risk of Parkinson's disease is more pronounced in younger or older diabetics
- To find out if there is a potential protective effect of anti-diabetic therapy on the risk of developing Parkinson's disease

The results of this systematic review and meta-analysis are significant as they will help contriute to our understanding of the association of diagnosis of diabetes mellitus and the risk of acquiring Parkinson's disease. The results will also help understand the effects of taking anti-diabetic therapy on the incidence of Parkinson's disease in the diabetic population.

Chapter 2: Methods and Materials

2.1 Study Selection for Meta-Analysis

A systematic review and meta-analysis of the published literature was performed following the procedure outlined in the flowchart below (Figure 1). Relevant studies were searched in the PubMed and Science Direct databases using a combination of the keywords – "Diabetes" and "Parkinson's Disease". Studies were included in the meta-analysis if they were population-based or cohort-based, published between 2005 and 2020, and reported a link between diabetes and Parkinson's disease. Review articles, case reports, editorials, and clinical guidelines were excluded from the meta-analysis. Studies that did not provide a quantitative link between diabetes and Parkinson's disease were also excluded. Additionally, studies that used patients with Parkinson's disease as case subjects and identified the number of these patients with diabetes were also excluded from the meta-analysis, as our objective was to analyze if diabetes was a risk factor for the development of Parkinson's disease.

Studies were evaluated by scanning titles, abstracts, and methods section (where relevant) to check if they met the inclusion criteria. The reference lists of the selected articles were also checked to find relevant studies that could be included in the meta-analysis. Finally, those studies were included in the list which either reported the odds ratio or provided sufficient data to calculate the odds ratio for the link between diabetes and Parkinson's disease.

2.2 Data Extraction

Each selected study was thoroughly scanned to extract study characteristics such as the first author's last name, year of publication, study design, characteristics of population studied such as geographical location, age, and gender, age of onset of Parkinson's disease, sample size, other co-morbidities and risk factors, and other details where available.

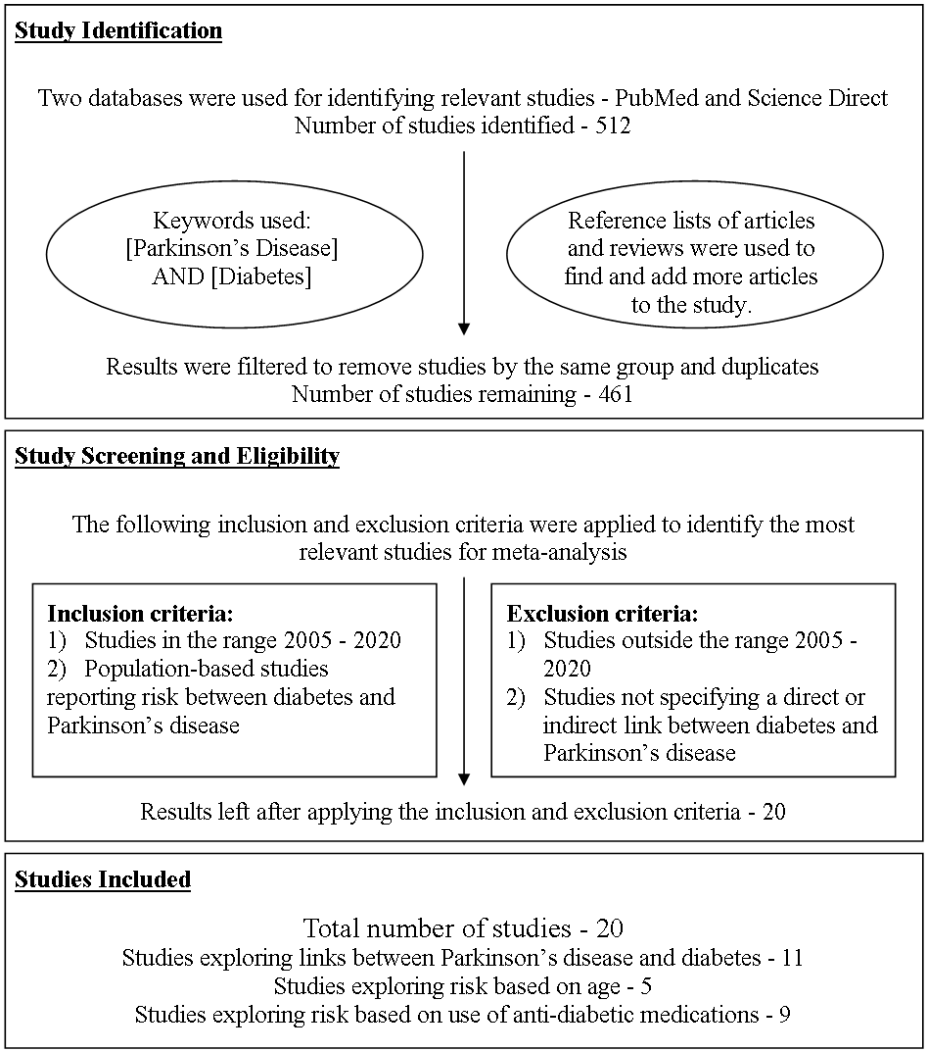

Figure 1: A flowchart providing an outline of the procedure used to select relevant studies for the meta-analysis

2.3 Meta-Analysis

The data was analyzed using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, 2014). Outcomes from each study were pooled for different meta-analyses to acquire the overall odds ratio (OR) for analyzing the risk of acquiring Parkinson's disease in diabetic subjects using 95% Confidence Intervals (CIs) and the generic inverse variance method. Calculation of odds ratio provides a convenient measure of the association between a given exposure and an outcome. It is the odds of an outcome in the presence of the exposure as compared to the odds of the outcome in the absence of the exposure (Szumilas, 2010). Heterogeneity among the studies was reported using Chi^2 value, P value, and I^2 statistic.

Depending on the assessed heterogeneity, a fixed effects model was used for the meta-analyses (Singh et al., 2017).

Three different meta-analyses were performed. One assessed the risk of acquiring Parkinson's disease in diabetic subjects in the general population. The second investigated an age-dependent association between diabetes and the risk of acquiring Parkinson's disease in order to find out if this risk was more pronounced in older age groups. The third meta-analyses investigated if the use of any class of anti-diabetic medication showed an effect on the risk of acquiring Parkinson's disease in the diabetic cohort. Forest plots were generated for each outcome and the odds ratio, Chi^2 value, and the strength of overall effect was calculated for each plot.

Chapter 3: Results

3.1 Characteristic Features of Articles Included in the Study

The databases PubMed and Science Direct were searched using the keywords ‘Diabetes’ and ‘Parkinson’s Disease’, and an initial list of 461 studies was obtained. After applying the inclusion and exclusion criteria on the studies, a final list of 20 studies was obtained which quantitatively studied the link between diabetes and Parkinson’s disease in a well-defined cohort. The characteristic features of the included studies are given in Table 2.

All the 20 studies compared the risk of acquiring Parkinson’s disease between diabetic and non-diabetic groups. Out of these studies, 11 studies were used in the meta-analysis to study the general association between diabetes and the risk of Parkinson’s disease, 5 were used to provide an age-based comparison, and 9 studies were used to understand the effect of anti-diabetic medication use on the risk of Parkinson’s disease. The year range of the studies varied from 2007 to 2020. The sample sizes in the studies varied from as low as 106 to as high as 13,568,931. Some of the studies were retrospective and some were prospective; however, all studies were population-based using patient data from standard databases. The countries that have been represented in this meta-analysis include United Kingdom, United States, Norway, Taiwan, Finland, Korea, and Denmark. The age at baseline, follow-up period, percentage of male participants, and sample sizes of diabetic and control groups for all studies are provided in Table 2.

Study	Aim of Study	Population Studied	Country	Study Design	Age at Baseline (years)	Follow-up Time (years)	Male Gender (%)	Sample Size Diabetic/ Control	Number of Events Diabetic/ Control	Odds Ratio	Result of the Study
Becker et al., 2008	To identify the prevalence of diabetes in people with and without Parkinson's disease	General Practice Research Database	United Kingdom	Observati-onal study	≥ 40	3	60	106/424	35/215	0.95	Diabetes prevalence is closely similar between people with and without Parkinson's disease
Braked-al et al., 2017	To investigate the effects of glitazone drugs on risk of Parkinson's disease in diabetics	Norwegian Prescripti-on database	Norway	Retrospecti-ve cohort study	63.45± 11.15	6.95± 2.25	53.4	8,396/ 94,349	57/938	0.68	Use of glitazones reduces the risk of Parkinson's disease in diabetics
Brauer et al., 2015	To investigate the effects of glitazone drugs on risk of Parkinson's disease in diabetics	United Kingdom Clinical Practice	United Kingdom	Retrospecti-ve cohort study	62.7	6.1	56.8	44,597/ 120,373	175/517	0.91	Use of glitazones reduces the risk of Parkinson's disease in diabetics
Chang et al., 2020	To understand the influence of use of	National Health Insurance (NHI) database	Taiwan	Retrospect-ive cohort-based study	≥ 40	1	56.3	37,232/ 11,596	441/251	0.78	Pioglitazone lowers the risk of Parkinson's disease in a dose-

	pioglitazone and statin on the risk of Parkinson's disease in diabetics										dependent manner. The combination of pioglitazone and statins works best to reduce the risk of Parkinson's disease
Conno-lly et al., 2015	To understand the effects of thiazolidine-diones on the risk of Parkinson's disease in diabetics	Medicare database	United States	Retrospect-ive cohort-based study	77.63± 6.88	2.97	27	5,230/ 24,167	27/129	0.97	The use of thiazolidine-diones does not reduce the risk of Parkinson's disease in diabetics
de Pablo-Fernan-dez et al., 2018	To investigate the association between diabetes and risk of subsequent Parkinson's disease	Hospital Episode Statistics (HES) data	England	Retrospecti-ve record-linkage cohort study	≥ 25	-	52.9	1,236,000/ 781,115	12,483/ 1,769	1.32	The diagnosis of diabetes increases the rate of subsequent Parkinson's disease
Driver et al., 2008	To identify the association between diabetes and Parkinson's disease	US male physicians cohort	United States	Prospective cohort-based study	<55 to ≥ 65	23	100	2,410/ 19,431	47/509	1.34	Diabetes is not a preceding risk factor for Parkinson's disease

Hu et al., 2007	To identify the relationship between diabetes at baseline and Parkinson's disease	Social Insurance Institution's drug register data	Finland	Prospective cross-sectional study	44±11	18	48.7	1,098/ 50,454	24/609	1.80	Diabetes is associated with an increased risk of Parkinson's disease
Jeong et al., 2019	To investigate the effect of diabetes on the risk of Parkinson's disease	Korean National Health Insurance Service database	Korea	Prospective cohort study	≥ 40	7.3	50.1	798,190/ 6,005,411	7,489/ 25,954	2.18	Diabetes is associated with an increased risk of Parkinson's disease
Kuan et al., 2017	To investigate the effects of metformin exposure to the risk of Parkinson's disease in diabetics	National Health Insurance Research database	Taiwan	Retrospecti-ve cohort study	>50	12	50.6	4,651/ 4,651	148/61	2.27	Long-term metformin exposure in diabetes patients can increase the risk of Parkinson's disease
Lee et al., 2018	To study the association between diabetes with and without diabetic retinopathy and the risk of Parkinson's disease	Korean National Health Insurance Service database	Korea	Prospective cohort study	>30	5	54.1	1,343,437/ 13,568,931	8333/ 26,501	3.19	Diabetes and diabetic retinopathy are associated with an increased risk of Parkinson's disease

Lin et al., 2018	To understand the effects of thiazolidine-diones on the risk of Parkinson's disease in diabetics	National Health Insurance Research database	Taiwan	Retrospecti-ve cohort study	-	7.9	52.7	8,250/ 30,271	52/492	0.38	The use of thiazolidine-diones significantly reduces the risk of Parkinson's disease in diabetics
Rhee et al., 2020	To study the link between diabetes and risk of Parkinson's disease based on glucose tolerance status	National Health Insurance Service	Korea	Population-based cohort study	≥ 40	5	53.4	1,308,089/ 5,025,010	8,278/ 23,299	1.37	Diabetes is an independent risk factor for Parkinson's disease
Schern-hammer et al., 2011	To study the link between mid-life diabetes and Parkinson's disease	Danish Hospital Register	Denmark	Population-based case-control study	72.2± 10.2	-	58.1	608/ 10,974	126/1,805	1.36	Diabetes is associated with an increased risk of Parkinson's disease, especially at a younger age
Simon et al., 2007	To determine whether diabetes is associated with an increased risk of	Nurses' Health Study and Health Profession-als Follow-Up Study	United States	Prospective cohort-based study	30 – 75	12.6 in men and 22.9 in women	29.5	3,759/ 1,68,120	37/493	1.04	There is no significant relationship between diabetes and Parkinson's disease

	Parkinson's disease										
Sun et al., 2012	To study the risk between diabetes and Parkinson's disease	NHI Claim data	Taiwan	Population-based, retrospecti-ve cohort study	-	1	49.3	6,03,416/ 4,72,188	1,613/809	1.61	Diabetes is associated with an increased risk of Parkinson's disease, especially in women and younger people
Wahlq -vist et al., 2010	To investigate the influence of oral anti-hyperglyce-mic agents on the association between diabetes and Parkinson's disease	National Health Insurance database	Taiwan	Cohort study	≥ 50	11	48.7	18,152/ 18,152	429/459	0.93	Combination therapy with metformin and sulfonylurea can reduce the risk of Parkinson's disease in diabetes
Wu et al., 2018	To investigate the influence of pioglitazone on the association between diabetes and Parkinson's disease	Taiwan Longitudin -al Health Insurance database	Taiwan	Retrospect-ive cohort study	61.15± 10.75	5	46.7	7,906/ 7,906	119/138	0.86	There is no significant association between pioglitazone use and risk of Parkinson's disease
Xu et	To study the	National	United	Prospective	62±5	10	62	21,611/	172/	1.41	Diabetes is

al., 2011	link between diabetes and Parkinson's disease at a later age	Institutes of Health-AARP Diet and Health Study	States	study				2,67,051	1,393		associated with a higher future risk of Parkinson's disease
Yang et al., 2017	To investigate the risk of Parkinson's disease in diabetic patients	National Health Insurance Research database	Taiwan	Retrospecti-ve cohort study	≥ 20	7.3	53.36	16,606/ 19,688	411/ 1,239	0.38	Diabetes is associated with a higher risk of Parkinson's disease

Table 2: Characteristic features of studies included in the meta-analysis

3.2 Risk of Developing Parkinson's Disease in Diabetics

Data from 11 finalized studies was extracted and meta-analyzed to identify the risk of acquiring Parkinson's disease in diabetic and non-diabetic cohorts. The total diabetic population included in the meta-analysis was 4,119,018 individuals and the total control population was 25,696,876 individuals. Out of these, the number of people who developed Parkinson's disease was 26,704 and 82,819 respectively.

The raw data that was extracted from the studies was used to generate a forest plot using the RevMan software (Figure 2). This plot indicates that people with diabetes have a higher risk of acquiring Parkinson's disease as compared to people without diabetes. The odds ratio for the data was 2.08 with a confidence interval of 95% and P value less than 0.00001. The odds ratio for each individual study varied from 0.48 to 3.38, with 9 out of the 11 studies reporting an odds ratio greater than 1.0.

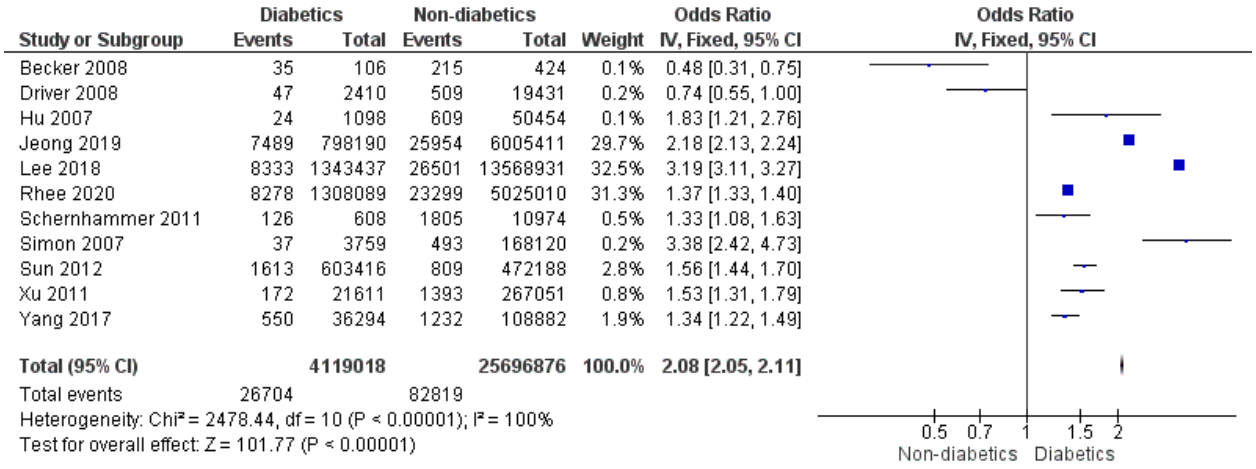

Figure 2: Forest plot showing the relative risk of developing Parkinson's disease between diabetics and non-diabetics

3.3 Influence of Age on the Risk of Developing Parkinson's Disease in Diabetics

Five out of the 20 studies were used to analyze the influence of age on the risk of developing Parkinson's disease in the diabetic cohort. Based on age, two groups of the diabetic population were studied – people above age 60 and people below age 60. The group of individuals aged below 60 comprised of 1,687,510 individuals and the group of individuals aged above 60 comprised of 2,000,554 individuals. Among these two groups, the number of people

who acquired Parkinson's disease were 2,908 (0.0017% of the population below 60 years) and 20,962 (0.01% of the population above 60 years respectively.

The raw data that was extracted from the studies was used to generate a forest plot using the RevMan software (Figure 3). This plot indicates that diabetics over the age of 60 years have a higher risk of acquiring Parkinson's disease as compared to diabetics who are below 60 years of age. The odds ratio for the data was 5.95 with a confidence interval of 95% and P value less than 0.00001. The odds ratio for each individual study varied from 0.66 to 10.48, with 4 out of 5 studies reporting a significant age-related association with the risk of acquiring Parkinson's disease in the diabetic population.

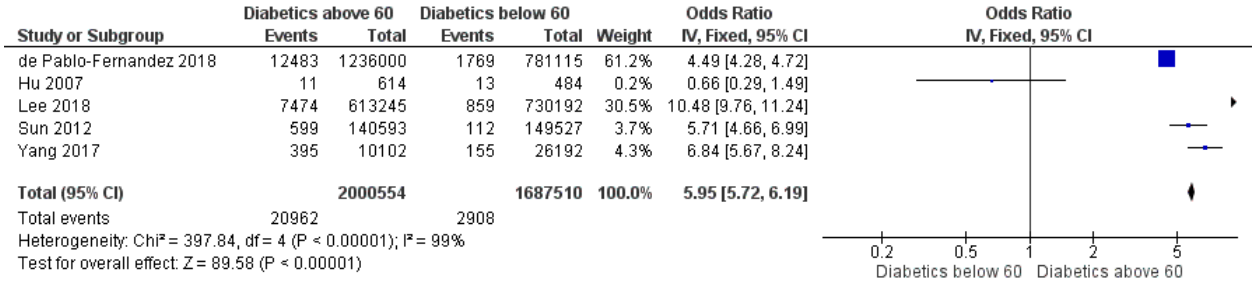

Figure 3: Forest plot showing the relative risk of developing Parkinson's disease between diabetics aged below 60 and above 60

3.4 Influence of Anti-Diabetic Medication Use on the Risk of Developing Parkinson's Disease in Diabetics

Nine out of the 20 studies were used to analyze the influence of the use of different classes of anti-diabetic medications on the risk of developing Parkinson's disease in the diabetic cohort. The number of people on one or more anti-diabetic medications was 151,020 and the number of people not taking any anti-diabetic medication was 331,153. Among these, the number of people who developed Parkinson's disease was 1,859 (0.0123% of people on anti-diabetic medications) and 4,224 (0.0127% of people not on any anti-diabetic medication) respectively.

The raw data that was extracted from the studies was used to generate a forest plot using the RevMan software (Figure 4). This plot indicates that diabetics who are on anti-diabetic medications have a lower risk of acquiring Parkinson's disease as compared to diabetics not on

any anti-diabetic medication. The odds ratio for the data was 0.65 with a confidence interval of 95% and P value less than 0.00001. The odds ratio for each individual study varied from 0.38 to 2.47, with 8 out of 9 studies reporting a significant association between the risk of acquiring Parkinson's disease in the diabetic population and the use of anti-diabetic medications.

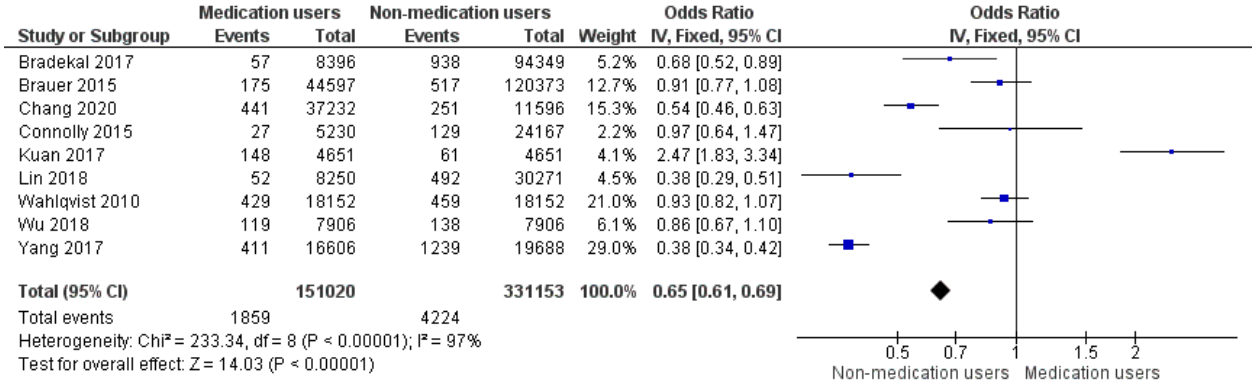

Figure 4: Forest plot showing the relative risk of developing Parkinson's disease between diabetics on anti-diabetic medication and diabetics not taking any anti-diabetic medication

Chapter 4: Discussion

The link between diabetes and Parkinson's disease has mixed findings in the literature. Some studies report a strong risk of acquiring Parkinson's disease for diabetic patients (Simon et al., 2007; Lee et al., 2018), whereas others prove little or no association between the two conditions (Becker et al., 2008; Driver et al., 2008). In the present study, a meta-analysis of 20 studies was carried out to investigate the relationship between diabetes and Parkinson's disease with respect to factors such as age and use of anti-diabetic medications. A general analysis of the diabetic population found that people with diabetes had a 67.5% (OR = 2.08) higher chance of acquiring Parkinson's disease as compared to the non-diabetic population. Out of the 11 studies used for the meta-analysis, 9 studies reported a strong link between diabetes and Parkinson's disease and 2 studies reported a negative association between the two conditions. Among the 9 studies that reported a positive link, Simon et al. (2007) reported the strongest association with an odds ratio of 3.38. The reason for such a strong link could be its large sample size and use of self-reports of diabetes for classification. This study also had a high follow-up rate which indicates that as the participants were followed for a longer time, the number of people who developed a diagnosis of Parkinson's disease were more leading to a higher OR value. Also, reported Parkinson's disease cases by Becker et al. (2008) and Driver et al. (2008) demonstrated a negative association between diabetes and Parkinson's disease. Becker et al. (2008) used an observational methodology and a nested case-control analysis to investigate diagnoses of Parkinson's disease in diabetics as well as diagnoses of new-onset diabetes in patients with Parkinson's disease. One of the limitations of their study was that they considered dates recorded in the UK health database as the diagnosis date for both diabetes and Parkinson's disease and this may have been misleading as diabetes and Parkinson's disease are slow-onset conditions. Driver et al. (2008) investigated male physicians in the US and they not only found minimal association between diabetes and Parkinson's disease, but also reported decreased severity of Parkinson's disease in diabetic patients. The other studies in the meta-analysis showed varying risks of acquiring Parkinson's disease in people with diabetes when compared to people without diabetes ranging from 33% to 83%. The reason for this variation may be due to several factors such as the

age and gender of the population tested, ethnicity, sample size, method of diagnoses, and presence of co-morbidities in the tested population.

Five studies were used to investigate the risk of acquiring Parkinson's disease in diabetics below the age of 60 and diabetics above the age of 60. Out of these studies, 4 studies showed a very strong association between diabetes and Parkinson's disease in older age with OR value greater than 4.0, and 1 study showed a negative association between these two conditions in the elderly (Hu et al., 2007). Lee et al. (2018) used a prospective approach to understand the link between diabetes and Parkinson's disease and surveyed a large cohort in the Korean population. The reasons for their strong link between diabetes, Parkinson's disease, and older age (OR = 10.48) may be their extremely large sample size and inclusion of people above the age of 30 ensuring that a large population was covered in the study. On the other hand, Hu et al. (2007) prospectively surveyed a cohort in Finland and did not report a link between risk of acquiring Parkinson's disease and increasing age in the diabetic population. One reason for this could have been that a few patients died during the 18-year long study and were not included in the final results, thus leading to a possibility of bias in the final risk calculation.

Nine studies were used to investigate the effect of use of anti-diabetic medications in the diabetic cohort on the subsequent risk of developing Parkinson's disease. Out of these, 1 study showed an increased risk of Parkinson's disease with the use of anti-diabetic medication (Kuan et al., 2017), whereas the remaining 8 studies showed different degrees of reduction in the risk of developing Parkinson's disease ranging from 3% to 62%. Kuan et al. (2017) conducted a retrospective study in a Taiwan cohort analyzing the risk of Parkinson's disease associated with long-term exposure to metformin in diabetics. Interestingly, long-term exposure to metformin was not only observed to increase the risk for Parkinson's disease, but also other neurodegenerative disorders such as dementia and Alzheimer's disease. On the other hand, Wahlqvist et al. (2010) analyzed the risk of Parkinson's disease with and without treatment with sulfonylureas along with metformin, and found that the treatment group demonstrated a reduced risk of Parkinson's disease as compared with the control group. Interestingly, treatment with metformin alone or sulfonylureas alone contributed to an increased risk of Parkinson's disease whereas a combination therapy considerably reduced Parkinson's disease risk in the diabetic cohort. Other studies that were included in the meta-analysis analyzed the use of glitazones,

pioglitazones, statins, and thiazolidinediones in the experimental group and reported a reduction in the risk of Parkinson's disease for all these treatment regimens.

A meta-analysis conducted by Yue et al. (2016) on the risk of Parkinson's disease in diabetics using 7 studies found that people with diabetes had a 38% higher chance of developing subsequent Parkinson's disease. Another meta-analysis by Cereda et al. (2011) used 4 studies and indicated a 37% higher risk of developing Parkinson's disease in the diabetic population. A meta-analysis conducted by Mounika et al. (2012) found a 34% increase in the risk of Parkinson's disease in the diabetic cohort. The difference in the percentages between these meta-analyses and our findings could be due to the difference in the number of studies used and the inclusion of more recent studies in our meta-analysis. However, our results are in contrast to the results of a meta-analysis published by Lu et al. (2014) who reported a negative association between diabetes and the subsequent risk of Parkinson's disease. The primary difference between this study and our investigation was that this meta-analysis used observational studies whereas we have used cohort and case-control studies for our meta-analysis. Observational studies usually have the problem of confounding and the effect sizes are generally small. In contrast, data from cohort studies are more reliable because of causal hypothesis verification (Lu et al., 2014).

A meta-analysis conducted by Zhu et al. (2019) aimed to identify the effects of use of thiazolidinediones on the risk of Parkinson's disease and found that use of this medication reduced the risk of Parkinson's disease by 30% as compared to the control group. Another meta-analysis conducted by Hussain et al. (2020) to investigate the protective effects of thiazolidinediones found a 19% risk reduction in the experimental cohort as compared to the control group. This protective effect was especially pronounced in the Caucasian population which showed a 22% risk reduction.

Despite the documented therapeutic potential of metformin in the treatment of Parkinson's disease (Rotermund et al., 2018), our meta-analysis found that metformin users had a higher risk of developing Parkinson's disease as compared to users of other anti-diabetic medications. This finding is consistent with a meta-analysis conducted by Ping et al. (2020) who also reported a significant increase in the risk of Parkinson's disease in the metformin treatment group as compared to the control group.

Although the molecular mechanisms that lead to cognitive decline in diabetes are still unclear, several cohort studies have reported different risks of acquiring Parkinson's disease in different diabetic populations from around the world. One longitudinal study that examined the occurrence of Parkinsonian symptoms in the diabetic population found that diabetes was associated with rigidity and gait, but not with bradykinesia or tremor during a 9-year follow-up period. Additionally, people who suffered from stroke faced a decreased risk of acquiring gait but not rigidity (Arvanitakis et al., 2004). These results indicate the presence of specific physiological mechanisms that are disrupted in people with diabetes and lead to specific neurological symptoms.

Several intrinsic pathways have been implicated in the pathogenesis of both Parkinson's disease and diabetes, and dysregulation of these pathways have been described as common underlying mechanisms for predisposing people to these conditions. Systemic chronic inflammation is observed in both diseases (Chen et al., 2008) along with oxidative stress, abnormal dopamine levels, and mitochondrial dysregulation (Schernhammer et al., 2011). Additionally, *in vitro* studies have also demonstrated that insulin has the potential of regulating dopaminergic activity in the brain (Craft and Watson, 2004).

Most people with diabetes mellitus are prescribed metformin as the first line of treatment. It works by inhibiting glucose output in the liver, improves sensitivity of peripheral tissues to insulin, and increases glucose uptake thereby lowering blood sugar levels (Zhou et al., 2018). Apart from diabetes, it is also used in the treatment of cardiovascular diseases such as atherosclerosis and congestive heart failure, high blood pressure, obesity, pre-eclampsia, gestational diabetes, breast cancer, and ovarian cancer (Alzaid et al., 2017). Recent studies have also shown that metformin plays a role in inhibiting inflammatory responses, improving cognitive impairment, and treating autism. This highlights the positive role of metformin in neuroprotection and its potential application in the treatment of Parkinson's disease (Lu et al., 2020).

Despite its promising role in the treatment of neurodegenerative disorders, some studies have reported that treatment with metformin may aggravate neuronal damage and increase the risk of Parkinson's disease (Allard et al., 2016). Population studies aimed at analyzing the influence of metformin use on future risk of Parkinson's disease have shown mixed results. This

could be attributed to varying sampling strategies and diagnostic criteria, different dosages and exposure times of metformin, and treatment with either metformin alone or in combination with another anti-diabetic medication (Ping et al., 2020). All these factors can lead to differences in the results of these cohort or case-control studies aimed at analyzing the therapeutic effects of metformin in preventing or delaying the development of Parkinson's disease. In contrast, use of other anti-diabetic therapies such as glitazone, pioglitazone, statin, and thiazolidinedione have all demonstrated a decrease in the risk of development of Parkinson's disease in the future. There is clearly a shortage of studies in this regard and studies with larger sample sizes and standardized procedures need to be undertaken in order to confirm the effects of use of specific anti-diabetic medications to generate a neuroprotective effect in diabetic patients.

There are several strengths and limitations of this investigation. One of the main strengths of this meta-analysis is that it included 20 population-based cohort and case-control studies that provided high quality data for analysis. This study had a large sample size of over 25,000,000 participants thereby providing credibility to the results. An important limitation of the study was that due to unavailability of information in certain studies, pooling of data by diagnostic criteria or type of Parkinson's disease could not be performed. Additionally, data available for use of anti-diabetic medication was also limited and showed several discrepancies which could not be explained due to the small sample size in these cases. Also, there were different confounding factors in different studies such as the duration of diabetes, HbA1c levels, and vitamin B_{12} levels that varied between studies and were not taken into account for the meta-analysis.

Chapter 5: Conclusions

The present study investigated the association between diabetes mellitus and Parkinson's disease by conducting a meta-analysis of 20 population-based studies. Consistent with results published in the literature, this study found that a diagnosis of diabetes can increase the risk of subsequent Parkinson's disease for these patients. Also, the prevalence of Parkinson's disease is much higher in older diabetics as compared to younger diabetics indicating age to be an important risk factor for the development of Parkinson's disease. As several anti-diabetic medications have shown to play important roles in improving cognition and promoting neuroprotection, it is hypothesized that long-term use of these medications in diabetes should play a role in delaying or preventing the onset of Parkinson's disease. Our study found this to be true for all anti-diabetic medications except for metformin which was shown to increase the risk of Parkinson's disease upon long-term exposure.

Despite the strong links that have been demonstrated between diabetes and neurodegenerative disorders, there is still a lot that is unknown regarding their shared mechanisms. Elucidating this will provide insights into prevention of cognitive decline in diabetic patients. As both these diseases are extremely prevalent worldwide, understanding and addressing the link between diabetes and Parkinson's disease will go a long way in reducing the health and economic burden of these two conditions. Not only will it be useful for hospitals and other healthcare organizations, but it will also be beneficial for people suffering from diabetes by informing them of their lifetime risk of acquiring Parkinson's disease in the future.

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