PharmacoAnalytics: Assessing the Relationship Between Glucagon-like Peptide-1 Receptor Agonist (GLP-1 RA) Utilization and Dementia Incidence

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PharmacoAnalytics: Assessing the Relationship Between Glucagon-like Peptide-1 Receptor Agonist (GLP-1 RA) Utilization and Dementia Incidence

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Aims: To evaluate whether GLP-1 RAs, a newer generation of antidiabetic medication, will lower dementia risk compared to all other antidiabetic medications in the type 2 diabetes population.

Materials and Methods: All type 2 diabetes Mellitus (T2DM) patients who dispensed antidiabetic medications from June 2005 to December 2022 in the National Alzheimer's Coordinating Center (NACC) database entered the study. A propensity score matching a ratio of 1 to 2 was used to balance baseline covariates. Kaplan-Meier analysis was applied to compare the probability of dementia incidents over time. A Multivariate Cox regression model was performed to obtain significant predictors, presenting adjusted hazard ratios (aHR) and Confidence Intervals (CIs) for the time to dementia incidence.

Results: After 1 to 2 propensity score matching, the final cohort consisted of 133 GLP-1 RA users and 266 non-users. Kaplan-Meier demonstrated that GLP-1 users were associated with a lower risk of developing dementia compared to non-users (p=0.0123). The Multivariate Cox regression model identifies GLP-1 RA (aHR 0.42, 95%Confidence Interval (CI): [0.22-0.80], p=0.009) and female (aHR: 0.50, 95%CI: [0.29-0.87], p=0.01) as protective factors for dementia, while age (aHR: 1.07, 95%CI: [1.03-1 .10], p=0.01), 2 pairs of APOE4 genes (aHR: 2.42, 95%CI: [1.43-4.09], p=0.001), and depression (aHR: 3.30, 95%CI: [1.87-5.84], p<0 .0001) were associated with a higher risk of dementia.

Conclusion: GLP-1 RAs were associated with a lower risk of dementia incidence in the T2DM population. Further studies are warranted.

Keywords: dementia, type 2 diabetes mellitus, glucagon-like peptide-1 receptor agonist, antidiabetic medication, NACC

Table of Contents

List of Tables

List of Figures

List of Abbreviation

AD	Alzheimer's Disease
VD	Vascular Dementia
DM	Diabetes Mellitus
ChEI	Cholinesterase Inhibitors
NMDAR	N-methyl-D-aspartate Receptor
Aβ	Amyloid-beta
CSF	Cerebrospinal Fluid
APOE4	E4 form of Apolipoprotein E
BBB	Blood Brain Barrier
CNS	Central Nervous System
NFT	Neurofibrillary Tangles
T2DM	Type 2 Diabetes Mellitus
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-alpha
AMPK	Adenosine Monophosphate-activated Protein Kinase
IR	Insulin Resistance
TZD	Thiazolidinediones
DPP-4I	Dipeptidyl Peptidase 4 Inhibitors
GLP-1	Glucagon-Like Pepetide-1
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
SGLT2	Sodium-Glucose Cotransporter-2

MoCA	Montreal Cognitive Assessment
NACC	National Alzheimer's Coordinating Center
ADRC	Alzheimer's Disease Research Center
ADA	American Diabetes Association
NIH	National Institute on Aging
UDS	Uniformed Dataset
RCT	Randomized Clinical Trials
SD	Standard Deviation
PSM	Propensity Score Matching
KM	Kaplan Meier
HR	Hazard Ratio
aHR	Adjusted Hazard Ratio
CI	Confidence Interval

Preface

This project was conceived and designed by Dr. Ying Xue. All data cleaning and statistical analysis were conducted by Junnan Qi.

We acknowledge the generous support provided by Dr. Xue's funding from the Competitive Medical Research Fund of the UPMC Health System, the University of Pittsburgh, and the National Institute on Aging of the National Institutes of Health under award number R56AG074951.

1.0 Introduction

This chapter aims to provide a background introduction to this project.

1.1 Dementia

Dementia is a broad term used to describe neurodegenerative brain disease, caused by damage to the neurons. Since neurons are fundamental to cognitive functions, symptoms of dementia include memory loss, deteriorated thinking abilities, difficulties in performing daily activities, and potential mood and personality alterations in the later stages. Dementia can begin even 20 years or more before the symptoms manifest.[1-3]

Alzheimer's Disease (AD) is the most prevalent type of dementia, which accounts for approximately 60 to 80 percent of all dementia cases. AD is signature by the accumulation of beta-amyloid (Aβ) proteins outside the neurons and the neurofibrillary tangles (NFT) inside the neuron. Although the sequence of events is not fully understood, beta-amyloid may form before the tau protein accumulation, suggesting that the tau aggregation could be the subsequent event following an increase in Aβ levels.[4]

Vascular dementia (VD), the second common type of dementia, is distinguished by brain blood vessel injury leading to inadequate blood, oxygen, or nutrient supply. While 5 to 10 percent of the individuals are diagnosed solely as VD, it is more frequently observed as a mixed pathology, involving brain changes characteristic of both AD and VD[5,6], particularly prevalent at advanced

age.[7,8] Frontotemporal degeneration (FTD), Hippocampal Sclerosis (HS), Lewy body disease, and Parkinson's disease are other types of common dementia types.

Currently, the global prevalence of dementia now exceeds 55 million and is projected to double every two decades.[4] Additionally, the cost of dementia care is also expected to continue rising, reaching an estimated 245 billion dollars.[4] Age, especially 65 or older, is a well-known risk factor for dementia, while the baby-boomer generation already entered this vulnerable age range.[9] The heightened prevalence and cost indicate the urgent need for therapeutic intervention.

1.1.1 Drug Treatment

There are three main categories of medications prescribed for treating dementia: Cholinesterase inhibitors (ChEIs), memantine, and monoclonal antibodies. ChEI medications, such as donepezil, rivastigmine, and galantamine functioned by inhibiting the activity of cholinesterase, an enzyme responsible for breaking down acetylcholine. Acetylcholine is a neurotransmitter that plays a vital role in memory, learning abilities, and synapse plasticity.[10]

Following ChEI, memantine was approved by the FDA in 2003. Memantine acts as an uncompetitive antagonist for the N-methyl-D-aspartate receptor (NMDAR), lowering the brain's excitatory neurotransmitter glutamate level. This helps to mitigate neuronal damage due to persistent stimulation. However, both ChEI and memantine aim to improve symptoms rather than affecting the underlying changes in the brain that cause the symptoms.[4]

Monoclonal antibodies represent the latest generation of anti-dementia medication, approved by the FDA in 2021, aimed at altering the underlying biology of dementia. These immunotherapies are designed to target and bind to the amyloid-beta (Aβ) plaques already formulated in the patient's brain. Monoclonal antibodies are approved for early-stage patients who

demonstrate evidence of Aβ accumulation based on brain imaging or cerebrospinal fluid (CSF) volume. However, they are not curable treatments and unsuitable for all individuals.[4]

1.1.2 Non-Drug Treatment

Non-pharmacological interventions are commonly combined with medication treatments to improve or maintain cognitive function, daily activities, or life qualities. Modalities such as physical activity, emotional therapy, and memory exercises are effective in mitigating agitation, aggression, and depression associated with dementia.[11]

1.1.3 Current Concerns

Although there are currently three main categories of medications for treating dementia, their real-world effectiveness is still limited, mainly by delaying progress or alleviating the symptoms. Given the high mortality rate and the projected increase in the number of dementia patients, finding potential treatments has become an urgent necessity.

1.2 Risk Factors of Dementia

Dementia, a complex neurological condition, remains incompletely understood. Nonetheless, there are well-established unmodifiable, and modifiable risk factors that increase the patient's susceptibility to the condition.

1.2.1 Unmodifiable Risk Factors

Among patients with AD older than 65, or called late-onset Alzheimer's, the most significant unmodifiable risk factors include age, the presence of the e4 form of apolipoprotein E (APOE4) gene, and family history.

Age stands out as the paramount risk factor among the three unmodifiable factors. The prevalence of dementia rises dramatically with the increase in age. Approximately 33.3 percent of individuals aged 85 or older are affected by dementia, compared to 13.1 percent of those aged 75 to 84, and 5 percent of people aged 65 to 74.[4] It's crucial to acknowledge that dementia is not simply a natural part of aging, and advancing in age alone is not the sole cause of dementia. The development of dementia often involves a complex interplay of various factors.[12]

Genetic information is another risk factor that could contribute to dementia. In 2022, 31 new genes have been identified to influence the biological processes involved in AD or related dementia.[13] However, the e4 form of the APOE gene remains the strongest impact, especially for late-onset AD. Individuals with two pairs of APOE4 genes can have up to 12-fold elevated risk of dementia incidents compared to those with only one pair, which is a three-fold higher risk.[14,15]

Family history represents another unmodifiable risk factor contributing to dementia. Individuals with one first-degree relative diagnosed with dementia are more susceptible to developing dementia, while those with multiple affected first-degree relatives face even greater risk.[16]

Although age, genetics, and family histories cannot be altered, they typically do not play a role alone. Often modifiable risk factors can combine with nonmodifiable ones to increase the risk of cognitive dysfunction.

1.2.2 Modifiable Risk Factors

Addressing modifiable risk factors can significantly delay or prevent dementia. The Lancet Commission's 2020 report suggests that by addressing modifiable risk factors, it's possible to reduce the number of dementia cases by approximately 40%.[17]

Smoking[18], inactivity[19,20], and low education levels[21] are risk factors that have long been demonstrated to be associated with dementia. A healthy diet includes Mediterranean, Dietary Approaches to Stop Hypertension (DASH)[22,23], vitamin E[24], or vitamin D[25] has shown beneficial effects in dementia.

Cardiovascular disease and cerebrovascular disease, such as atherosclerosis or stroke, can restrict the oxygen and blood supply into the brain. Normally, the brain requires 20 percent of the body's oxygen and energy supply to function properly. However, the constricted supply, either resulting from blocked or narrowed vessels, significantly increases the risk of dementia.[26]

Hypertension is another comorbidity associated with dementia. Hypertension has been identified when patients' systolic blood pressure is over 140 mmHg and diastolic is lower than 90 mmHg. A meta-analysis including 34,519 hypertensive patients demonstrated untreated patients had a 42% higher risk of developing dementia.[27]

Hypercholesteremia is a disease identified by the high cholesterol level in the blood. High cholesterol levels could lead to the blockage of the arterials in the brain, which has also been demonstrated to elevate the risk of dementia.[28]

Diabetes, characterized by persistent hyperglycemia or insulin resistance, is a metabolic disorder that has emerged as a new risk factor contributing to dementia. Recently, diabetes, especially type 2 diabetes mellitus (T2DM) has been demonstrated to elevate the dementia risk by 2-fold.[29]

Due to the growing concerns about dementia, there has been an increased focus on patients with T2DM.

1.3 Diabetes Mellitus

Diabetes Mellitus (DM) is a metabolic disorder signature by persistent hyperglycemia or insulin resistance. It is mainly categorized into three types: Type 1 diabetes, Type 2 diabetes, and Gestational diabetes.

Type 1 diabetes mellitus(T1DM) is a condition where the immune system attacks and destroys beta cells, the insulin-producing cells in the pancreas. This disease usually occurs in childhood period and requires lifelong insulin injection.[30]

T2DM is the most prevalent type of diabetes, accounting for 90 to 95 percent of all cases, and occurs when your body cannot respond to insulin properly.[30]

Gestational Diabetes Mellitus (DGM) is a diabetes incident during pregnancy and is a marker for developing T2DM in later life.[31]

Since T2DM accounts for the majority of diabetes cases researchers have conducted numerous studies on its association with dementia.

1.4 Linkage between T2DM and Dementia

Although the etiology of how dementia develops is still unclear, insulin resistance has been hypothesized to underlie the association between T2DM and dementia.

1.4.1 Insulin Function in the Brain

Insulin, a peptide secreted from pancreatic beta cells, has been shown to possess the ability to transverse the blood-brain barrier (BBB) within the central nervous system (CNS) through a receptor-mediated process.[32] It is likely that the majority of the insulin available in the brain was probably transported by this process.[33]

Recent evidence suggests that insulin receptors are abundant in the CNS, particularly in the hippocampus, hypothalamus, amygdala, olfactory bulb, cerebral cortex, and synapses of neurons, regions important for learning and memory function.[34,35] In addition to insulin receptor location in the CNS, insulin itself also plays an important role in cerebral glucose metabolism and utilization. It can modulate neurotransmitters, norepinephrine, and acetylcholine, which are important in cognitive function.[36,37] Interestingly, a preclinical study involving rodents trained in memory tasks demonstrated an elevated expression of insulin receptors in the hippocampal, indicating the correlation between the learning process and alterations in insulin signaling molecules.[37]

Insulin, beyond its crucial roles in maintaining glucose homeostasis, promoting cell growth, and regulating metabolism, also plays a significant role in the CNS.[38-40] Insulin can traverse the blood-brain barrier (BBB) to support overall brain health, including neuron plasticity, memory function, and cognitive capabilities.[41,42] In cases of insulin resistance, there is a downregulation of insulin receptors at the BBB, leading to a decrease in the transportation of insulin into the brain[43]. It has been noted that AD brains exhibit diminished glucose metabolism rates in the brain, particularly within regions associated with memory and cognitive function.[44]

Since insulin plays a vital role in neuron health, learning, and memory tasks, insulin resistance has been hypothesized to be associated with the risk of developing neurodegenerative diseases.

1.4.2 Insulin Resistance and Neuroinflammation

Neuroinflammation is another factor that emerged as a common pathology linking T2DM and dementia.

Several studies highlight elevated levels of cytokines and proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), in the brain of dementia patients.[45,46] In addition, individuals with metabolic disorders have been shown to have a higher level of proinflammatory cytokines in the tissues. Recent research underscores the role of increased TNF-α levels as a potential driver of insulin resistance in both the central and peripheral nervous systems, fostering chronic inflammation.[47]

Thus, impaired insulin signaling due to insulin resistance leads to higher levels of inflammatory cytokines and mediators, thereby leading to chronic neuroinflammation of neurons in the brain.

1.4.3 Insulin Resistance in neurodegenerative disease

Insulin resistance, defined as the insensitivity to insulin in the target tissues, also indicates the disrupted insulin signaling pathway.[48] The disruption of the signaling pathway makes the neuron more vulnerable to oxidative stress, which further increases the risk of neuroinflammation and dysfunction.[49] In preclinical studies, a correlation has been shown between reduced insulin

levels in CSF and poor cognitive performance.[50] Moreover, the phosphorylation of insulin signaling molecules is decreased in dementia patients and even decreased more in patients who had both T2DM and dementia.[51]

Moreover, AD, one specific type of dementia, had been signature by the abnormal hyperphosphorylation of tau. Tau protein, which acts as a neuron stabilizer, can be hyperphosphorylated and abnormally aggregated and form neurofibrillary tangles (NFTs). Tau phosphorylation is typically controlled by various kinases, including glycogen synthase kinase-3 beta (GSK3β), cyclin-dependent kinase 5, and protein phosphatase 2A. These kinases and phosphatases play crucial roles as targets of insulin regulation.[52,53] Therefore, impaired insulin signaling pathways can lead to kinase dysfunction, resulting in tau hyperphosphorylation and aggregation.[54]

Additionally, insulin resistance is associated with increased formation of Aβ plaques. Aβ peptides in the brain compete with insulin for binding to insulin receptors, thereby reducing the binding affinity and signaling. In the context of insulin resistance, the decreased availability of insulin for binding to insulin receptors may potentially increase the Aβ binding, leading to the aggregation of Aβ plaques in the neurons and further impairing cognitive function.[49,55]

1.4.4 Clinical Evidence toward T2DM and Dementia

Preclinical studies have been demonstrating the potential linkage between T2DM and dementia. Importantly, real-world clinical evidence has demonstrated consistent results.

A prospective, community-based cohort study found that high blood glucose levels are associated with an elevated risk of dementia even in the population without T2DM.[56]

Moreover, a pooled study that includes 2.3 million subjects from 14 studies demonstrated that T2DM patients have a 60% increased risk of developing dementia.[57] This mounting evidence, with some papers designating the linkage between diabetes and dementia as 'type 3 diabetes', indicates the rising concerns about the T2DM population.[58]

1.5 Antidiabetic Medication

Given the close relationship between insulin resistance, or T2DM, and the higher risk of dementia, studies have focused on antidiabetic medications - those used to improve insulin signaling - to assess whether their potential efficacy is a potential therapeutic approach to reduce the risk of dementia in the T2DM population.

The older generation of antidiabetic medication includes metformin, insulin, sulfonylureas, and thiazolidinediones (TZD). Newer generations of antidiabetic medications include Dipeptidyl peptidase-4 inhibitors (DPP-4i), Sodium-glucose cotransporter-2 (SGLT2) inhibitors, and Glucagon-like peptide-1 Receptor Agonist (GLP-1 RA).

1.5.1 Older Generation of Antidiabetic Medication

Metformin, the conventional first-line antidiabetic medication, was the first to be studied. Metformin reduces the glucose level by increasing the muscle glucose uptake through 5'-adenosine monophosphate-activated protein kinase (AMPK) activation.[59] AMPK has been demonstrated to act as a neuroprotective factor.[60] Metformin can increase the insulin receptor expression and tyrosine kinase activity[61], reduce inflammation and oxidative stress[62], inhibit

mammalian target of rapamycin (mTOR) pathway[63], and further decrease the Aβ burden in the brain through the activation of the AMPK-dependent or independent pathways.[64] Real-world observational studies consistently demonstrate the result that metformin could help reduce the risk of dementia or improve cognitive function.[65]

Sulfonylureas reduce blood glucose by directly stimulating the pancreatic beta cells to release more insulin. However, they have not been demonstrated to improve cognitive function. In a retrospective cohort study, sulfonylureas were found to potentially increase the risk of dementia when compared to DPP-4i.[66] This could contribute to the higher hypoglycemia risk of the sulfonylureas[67], and hypoglycemia has been shown to increase the risk of dementia.[68]

TZDs act as insulin sensitizers, enhancing the insulin sensitivity in the body to reduce the blood glucose level. Like sulfonylureas, TZDs have also shown controversial results regarding dementia. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND), rosiglitazone, a type of TZD, was demonstrated to increase the dementia risk or worsen cognitive function.[69] However, another retrospective cohort study using the Chinese Yinzhou Regional Health Care Database (YRHCD) demonstrated that TZD could decrease the risk of dementia.[70]

Insulin facilitates the glucose uptake from the bloodstream into the cells, thereby decreasing blood glucose levels. Insulin receptors (IRs) are abundantly expressed in the cerebral cortex, and cerebellum[71,72], regions responsible for memory and learning.[73] In preclinical studies, insulin has been shown to increase synaptic plasticity and improve cognitive function.[74] However, clinical evidence is currently controversial, likely due to the indication of insulin use, which is typically prescribed to patients with higher severity of T2DM.[75,76]

Although the results for some older generations of antidiabetic medications remain controversial, current findings still demonstrate the feasibility of using antidiabetic drugs to decrease the risk of dementia in the T2DM population.

1.5.2 Newer Generation of Antidiabetic Medication

Since the older generation of antidiabetic medications showed the potential to decrease the risk of dementia, there has been increased concern regarding the newer generation of antidiabetic medications.

DPP-4i, also known as gliptins, was first approved by the FDA in 2006. DPP-4 is a transmembrane protein that degrades the GLP-1 hormone, which plays an important role in maintaining glucose levels by preventing GLP-1 from binding to its receptor and exerting its action.[77] DPP-4i reduces blood glucose by inhibiting the activity of DPP-4, thus increasing the GLP-1 levels and stimulating insulin secretion to further decrease blood glucose.[78]

A cross-sectional study performed in China, including a 1229 Chinese elderly population, demonstrates that hyperactivity of DPP-4 contributes to accelerated cognitive decline and lower Montreal cognitive assessment (MoCA) score.[79] In preclinical studies, DPP-4i has demonstrated the ability to decrease the Aβ levels, Tau phosphorylation, and neuroinflammation in the mice brain.[80,81]

Epidemiological studies demonstrate the consistent result that DPP-4i can decrease the risk of dementia. In a retrospective longitudinal study including 240 T2DM patients, DPP-4i showed slower cognitive decline, specifically in executive and attention region.[82]

As a newer generation of antidiabetic medication, DPP-4i has been compared to the older generation of antidiabetic medication. In a case-control study utilizing the FDA Adverse Event

Reporting System (FAERS), sitagliptin had a superior ability to reduce AD risk compared to metformin monotherapy.[83]

SGLT2 inhibitors are the newest generation of antidiabetic medications approved in 2013. SGLT2 inhibitors block the activity of SGLT2 expressed in the proximal tubule of the kidneys, thus inhibiting the reabsorption of the glucose and increasing its excretion, ultimately reducing blood glucose. In the mice model, SGLT2 inhibitors have shown the ability to reduce the Aβ accumulation and Tau phosphorylation, as well as enhance the hippocampal-dependent cognitive, memory, and learning functions. Although the observational studies are still limited, there is a retrospective cohort study using the Canadian insurance database that demonstrated the ability of SGLT2 inhibitors to reduce the incidence of dementia in the T2DM population.[84]

1.5.3 GLP-1 RA

GLP-1 RA, another antidiabetic medication initially approved in 2005, has been designated as the second-line therapeutic intervention for T2DM. Currently, the majority of the FDA-approved GLP-1 RAs are administered through injection, except for the oral drug semaglutide, which was approved in 2019.

GLP-1 RAs mimic the action of the natural incretin hormone GLP-1 by binding it to the GLP-1 receptor. This activation leads to increased insulin secretion, enhanced insulin sensitivity, and inhibition of glucagon secretion, all of which contribute to better control of blood glucose levels in T2DM patients. Moreover, as incretin-based medications, GLP-1 RAs also have shown promising effectiveness in reducing blood glucose, cardiovascular diseases, and kidney disease.[85,86]

Furthermore, the presence of GLP-1 neurotransmitter receptors has been identified in the central nervous systems such as the hippocampus and brainstem, highlighting their potential significance in memory and learning.[87] Preclinical studies substantiated that GLP-1 RA can attenuate dementia-related pathologies by restoring vascular integrity, reducing neuroinflammation, and alleviating oxidative stress in the brain.[88,89] Although GLP-1 RA showed a promising effect in preclinical studies, the clinical studies focused on GLP-1 RAs remain restricted[90], limited to one case-control study and a retrospective cohort study.[91,92] The effectiveness of GLP-1 RA compared to all other anti-diabetic medications in reducing dementia risk is still unclear.

2.0 Aim of this Project

This project aimed to determine whether the use of the GLP-1 RA was associated with a lower probability of all-cause dementia incidence compared to all other antidiabetic medications.

3.0 Methods

This section aims to provide detailed information on the methods used in this study.

3.1 Data Source

Funded by the National Institute on Aging (NIH), the National Alzheimer's Coordinating Center (NACC) longitudinal database was first established in 1999. In 2005, NIH assigned NACC to develop a standardized protocol, Uniformed Data Set (UDS), which collected data from over 42 Alzheimer's Disease Research Centers (ADRCs) across the United States.[93] Each ADRC has a distinct protocol for recruiting participants, but all ADRCs are administered standardized evaluation forms and obtain consent from all participants or their representatives. Each participant provided demographic characteristics, medical history, family history, physical and neurological examinations, clinician diagnoses, and medication utilization during each visit annually.[94] The uniformed dataset (UDS) version 3.0 was used in this study.[95] Detailed information on UDS is available at http://www.alz.washington.edu.

3.2 Study Design

This retrospective cohort study included all type 2 diabetes participants in the NACC dataset from June 2005 to December 2022 (n=6,994).

Patients who did not report the use of antidiabetic medications (n=3,119), had dementia at the index date (n=664), had a history of dementia (n=49), or had no available follow-ups (n=129) were excluded from this study. We further grouped the participants into GLP-1 RA users or non-users based on reported medication exposure. Other medications include the use of metformin, insulin, TZD, sulfurylases, DPP-4i, and SGLT2 inhibitors. The index date was defined as the earliest date of reported antidiabetic medication use (Figure 1).

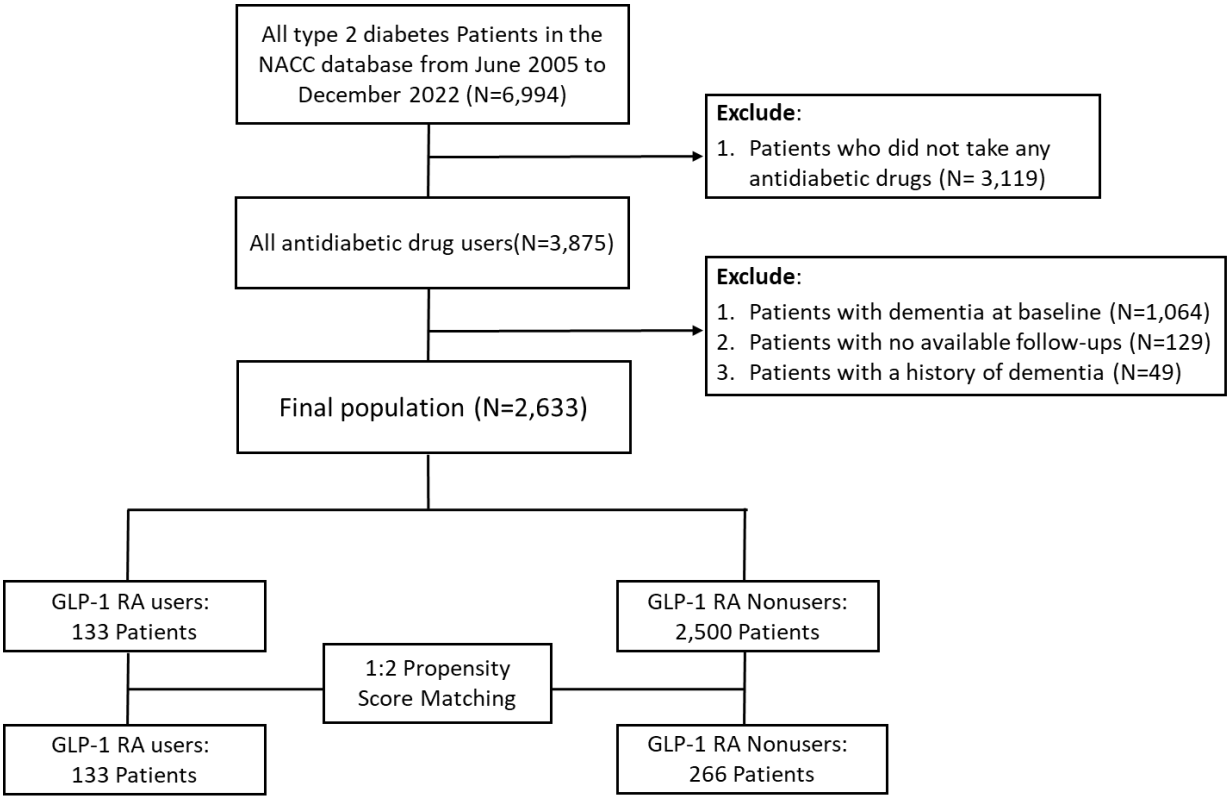

Figure 1: Population selection criteria for this cohort. Patients who meet all inclusion and exclusion criteria are included in this study.

All patients with T2DM will be included in this study, which includes 133 GLP-1 RA users and 2500 GLP-1 RA Nonusers. After 1:2 propensity score matching, the final cohort consisted of 133 GLP-1 RA users and 266 GLP-1 RA nonusers.

3.3 Outcome Definition

This study recruited an intention-to-treat approach. The outcome of this study is time to the new onset of all-cause dementia. The incidence of all-cause dementia was identified by professional clinicians when participants met the all-cause dementia criteria under the UDS coding guidelines.[96] The censoring date was determined as the end of the follow-ups or the end of the study.

3.4 Statistical Analysis

Baseline Characteristics were presented as mean with standard deviation (SD) for continuous variables, while percentages along with the total number of participants were presented for categorical variables. To assess the balance of baseline covariates, two-sample *t*-tests were used for continuous variables, while two-tailed chi-square tests or Fisher's exact tests were applied for categorical variables.

Propensity score matching (PSM), using a 1:2 greedy nearest neighbor approach, was performed based on participants' demographic information, genetic profiles, prior comorbidities, and medication usage, including metformin, insulin, DPP-4I, TZD, SGLT2 inhibitors, and sulfonylureas, as well as the length of their follow-up periods. A *p*-value less than 0.05 was considered as statistically significant difference between the two groups.

The Kaplan-Meier (KM) survival analysis was performed to visualize and compare the probability of dementia incidents over time between the GLP-1 RA users and non-users. The log-

rank test was used to assess the difference between probability curves and a conventional threshold $p<0.05$ was used to identify the significance in this analysis.

The multivariate Cox proportional regression model was conducted to identify significant risk predictors related to dementia incidents. Adjusted hazard ratio (aHR) was obtained with 95% Confidence Intervals (CI), and risk factors were identified when *p*-value <0.05. All statistical analyses were performed by SAS 9.4 (SAS Institute lnc., Cary, NC, USA).

3.4.1 Propensity Score Matching

Randomized clinical trials (RCTs), distinguished by their rigorous study design, are widely acknowledged as the standard approach for estimating the treatment effects, exposures, or interventions on outcomes. RCTs ensure the allocation of the treatments is randomized, minimizing the potential for confounding by the unmeasured or measured baseline characteristics.[97]

While RCTs are considered the gold standard, their costliness and potential ethical issues in patient recruitment make them unfeasible to all studies. Observational studies, or nonrandomized studies, are gaining more interest in studying the treatment effects.

However, in observational studies, the treatment prescriptions are usually defined by the patient's baseline characteristics. Therefore, systemic differences in baseline characteristics between untreated and treated patients may result in confounding results.

Propensity score, initially introduced by Rosenbaum and Rubin, is a balancing metric used to ensure the similarity of baseline covariates distribution between treated and untreated groups.[98] In other words, patients with the same propensity score are expected to exhibit a similar distribution of baseline covariates.

PSM, one of the common methods used to balance the baseline covariates, enables the Average Treatment Effect on Treated (ATT) estimation. Treated patients are matched to untreated patients based on similar propensity scores to reduce the bias.[99]

In this study, we utilized the greedy nearest neighbor propensity score matching. This approach involves matching treated subjects with untreated subjects based on the closest scores until all treated subjects have been paired according to the predefined ratio.[100]

3.4.2 Kaplan-Meier Analysis

KM analysis, first introduced in 1958 by Edward L. Kaplan and Paul Meier, provides methods for analyzing time-to-event observational data.[101] KM curves are particularly useful for comparing survival functions between two or more groups. Moreover, KM provides a visual presentation of survival functions, or probabilities, over time, making them effective and important tools in evaluating the difference between groups.

The log-rank test is the most commonly used test in KM analysis to determine whether two groups have statistically significant differences in survival outcomes. This test calculates the chi-square at each time point where an event occurs and then sums these values together as the final result.[102] Conventionally, a *p*-value less than 0.05 will be considered as a significant difference between the two groups.

Although KM is a widely accepted and valuable method, it does have limitations. Firstly, KM does not provide the estimation of the relative risk, which is important in evaluating the magnitude of the difference between groups.[103] Secondly, KM only considers treatment as the independent variable and does not account for other potential confounders that may bias the

result.[104] Due to the existence of these limitations, a multivariate cox regression model was further applied to check the result.

3.4.3 Cox regression Model

The Cox regression model, first introduced by David Cox as an extension of KM, incorporates patients' characteristics into the model.[105] This model is a semiparametric method, meaning it does not assume the survival times distribution.[106]

The Cox regression model provides HR and 95% CI for each variable included in the model. In binary variables (e.g., female vs male), HR represents the two hazard rates ratio of the outcome. In continuous variables (e.g., age), HR represents the hazard rate change magnitude.[107]

The multivariate Cox regression model used in this study involves including all covariates simultaneously. This means that when evaluating the effect of one covariate, all other covariates are controlled during the analysis. Like KM analysis, *p*-values less than 0.05 were identified as statistically significant. HRs larger than 1 indicate a higher risk toward the outcome or event, while HRs less than 1 indicate a lower risk, as the reference level is always set to 1.[108]

4.0 Result

This section aimed to demonstrate the result generated from the statistical analysis.

4.1 Baseline Characteristics

The unmatched population identified 2,633 patients with an average follow-up of 53.2 months, of which 133 were GLP1 RA users and 2,500 were non-users. GLP-1 RA users vs. non-users were significantly younger (69.3 vs. 72.1), with higher co-prescription of insulin (27.8% vs. 17.7%) and SGLT2 inhibitors (7.5% vs. 0.8%). GLP1 non-users, on the other hand, exhibit a greater prevalence of hypertension (76.4% vs. 42.1%), hypercholesterolemia (75.4% vs. 42.1%), and were more likely to be living alone (31.5% vs. 22.6%). PSM was performed to balance the baseline covariates between two groups based on a 1 to 2 ratio, which indicated each user was matched to 2 non-users based on their propensity scores. The matched population consisted of 133 GLP-1 RA users and 266 non-users, with females representing 53.88% of this population, and a mean age of 68.8 (SD:8.2). All baseline covariates were balanced after PSM, evidenced by *p*-value greater than 0.05. All characteristics of baseline covariates are summarized in Table 1.

Table 1: Baseline characteristics for GLP-1 RA users and non-users

	Before Matching			After Matching		
	GLP-1 user (N=133)	GLP1 Non-user (N=2500)	p-value	GLP-1 user (N=133)	GLP1 Non-user (N=266)	p-value
Patient Characteristics						
Age(years) mean (sd)	69.3(6.7)	72.1(8.1)	**<0.0001***	69.3(6.7)	68.2(8.9)	0.19
Female	57.9(77)	55.3(1383)	0.56	57.9 (77)	51.9(138)	0.26
Lives alone	22.6(30)	31.5(787)	**0.03***	22.6(30)	21.8(58)	0.86
2 copies of E4 alleles	24.8(33)	26.5(663)	0.66	24.8(33)	25.2(67)	0.93
Comorbidities						
Hypertension	45.9(61)	76.4(1911)	**<0.0001***	45.9(61)	43.9(117)	0.72
Hypercholesterolemia	42.1(56)	75.4(1876)	**<0.0001***	42.1(56)	43.3(126)	0.93
Depression	12.9(17)	16.8(419)	0.23	12.9(17)	18.4(49)	0.15
Other Antidiabetic Medications						
Metformin	72.9(97)	69.4(1736)	0.39	72.9(97)	71.8(191)	0.81
Sulfonylureas	24.8(33)	31.2(779)	0.12	24.8(33)	24.8(66)	1.0
Thiazolidinediones	7.5(10)	11.6(289)	0.15	7.5(10)	5.0(24)	0.61
DPP-4 inhibitors	3.8(5)	7.5(188)	0.10	3.8(5)	2.6(7)	0.19
Insulin	27.8(37)	17.7(442)	**0.003***	27.8(37)	22.9(61)	0.29
SGLT2 inhibitors	7.5(10)	0.8(21)	**<0.0001***	7.5(10)	5.26(14)	0.37

Note: *p<0.05. Categorical variables are presented as percentages followed by number of participants. Continuous variables are presented as mean and sd (standard deviation).

4.2 Kaplan Meier Analysis

Over a mean follow-up of 45.0 months, 70 participants (17.5%) were newly identified with the incidence of all-cause dementia in this study. The average time to dementia in the GLP-1 RA user group is 42.3 months, compared to 39.2 months in non-users. The KM curve was conducted to analyze and visualize the difference in dementia incident probability over time.

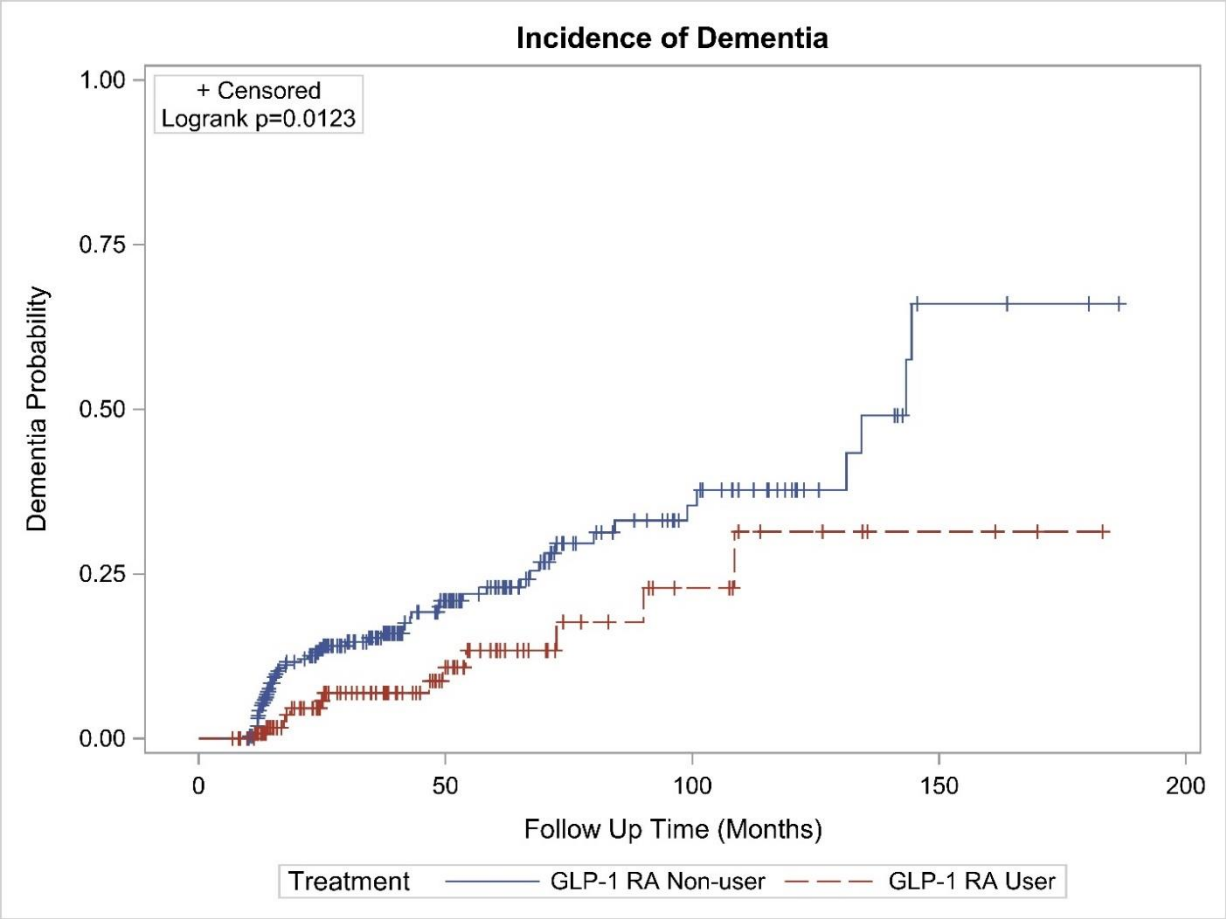

Figure 2: Kaplan-Meier curves for GLP-1 users and non-users. This figure demonstrated the dementia probability of two groups after a 1:2 propensity score matching.

4.3 Cox Regression Model

The multivariate Cox regression model was conducted to identify the risk factors associated with dementia while controlling for other confounding variables. The result demonstrated that age (aHR: 1.07, 95%CI: [1.03-1.10], p<0.0001), depression (aHR: 3.30, 95%CI: [1.86-5.81], p<0.0001), and 2 copies of AEOP4 genes (aHR: 2.44, 95%CI: [1.45-4.11], p=0.0008)

were associated with a higher risk of developing dementia. GLP-1 RA usage (aHR: 0.42, 95%CI: [0.22-0.80], p=0.009), and female (aHR: 0.50, 95%CI: [0.29-0.85], p=0.01) contributed to lower the risk of dementia over time. The comprehensive multivariate Cox regression results are summarized in Table 2.

Table 2: Multivariate Cox regression Model with HR and 95% CI after 1:2 propensity score matching

	Multivariate		
	HR	95% CI	p-value
Patient Characteristics			
Age	1.07	1.03-1.10	**<0.0001***
Female	0.50	0.29-0.87	**0.01***
Livs Alone	0.57	0.28-1.15	0.12
2 copies of E4 alleles	2.24	1.43-4.09	**0.0009***
Comorbidities			
Hypertension	1.36	0.79-2.32	0.27
Hypercholesterolemia	0.82	0.48-1.39	0.46
Depression	3.30	1.87-5.84	**<0.0001***
Antidiabetic drug use			
GLP-1 RA	0.42	0.22-0.80	**0.009***
Metformin	1.26	0.66-2.42	0.48
Sulfonylureas	1.27	0.71-2.27	0.42
Thiazolidines	1.47	0.67-3.26	0.34
DPP-4 inhibitors	2.84	0.78-10.35	0.11
Insulin	1.64	0.84-3.19	0.15
SGLT2 inhibitors	0.40	0.05-3.16	0.39

Note: *p<0.05. Abbreviation: HR, hazard ratio; CI, confidence interval; GLP-1 RA, Glucogan-like peptide-1 Receptor Agonist; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT2 inhibitors, Sodium-glucose cotransporter-2 inhibitors.

5.0 Discussion

Our study demonstrated that GLP-1 RA users, compared to non-users, were associated with a reduced probability of developing dementia in the type 2 diabetes population. Over up to the 186.5 months of follow-up, GLP-1 RA users showed a 60% lower risk of dementia compared to the non-users.

5.1 Mechanism of GLP-1 RA and Dementia

Although the clear mechanism of how GLP-1 RA reduces dementia incidents is not fully understood, some potential mechanisms could explain the relationship.

5.1.1 GLP-1

GLP-1 receptor is a peptide hormone composed of 30 amino acids, synthesized in both the intestinal and the CNS.[109] In the brain, GLP-1 can be produced by the nucleus tractus solitaries (NTS), and then transported to other regions such as the hypothalamus, cortical cortex, and thalamic.[110]

GLP-1 receptor part of the B class G-protein coupled receptor family demonstrates high affinity and plays a crucial role in most of the actions attributed to GLP-1.[111] GLP-1 receptor was identified to be expressed in CNS, including dendrite and cell body of the hippocampus to extensively affect the neurological activities, synapse plasticity, and cognitive functions.[111-113]

GLP-1 has the ability to cross the BBB and actively participate in brain activities. After GLP-1 binds to its receptor, it activates the insulin signaling pathway. This activation leads to an augmentation of the signaling cascade, subsequently enhancing brain insulin sensitivity.[109]

5.1.2 GLP-1 RA

GLP-1 RA, one of the newer generations of antidiabetic medications, was first approved in 2005 by FDA. GLP-1 RA works by mimicking the action of GLP-1, inhibiting glucagon secretion, stimulating insulin secretion, and enhancing insulin sensitivity in the brain.[114]

Recently, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (RASD) recommended that GLP-1 RA can be used as the first-line therapy based on patients' preference, particularly for those who wish to avoid hypoglycemia.[115,116] In addition, GLP-1 RA has demonstrated a superior ability to reduce blood glucose without causing severe hypoglycemia.[117,118]

5.1.3 GLP-1 RA and Dementia

Due to increasing importance and better glucose control ability, the GLP-1 RAs gained more focus in preclinical studies.[117,118] In preclinical studies, GLP-1 RAs have shown the ability to enhance insulin sensitivity and insulin-signaling pathways, exerting the neuroprotective function.[119,120] This ability is also attributed to their capacity to inhibit the generation of reactive oxygen species (ROS) induced by advanced glycation end products (AGEs), suppress neuroinflammation, and enhance mitochondrial capability. These actions ultimately contribute to the rescue of neuronal cells from death.[121-124]

Second, GLP-1 RAs exhibit potential in mitigating key pathological features of AD, including the reduction of Aβ peptide accumulation and the suppression of Tau hyperphosphorylation and aggregation—crucial biomarkers in AD induced by the impaired insulin signaling pathway.[125] In vivo studies have demonstrated that GLP-1 RA can protect vessels from Aβ-induced damage and lesions in APP/PS1 mice.[126] A meta-analysis, incorporating 26 preclinical papers assessing GLP-1 RAs' impact on Aβ deposition and tau phosphorylation, revealed their effectiveness in reducing Aβ plaques and p-Tau levels.[127] Liraglutide, an approved GLP-1 RA, displayed diminished plaques in the cortex region, reduced inflammatory response, elevated young neuron counts in the dentate gyrus, and suppressed tau hyperphosphorylation.[128,129]

Additionally, exenatide and dulaglutide, two other GLP-1 RAs, also exhibit the ability to reduce the Aβ plaque accumulation and tau phosphorylation.[130-132] These findings collectively suggest that GLP-1 RAs hold promise in alleviating dementia, offering a potential avenue for therapeutic intervention.

5.2 Significant Factors Contribute to Dementia

In addition to GLP-1 RAs, our findings also demonstrated the significant impact of age, the presence of two pairs of APOE4 genes, and depression on the risk of developing dementia risk, which aligns with previous studies.

5.2.1 Age

Age, a well-established risk factor, notably elevates the vulnerability to dementia, particularly in individuals aged 65 and older.[9] The significance of this age-related risk is widely acknowledged in dementia research.

In our study, the Cox regression model provided an HR exceeding 1 (HR=1.07) with a corresponding *p*-value below 0.05 ($p<0.0001$). This finding suggests that age is significantly associated with a heightened dementia risk, consistent with prior research. Specifically, our results indicate that for each additional year of age, patients experience a 7 percent higher likelihood of developing dementia.

5.2.2 Depression

Depression emerges as a notable risk factor, significantly contributing to the likelihood of developing dementia, which is also demonstrated as a risk factor in this study.

Depression is a serious mood disorder that will affect patients' daily lives, or even lead to suicidal activities if left untreated. Recently, more studies have been focused on the association between depression and dementia incidents, and most of the studies demonstrate the consistent result that depression will increase the risk of dementia.[133,134]

The Cox regression model, in our study, revealed an HR of 3.30, accompanied by a p-value below 0.0001. This implies that individuals with depression are at more than a three-fold increased risk of developing dementia.

5.2.3 APOE4 Genes

APOE4 genes stand out as the strongest genetic factor for developing dementia and can be used as a biomarker to determine disease susceptibility.[135] Around 40% of demented patients carry at least one pair of APOE4 genes[136], and the risk of dementia can increase up to 12-fold in those carrying two pairs of genes.[137] Our study demonstrated that participants with 2 pairs of APOE4 genes will increase the dementia risk by 2-fold.

Our investigation also delved into gender disparities in dementia risk beyond genetic considerations.

5.2.4 Sex

Previous studies emphasized females as a dementia risk factor.[138] Interestingly, our findings presented an unexpected twist—males exhibit a higher risk. Remarkably, this observation aligns with a previous NACC database study, raising the possibility that divergent data structures may contribute to the observed sex differences in dementia risk.[139]

5.3 Strengths of this Study

Our study had several strengths. First, there is a scarcity of research focusing on evaluating the impact of GLP-1 RAs, which leaves a knowledge gap on whether GLP-1 RA could be a promising treatment option for the T2DM population concerning dementia risk.[90] While both the Danish case-control study and a retrospective analysis using Medicare data suggest an association

between GLP-1 RA use and a reduced incidence of dementia, it's crucial to note that these studies employed logistic regression methods, potentially introducing bias by not accounting for the time between drug use and the incidence date.[91,92] Moreover, the 2022 ADA Standards of Medical Care in Diabetes recommend GLP-1 receptor agonists as a first-line treatment for type 2 diabetes due to their superior glycemic efficacy.[30] Consistent guidelines have been adopted by the American Association of Clinical Endocrinologists and the American College of Endocrinology since 2020, emphasizing the utilization of GLP-1 RAs as the preferred first-line therapy.[140] Given the increasing significance of GLP-1 RAs as a primary antidiabetic drug and the established correlation between T2DM and dementia, there exists a notable gap in the current literature concerning the comparative impact of GLP-1 RAs against all other available medications. To the best of our knowledge, our study is the first to compare the impact of GLP-1 RAs to all other medications on dementia risk.

Second, our study applies PSM to mitigate potential bias. Considering the potential for selection bias in the use of GLP-1 RAs in the T2DM population and acknowledging the inherent biases in observational studies, we implemented PSM to address these challenges. PSM is used to systematically balance all covariates that may act as potential confounders. PSM enhances the comparability between two groups by aligning participants based on treatment likelihood similarity.[100] This approach reduces selection bias, bolstering the study's reliability in assessing the beneficial impact of GLP-1 RAs.

Moreover, the NACC database was designed for AD and related dementia research and assesses cognitive status during each visit, providing standardized clinical diagnoses across all ADRC centers[93]. This systematic approach reduces challenges in dementia diagnosis faced in primary care, where reliance on clinician judgment, brief interactions, and concurrent conditions

can complicate the process.[141] By applying standardized criteria, NACC maximized consistency and accuracy, meanwhile minimizing the likelihood of delayed dementia detection and diagnostic bias.[142]

5.4 Limitations of this Study

Our study is also subject to limitations. First, the nature structure of the NACC database may lead to selection bias for this study. The NACC database was originally designed for studying mental diseases related to dementia, and relies on voluntary participation and self-reporting, introducing selection bias. Participants who choose to enroll in this study may exhibit heightened concerns or early manifestations of cognitive decline, potentially limiting the generalizability of our findings to the broader population.

Second, the NACC data lack laboratory baseline data, such as Hemoglobin A1C (Hb1AC), creatinine levels, or glomerular filtration rate (GFR). These variables could be considered unmeasured confounders, potentially influencing medication prescribing decisions.[30]

Thirdly, we were unable to control lifestyle factors such as body mass index (BMI) and smoking status, both of which are risk factors for dementia as demonstrated in some studies. This suggests the presence of additional potential confounders.

Finally, this database lacks the refill information, which makes the measurement of drug adherence infeasible.

5.5 Clinical Implications and Further Directions

Our observational study demonstrates that GLP-1 RAs can reduce the risk of dementia in individuals with T2DM. These findings highlight a proactive approach to mitigating cognitive dysfunction in susceptible populations, underscoring the need for further investigation through rigorous clinical trials to confirm their neuroprotective effects.

6.0 Conclusion

In conclusion, this retrospective cohort study indicated that GLP-1 RA users had a lower risk of developing dementia than non-users over a mean follow-up of 45 months. It is crucial to note that this study establishes an association rather than a causative relationship. Thus, further studies are warranted.

Bibliography

1. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol.* 2013;12(4):357-367.

2. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *New England Journal of Medicine.* 2012;367(9):795-804.

3. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years. *Journal of Neuropathology & Experimental Neurology.* 2011;70(11):960-969.

4. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2023;19(4):1598-1695.

5. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol.* 2017;134(2):171-186.

6. Brenowitz WD, Hubbard RA, Keene CD, et al. Mixed neuropathologies and estimated rates of clinical progression in a large autopsy sample. *Alzheimers Dement.* 2017;13(6):654-662.

7. Jellinger KA, Attems J. Prevalence of dementia disorders in the oldest-old: an autopsy study. *Acta Neuropathol.* 2010;119(4):421-433.

8. Kawas CH, Kim RC, Sonnen JA, Bullain SS, Trieu T, Corrada MM. Multiple pathologies are common and related to dementia in the oldest-old: The 90+ Study. *Neurology.* 2015;85(6):535-542.

9. Guerreiro R, Bras J. The age factor in Alzheimer’s disease. *Genome Medicine.* 2015;7(1):106.

10. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. *Neuron.* 2012;76(1):116-129.

11. Watt JA, Goodarzi Z, Veroniki AA, et al. Comparative Efficacy of Interventions for Aggressive and Agitated Behaviors in Dementia: A Systematic Review and Network Meta-analysis. *Ann Intern Med.* 2019;171(9):633-642.

12. Nelson PT, Head E, Schmitt FA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol.* 2011;121(5):571-587.

13. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nature Genetics.* 2022;54(4):412-436.

14. Loy CT, Schofield PR, Turner AM, Kwok JB. Genetics of dementia. *Lancet.* 2014;383(9919):828-840.

15. Holtzman DM, Herz J, Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. *Cold Spring Harb Perspect Med.* 2012;2(3):a006312.

16. Lautenschlager NT, Cupples LA, Rao VS, et al. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? *Neurology.* 1996;46(3):641-650.

17. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 2020;396(10248):413-446.

18. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS One.* 2015;10(3):e0118333.

19. Ogino E, Manly JJ, Schupf N, Mayeux R, Gu Y. Current and past leisure time physical activity in relation to risk of Alzheimer's disease in older adults. *Alzheimers Dement.* 2019;15(12):1603-1611.

20. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of Physical Activity on Cognitive Decline, Dementia, and Its Subtypes: Meta-Analysis of Prospective Studies. *Biomed Res Int.* 2017;2017:9016924.

21. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord.* 2011;25(4):289-304.

22. Walker ME, O'Donnell AA, Himali JJ, et al. Associations of the Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay diet with cardiac remodelling in the community: the Framingham Heart Study. *Br J Nutr.* 2021;126(12):1888-1896.

23. Shannon OM, Ranson JM, Gregory S, et al. Mediterranean diet adherence is associated with lower dementia risk, independent of genetic predisposition: findings from the UK Biobank prospective cohort study. *BMC Medicine.* 2023;21(1):81.

24. Zhao R, Han X, Zhang H, et al. Association of vitamin E intake in diet and supplements with risk of dementia: A meta-analysis. *Frontiers in Aging Neuroscience.* 2022;14.

25. Ghahremani M, Smith EE, Chen HY, Creese B, Goodarzi Z, Ismail Z. Vitamin D supplementation and incident dementia: Effects of sex, APOE, and baseline cognitive status. *Alzheimers Dement (Amst).* 2023;15(1):e12404.

26. Kuźma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: A systematic review and meta-analysis. *Alzheimers Dement.* 2018;14(11):1416-1426.

27. Lennon MJ, Lam BCP, Lipnicki DM, et al. Use of Antihypertensives, Blood Pressure, and Estimated Risk of Dementia in Late Life: An Individual Participant Data Meta-Analysis. *JAMA Netw Open.* 2023;6(9):e2333353.

28. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the Evidence on the Association between Serum Cholesterol and Risk of Late-Life Dementia: Review and Meta-Analysis. *J Alzheimers Dis.* 2017;56(1):215-228.

29. Dove A, Shang Y, Xu W, et al. The impact of diabetes on cognitive impairment and its progression to dementia. *Alzheimer's & Dementia.* 2021;17(11):1769-1778.

30. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. *Diabetes Care.* 2022;46(Supplement_1):S140-S157.

31. Mack LR, Tomich PG. Gestational Diabetes: Diagnosis, Classification, and Clinical Care. *Obstet Gynecol Clin North Am.* 2017;44(2):207-217.

32. Banks WA, Jaspan JB, Huang W, Kastin AJ. Transport of insulin across the blood-brain barrier: saturability at euglycemic doses of insulin. *Peptides.* 1997;18(9):1423-1429.

33. Banks WA, Jaspan JB, Kastin AJ. Selective, physiological transport of insulin across the blood-brain barrier: novel demonstration by species-specific radioimmunoassays. *Peptides.* 1997;18(8):1257-1262.

34. Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. *Nature.* 1978;272(5656):827-829.

35. Ghasemi R, Haeri A, Dargahi L, Mohamed Z, Ahmadiani A. Insulin in the brain: sources, localization and functions. *Mol Neurobiol.* 2013;47(1):145-171.

36. Freiherr J, Hallschmid M, Frey WH, 2nd, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs.* 2013;27(7):505-514.

37. Zhao W, Chen H, Xu H, et al. Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J Biol Chem.* 1999;274(49):34893-34902.

38. Craft S, Stennis Watson G. Insulin and neurodegenerative disease: shared and specific mechanisms. *The Lancet Neurology.* 2004;3(3):169-178.

39. Banks WA, Owen JB, Erickson MA. Insulin in the brain: There and back again. *Pharmacology & Therapeutics.* 2012;136(1):82-93.

40. Ketterer C, Tschritter O, Preissl H, Heni M, Häring H-U, Fritsche A. Insulin sensitivity of the human brain. *Diabetes Research and Clinical Practice.* 2011;93:S47-S51.

41. Cetinkalp S, Simsir IY, Ertek S. Insulin resistance in brain and possible therapeutic approaches. *Curr Vasc Pharmacol.* 2014;12(4):553-564.

42. Benedict C, Hallschmid M, Schultes B, Born J, Kern W. Intranasal insulin to improve memory function in humans. *Neuroendocrinology.* 2007;86(2):136-142.

43. Verdile G, Keane KN, Cruzat VF, et al. Inflammation and Oxidative Stress: The Molecular Connectivity between Insulin Resistance, Obesity, and Alzheimer's Disease. *Mediators of Inflammation.* 2015;2015:105828.

44. Huang J, van Zijl PCM, Han X, et al. Altered d-glucose in brain parenchyma and cerebrospinal fluid of early Alzheimer's disease detected by dynamic glucose-enhanced MRI. *Sci Adv.* 2020;6(20):eaba3884.

45. Sutherland K, Li T, Cao C. Alzheimer's disease and the immune system. *SOJ Neurol.* 2015;2(1):1-11.

46. Ng A, Tam WW, Zhang MW, et al. IL-1β, IL-6, TNF-α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. *Scientific reports.* 2018;8(1):12050.

47. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. *J Clin Invest.* 2017;127(1):1-4.

48. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu Rev Nutr.* 2005;25:391-406.

49. Kim B, Feldman EL. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. *Exp Mol Med.* 2015;47(3):e149.

50. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. *Neurobiol Aging.* 2010;31(2):224-243.

51. Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, Gong CX. Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. *J Pathol.* 2011;225(1):54-62.

52. Schubert M, Gautam D, Surjo D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci U S A.* 2004;101(9):3100-3105.

53. Iqbal K, Liu F, Gong CX, Alonso Adel C, Grundke-Iqbal I. Mechanisms of tau-induced neurodegeneration. *Acta Neuropathol.* 2009;118(1):53-69.

54. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harb Perspect Biol.* 2014;6(1).

55. Xie L, Helmerhorst E, Taddei K, Plewright B, Van Bronswijk W, Martins R. Alzheimer's beta-amyloid peptides compete for insulin binding to the insulin receptor. *J Neurosci.* 2002;22(10):Rc221.

56. Crane PK, Walker R, Hubbard RA, et al. Glucose Levels and Risk of Dementia. *New England Journal of Medicine.* 2013;369(6):540-548.

57. Chatterjee S, Peters SA, Woodward M, et al. Type 2 Diabetes as a Risk Factor for Dementia in Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than 100,000 Cases of Dementia. *Diabetes Care.* 2016;39(2):300-307.

58. Candasamy M, Mohamed Elhassan SA, Kumar Bhattamisra S, et al. Type 3 diabetes (Alzheimer's disease): new insight for promising therapeutic avenues. *Panminerva Med.* 2020;62(3):155-163.

59. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? *Diabetologia.* 2013;56(9):1898-1906.

60. Markowicz-Piasecka M, Sikora J, Szydłowska A, Skupień A, Mikiciuk-Olasik E, Huttunen KM. Metformin - a Future Therapy for Neurodegenerative Diseases : Theme: Drug Discovery, Development and Delivery in Alzheimer's Disease Guest Editor: Davide Brambilla. *Pharm Res.* 2017;34(12):2614-2627.

61. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clin Sci (Lond).* 2012;122(6):253-270.

62. Nesti L, Natali A. Metformin effects on the heart and the cardiovascular system: A review of experimental and clinical data. *Nutr Metab Cardiovasc Dis.* 2017;27(8):657-669.

63. Wang C, Yu JT, Miao D, Wu ZC, Tan MS, Tan L. Targeting the mTOR signaling network for Alzheimer's disease therapy. *Mol Neurobiol.* 2014;49(1):120-135.

64. Liao W, Xu J, Li B, Ruan Y, Li T, Liu J. Deciphering the Roles of Metformin in Alzheimer’s Disease: A Snapshot. *Frontiers in Pharmacology.* 2022;12.

65. Campbell JM, Stephenson MD, de Courten B, Chapman I, Bellman SM, Aromataris E. Metformin Use Associated with Reduced Risk of Dementia in Patients with Diabetes: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease.* 2018;65:1225-1236.

66. Wu CY, Iskander C, Wang C, et al. Association of sulfonylureas with the risk of dementia: A population-based cohort study. *J Am Geriatr Soc.* 2023;71(10):3059-3070.

67. Sola D, Rossi L, Schianca GP, et al. Sulfonylureas and their use in clinical practice. *Arch Med Sci.* 2015;11(4):840-848.

68. Alkabbani W, Maxwell CJ, Marrie RA, Tyas SL, Lega IC, Gamble JM. Hypoglycaemia and the risk of dementia: a population-based cohort study using exposure density sampling. *Int J Epidemiol.* 2023;52(3):908-920.

69. Seaquist ER, Miller ME, Fonseca V, et al. Effect of thiazolidinediones and insulin on cognitive outcomes in ACCORD-MIND. *Journal of Diabetes and its Complications.* 2013;27(5):485-491.

70. Zhao H, Zhuo L, Sun Y, Shen P, Lin H, Zhan S. Thiazolidinedione use is associated with reduced risk of dementia in patients with type 2 diabetes mellitus: A retrospective cohort study. *Journal of Diabetes.* 2023;15(2):97-109.

71. Unger JW, Betz M. Insulin receptors and signal transduction proteins in the hypothalamo-hypophyseal system: a review on morphological findings and functional implications. *Histol Histopathol.* 1998;13(4):1215-1224.

72. Werther GA, Hogg A, Oldfield BJ, et al. Localization and characterization of insulin receptors in rat brain and pituitary gland using in vitro autoradiography and computerized densitometry. *Endocrinology.* 1987;121(4):1562-1570.

73. Spinelli M, Fusco S, Mainardi M, et al. Brain insulin resistance impairs hippocampal synaptic plasticity and memory by increasing GluA1 palmitoylation through FoxO3a. *Nat Commun.* 2017;8(1):2009.

74. Moult PR, Harvey J. Hormonal regulation of hippocampal dendritic morphology and synaptic plasticity. *Cell Adh Migr.* 2008;2(4):269-275.

75. Long C, Han X, Yang Y, Li T, Zhou Q, Chen Q. Efficacy of intranasal insulin in improving cognition in mild cognitive impairment or dementia: a systematic review and meta-analysis. *Frontiers in Aging Neuroscience.* 2022;14.

76. Alkabbani W, Maxwell CJ, Marrie RA, Tyas SL, Lega IC, Gamble J-M. Insulin Use in Type 2 Diabetes and the Risk of Dementia: A Comparative Population-Based Cohort Study. *Diabetes Care.* 2023;46(8):1492-1500.

77. Röhrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. *Front Immunol.* 2015;6:386.

78. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. *J Diabetes Investig.* 2010;1(1-2):8-23.

79. Chen B, Zheng T, Qin L, et al. Strong Association between Plasma Dipeptidyl Peptidase-4 Activity and Impaired Cognitive Function in Elderly Population with Normal Glucose Tolerance. *Front Aging Neurosci.* 2017;9:247.

80. Chen S, Zhou M, Sun J, et al. DPP-4 inhibitor improves learning and memory deficits and AD-like neurodegeneration by modulating the GLP-1 signaling. *Neuropharmacology.* 2019;157:107668.

81. Kosaraju J, Holsinger RMD, Guo L, Tam KY. Linagliptin, a Dipeptidyl Peptidase-4 Inhibitor, Mitigates Cognitive Deficits and Pathology in the 3xTg-AD Mouse Model of Alzheimer's Disease. *Mol Neurobiol.* 2017;54(8):6074-6084.

82. Rizzo MR, Barbieri M, Boccardi V, Angellotti E, Marfella R, Paolisso G. Dipeptidyl peptidase-4 inhibitors have protective effect on cognitive impairment in aged diabetic patients with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci.* 2014;69(9):1122-1131.

83. Akimoto H, Negishi A, Oshima S, et al. Antidiabetic Drugs for the Risk of Alzheimer Disease in Patients With Type 2 DM Using FAERS. *Am J Alzheimers Dis Other Demen.* 2020;35:1533317519899546.

84. Wu CY, Iskander C, Wang C, et al. Association of Sodium-Glucose Cotransporter 2 Inhibitors With Time to Dementia: A Population-Based Cohort Study. *Diabetes Care.* 2023;46(2):297-304.

85. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.

86. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* 2021;9(10):653-662.

87. Heppner KM, Kirigiti M, Secher A, et al. Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (Macaca mulatta) brain. *Endocrinology.* 2015;156(1):255-267.

88. Zheng J, Xie Y, Ren L, et al. GLP-1 improves the supportive ability of astrocytes to neurons by promoting aerobic glycolysis in Alzheimer's disease. *Mol Metab.* 2021;47:101180.

89. Bailey J, Coucha M, Bolduc DR, et al. GLP-1 receptor nitration contributes to loss of brain pericyte function in a mouse model of diabetes. *Diabetologia.* 2022;65(9):1541-1554.

90. Wu C-Y, Shapiro L, Ouk M, et al. Glucose-lowering drugs, cognition, and dementia: The clinical evidence. *Neuroscience & Biobehavioral Reviews.* 2022;137:104654.

91. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. *Eur J Endocrinol.* 2019;181(5):499-507.

92. Zhou B, Zissimopoulos J, Nadeem H, Crane MA, Goldman D, Romley JA. Association between exenatide use and incidence of Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions.* 2021;7(1):e12139.

93. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set. *Alzheimer Dis Assoc Disord.* 2007;21(3):249-258.

94. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers. *Alzheimer Dis Assoc Disord.* 2006;20(4):210-216.

95. Besser L, Kukull W, Knopman DS, et al. Version 3 of the National Alzheimer's Coordinating Center's Uniform Data Set. *Alzheimer Dis Assoc Disord.* 2018;32(4):351-358.

96. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):263-269.

97. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology.* 1999;10(1):37-48.

98. ROSENBAUM PR, RUBIN DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70(1):41-55.

99. Imbens GW. Nonparametric Estimation of Average Treatment Effects Under Exogeneity: A Review. *The Review of Economics and Statistics.* 2004;86(1):4-29.

100. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res.* 2011;46(3):399-424.

101. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association.* 1958;53(282):457-481.

102. Rich JT, Neely JG, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan-Meier curves. *Otolaryngol Head Neck Surg.* 2010;143(3):331-336.

103. Stel VS, Dekker FW, Tripepi G, Zoccali C, Jager KJ. Survival analysis I: the Kaplan-Meier method. *Nephron Clin Pract.* 2011;119(1):c83-88.

104. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Testing for causality and prognosis: etiological and prognostic models. *Kidney Int.* 2008;74(12):1512-1515.

105. Cox DR. Regression Models and Life-Tables. *Journal of the Royal Statistical Society: Series B (Methodological).* 1972;34(2):187-202.

106. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. *Br J Cancer.* 2003;89(3):431-436.

107. Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. *Antimicrob Agents Chemother.* 2004;48(8):2787-2792.

108. Abd ElHafeez S, D'Arrigo G, Leonardis D, Fusaro M, Tripepi G, Roumeliotis S. Methods to Analyze Time-to-Event Data: The Cox Regression Analysis. *Oxid Med Cell Longev.* 2021;2021:1302811.

109. Yildirim Simsir I, Soyaltin UE, Cetinkalp S. Glucagon like peptide-1 (GLP-1) likes Alzheimer's disease. *Diabetes Metab Syndr.* 2018;12(3):469-475.

110. Calsolaro V, Edison P. Novel GLP-1 (Glucagon-Like Peptide-1) Analogues and Insulin in the Treatment for Alzheimer's Disease and Other Neurodegenerative Diseases. *CNS Drugs.* 2015;29(12):1023-1039.

111. Thorens B, Porret A, Bühler L, Deng S-P, Morel P, Widmann C. Cloning and Functional Expression of the Human Islet GLP-1 Receptor: Demonstration That Exendin-4 Is an Agonist and Exendin-(9–39) an Antagonist of the Receptor. *Diabetes.* 1993;42(11):1678-1682.

112. Campbell Jonathan E, Drucker Daniel J. Pharmacology, Physiology, and Mechanisms of Incretin Hormone Action. *Cell Metabolism.* 2013;17(6):819-837.

113. Hölscher C. Potential Role of Glucagon-Like Peptide-1 (GLP-1) in Neuroprotection. *CNS Drugs.* 2012;26(10):871-882.

114. Amori RE, Lau J, Pittas AG. Efficacy and Safety of Incretin Therapy in Type 2 DiabetesSystematic Review and Meta-analysis. *JAMA.* 2007;298(2):194-206.

115. Committee ADAPP. Summary of Revisions: Standards of Care in Diabetes—2024. *Diabetes Care.* 2023;47(Supplement_1):S5-S10.

116. Davies MJ, Aroda VR, Collins BS, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2022;45(11):2753-2786.

117. Latif W, Lambrinos KJ, Rodriguez R. Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs). In: *StatPearls.* Treasure Island (FL) ineligible companies. Disclosure: Katerina Lambrinos declares no relevant financial relationships with ineligible companies.

118. Meloni AR, DeYoung MB, Lowe C, Parkes DG. GLP-1 receptor activated insulin secretion from pancreatic β-cells: mechanism and glucose dependence. *Diabetes Obes Metab.* 2013;15(1):15-27.

119. Hölscher C. Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models. *Neuropharmacology.* 2018;136(Pt B):251-259.

120. Lv M, Xue G, Cheng H, et al. The GLP-1/GIP dual-receptor agonist DA5-CH inhibits the NF-κB inflammatory pathway in the MPTP mouse model of Parkinson's disease more

effectively than the GLP-1 single-receptor agonist NLY01. *Brain Behav.* 2021;11(8):e2231.

121. Athauda D, Foltynie T. The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. *Drug Discovery Today.* 2016;21(5):802-818.

122. Perry T, Lahiri DK, Chen D, et al. A Novel Neurotrophic Property of Glucagon-Like Peptide 1: A Promoter of Nerve Growth Factor-Mediated Differentiation in PC12 Cells. *Journal of Pharmacology and Experimental Therapeutics.* 2002;300(3):958-966.

123. Morales PE, Torres G, Sotomayor-Flores C, et al. GLP-1 promotes mitochondrial metabolism in vascular smooth muscle cells by enhancing endoplasmic reticulum-mitochondria coupling. *Biochem Biophys Res Commun.* 2014;446(1):410-416.

124. Yoon G, Kim YK, Song J. Glucagon-like peptide-1 suppresses neuroinflammation and improves neural structure. *Pharmacol Res.* 2020;152:104615.

125. Reich N, Hölscher C. The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: An in-depth review. *Frontiers in Neuroscience.* 2022;16.

126. Kelly P, McClean PL, Ackermann M, Konerding MA, Hölscher C, Mitchell CA. Restoration of cerebral and systemic microvascular architecture in APP/PS1 transgenic mice following treatment with Liraglutide™. *Microcirculation.* 2015;22(2):133-145.

127. Kong F, Wu T, Dai J, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: a systematic review and meta-analysis of preclinical studies. *Frontiers in Pharmacology.* 2023;14.

128. McClean PL, Jalewa J, Hölscher C. Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice. *Behavioural Brain Research.* 2015;293:96-106.

129. Jantrapirom S, Nimlamool W, Chattipakorn N, et al. Liraglutide Suppresses Tau Hyperphosphorylation, Amyloid Beta Accumulation through Regulating Neuronal Insulin Signaling and BACE-1 Activity. *Int J Mol Sci.* 2020;21(5).

130. Wang X, Wang L, Jiang R, Xu Y, Zhao X, Li Y. Exendin-4 antagonizes Aβ1-42-induced attenuation of spatial learning and memory ability. *Exp Ther Med.* 2016;12(5):2885-2892.

131. Zhou M, Chen S, Peng P, et al. Dulaglutide ameliorates STZ induced AD-like impairment of learning and memory ability by modulating hyperphosphorylation of tau and NFs through GSK3β. *Biochemical and Biophysical Research Communications.* 2019;511(1):154-160.

132. Yang Y, Ma D, Xu W, et al. Exendin-4 reduces tau hyperphosphorylation in type 2 diabetic rats via increasing brain insulin level. *Mol Cell Neurosci.* 2016;70:68-75.

133. Roberto Fernández Fernández, M.D. ,, Javier Ibias Martín, Ph.D. ,, María Araceli Maciá Antón, Ph.D. Depression as a Risk Factor for Dementia: A Meta-Analysis. *The Journal of Neuropsychiatry and Clinical Neurosciences.*0(0):appi.neuropsych.20230043.

134. Yu O-C, Jung B, Go H, Park M, Ha I-H. Association between dementia and depression: a retrospective study using the Korean National Health Insurance Service-National Sample Cohort database. *BMJ Open.* 2020;10(10):e034924.

135. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Jama.* 1997;278(16):1349-1356.

136. Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat Rev Neurosci.* 2009;10(5):333-344.

137. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol.* 2021;20(1):68-80.

138. Beam CR, Kaneshiro C, Jang JY, Reynolds CA, Pedersen NL, Gatz M. Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease. *J Alzheimers Dis.* 2018;64(4):1077-1083.

139. Wang G, Li W. Sex as a Risk Factor for Developing Cognitive Impairments in National Alzheimer's Coordinating Center Participants. *J Alzheimers Dis Rep.* 2021;5(1):1-6.

140. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2020 Executive Summary. *Endocrine Practice.* 2020;26(1):107-139.

141. Brayne C, Fox C, Boustani M. Dementia screening in primary care: is it time? *Jama.* 2007;298(20):2409-2411.

142. Qiu S, Joshi PS, Miller MI, et al. Development and validation of an interpretable deep learning framework for Alzheimer's disease classification. *Brain.* 2020;143(6):1920-1933.