

Risk of Parkinson's Disease (PD) in patients with diabetes using thiazolidinedione (TZD): A systematic review, meta-analysis, and meta-regression

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ABSTRACT

Background. Parkinson's Disease (PD) stands as the neurodegenerative disorder with the second highest incidence, leading to substantial disability and death rates. Research to date suggests a potential increased risk for PD development in individuals with diabetes, yet the correlation between PD and the use of antidiabetic drugs remains to be fully understood. This study aims to investigate the relationship between thiazolidinedione (TZD) use with the risk of PD in patients with diabetes.

Methods. A search of literature was carried out using certain keywords across four databases up until December 11th, 2022: Europe PMC, Scopus, Medline, and Cochrane Library. The review included all studies assessing the risk of Parkinson's Disease (PD) in patients with diabetes who were treated with thiazolidinediones (TZDs). The pooled risk ratios (RRs) with 95% confidence intervals (CIs) were determined using random-effects models.

Results. Our meta-analysis from 12 observational studies revealed that TZD use was associated with reduced risk of PD in patients with diabetes (RR 0.75; 95%CI: 0.63 – 0.91, $p=0.003$, $I^2 = 92\%$). The neuroprotective impact of thiazolidinediones (TZDs) against Parkinson's Disease (PD) did not show significant variation based on patient characteristics like age ($p=0.3380$), gender ($p=0.9761$), hypertension ($p=0.1849$), smokers ($p=0.1476$), stroke ($p=0.4810$), head injury ($p=0.5025$), and diabetes duration ($p=0.2533$).

Conclusions. This study suggests that the use of TZD in patients with diabetes has a positive neuroprotective effect on the risk of PD. However, to validate these results, further randomized clinical trials (RCTs) are necessary

Keywords: Parkinson's Disease, neurodegenerative, thiazolidinedione, antidiabetic, diabetes

List of abbreviations

AD – Alzheimer's disease

COX-2 – Cyclooxygenase-2

DM – Diabetes mellitus

DPP-4 – Dipeptidyl peptidase-4

GLP-1 – Glucagon-like peptide-1

IL-6 – Interleukin 6

iNOS – inducible nitric oxide

JNK – Jun N-terminal kinase

MAPK – Mitogen-activated protein kinase

MOOSE – Meta-analysis of Observational Studies in Epidemiology

MPP+ – N-methyl-4-phenylpyridinium

NF- κ B – Nuclear factor- κ B

NOS – Newcastle-Ottawa Scale

PD – Parkinson's Disease

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT – Randomized clinical trials

RR – Risk ratio

SGLT 2 – Sodium-glucose transporter-2

SOD – Superoxide dismutase

TNF- α – Tumor necrosis factor- α

TZD – Thiazolidinedione

T2DM – Type 2 diabetes mellitus

WHO – World Health Organization

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INTRODUCTION

Parkinson's disease (PD) is a long-term, neurodegenerative disorder marked by the loss of dopaminergic neurons in the substantia nigra [1]. These neurons produce the neurotransmitter dopamine which works in regulating muscle movement and body balance [1]. Reduced dopamine production will result in the loss of voluntary movement control over time [1]. Parkinson's disease (PD) stands as the second most prevalent neurodegenerative condition, following Alzheimer's disease (AD) [2,3]. The prevalence of this disease increases with age with a peak age of 60-70 years [2,3]. According to the data from the World Health Organization (WHO), the prevalence of PD has doubled in the last 25 years [4]. PD is estimated to affect more than 8.5 million individuals in 2019 with 5.8 million disability-adjusted life years and 329 thousand deaths [4]. This illustrates that PD has caused not only a health burden but also a social and economic burden around the world [4]. Therefore, the search for effective treatments and means of prevention is important to reduce these burdens.

Several well-known risk factors such as genetic susceptibility, age, exposure to pesticides, and head injury have been shown to increase the likelihood of developing PD [2,5]. On the other hand, tobacco smoking, consumption of coffee and caffeine, as well as physical activity can reduce the risk of developing PD [2,5]. Besides those factors, recent meta-analyses have also found that diabetes mellitus may be associated with an increased risk of PD [6,7]. This is hypothesized to be related to overlapping risk factors between DM and PD, such as age which is the main risk factor for both DM and PD [8,9]. In addition, both DM and PD are associated with chronic inflammation which plays an important role in the pathophysiology of the disease [8,9]. The next question that arises is whether antidiabetic drugs can also affect the risk of PD in the population of diabetes. Existing literature regarding antidiabetic agents, especially thiazolidinediones (TZD) on the risk of PD is still scarce and shows conflicting results. A study by Rhee SY et al. [10] showed that all antidiabetic medications, including TZD, significantly increased the risk of developing PD, whereas the study by Brauer et al [11] found no significant association between the use of TZD and the incidence of PD. On the other hand, in their study of 62,400 patients with type 2 diabetes mellitus (T2DM), Zhao H et al. [12] has demonstrated a reduced incidence of PD in the group using TZD as their antidiabetic agent. Considering the varied outcomes, our goal was to investigate the relationship between the use of thiazolidinedione (TZD) and the incidence of Parkinson's Disease (PD) in individuals with diabetes.

MATERIALS AND METHODS

Eligibility criteria

This systematic review and meta-analysis were conducted in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Studies qualified for inclusion in this review based on a set inclusion criteria structured around the PECOS approach, detailed as follows: (1) the population consisted of individuals with diabetes mellitus (DM) without a PD diagnosis at study initiation; (2) the exposure was the use of thiazolidinediones (TZDs) as the antidiabetic treatment; (3) the control group included patients without a history of TZD use but who were on alternative antidiabetic therapies (such as metformin, sulfonylureas, glinides, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, or insulin); (4) the outcome was the occurrence of PD; (5) the study design encompassed clinical trials and observational studies (including cohort, case-control, or cross-sectional studies). Studies were excluded from this review if one or more of the following exclusion criteria were present: (1) studies in a population of patients with Parkinson's Disease (PD); (2) studies assessing the effect of antidiabetic agents on the disease course and outcome of PD; (3) studies that are not available in full-text form; (4) case-series and case-reports; (5) non-primary research.

Search strategy and study selection

The literature searching process was conducted for articles published in English up to December 11th, 2022 using 4 databases: Europe PMC, Scopus, Medline, and Cochrane Library. The keywords used for searching the literature were as follows: "(thiazolidinediones OR glitazones OR pioglitazone OR rosiglitazone OR troglitazone) AND (diabetes OR diabetes mellitus OR DM OR type 1 diabetes OR T1D OR type 2 diabetes OR T2D) AND (Parkinson disease OR Parkinson's Disease OR PD)". The search methods applied for each database are outlined in Supplementary Table 1. Initially, two reviewers assessed articles by their titles and abstracts, eliminating any duplicates. Subsequent full-text evaluations were based on specific inclusion and exclusion guidelines. In cases of discrepancy, a third independent reviewer was consulted to reach a consensus.

Data extraction

Two independent reviewers conducted the data retrieval process to gather key details from the selected studies as follows: name of the authors, country of study, publication year, study design, number of samples, duration of follow-up, and characteristics of study participants (age, gender, duration of DM, hy-

TABLE 1. Baseline characteristics of the included studies

Study	Country	Design	Sample size	Follow up time (years)	DM duration (years)	Age (years)	Male (%)	HTN (%)	Smokers (%)	Stroke (%)	Head injury (%)
Brakedal B et al. [17] 2017	Norway	Retrospective cohort	102,745	6.9 ± 2	7.1 ± 3.3	64.1	54.9%	N/A	N/A	N/A	N/A
Brauer R et al. [18] 2015	UK	Retrospective cohort	164,970	5.2 ± 3.7	7.8 ± 3.5	63.3	56.5%	N/A	65.7%	N/A	3.2%
Brauer R et al. [11] 2020	UK	Retrospective cohort	59,568	3.4 ± 3	4.3 ± 4.1	63.5	59.6%	62.6%	66.3%	7.8%	3.9%
Chang YH et al. [19] 2021	Taiwan	Retrospective cohort	48,828	N/A	5.8 ± 4.4	57.9	56.3%	68.3%	N/A	6.6%	N/A
Connolly JG et al. [20] 2015	USA	Retrospective cohort	29,397	2.9 ± 1.6	N/A	78.5	27.1%	72.7%	N/A	9.1%	N/A
Deisinger C et al. [21] 2021	Austria	Retrospective cohort	177,315	N/A	N/A	64.3	60.7%	72.2%	9.8%	N/A	N/A
Lin HL et al. [22] 2018	Taiwan	Retrospective cohort	38,521	6.2 ± 4.4	N/A	54.6	54.2%	N/A	N/A	12.2%	N/A
Rhee SY et al. [10] 2020	South Korea	Retrospective cohort	1,308,089	6.3 ± 3.2	4.7 ± 3.9	60.4	56.6%	6.4%	21.5%	2.7%	N/A
Sunnarborg K et al. [23] 2022	Finland	Case-control	9,951	N/A	10.6 ± 1.3	63	59.8%	42.3%	N/A	N/A	1.3%
Tseng CH et al. [24] 2018	Taiwan	Retrospective cohort	22,022	2.9 years	6.4 ± 2.7	58.7	56.8%	80.5%	4.2%	21%	3.2%
Wu HF et al. [25] 2018	Taiwan	Retrospective cohort	15,812	5 years	N/A	61.2	46.7%	53.6%	N/A	18%	4.3%
Zhao H et al. [12] 2022	China	Retrospective cohort	62,400	6 ± 4.2	N/A	60.6	47.8%	N/A	30.6%	N/A	N/A

DM = diabetes mellitus; HTN = hypertension; N/A = not available

Supplementary TABLE 1. Literature search strategy

1A. Medline and Europe PMC Search String:

“(thiazolidinediones OR glitazones OR pioglitazone OR rosiglitazone OR troglitazone) AND (diabetes OR diabetes mellitus OR DM OR type 1 diabetes OR T1D OR type 2 diabetes OR T2D) AND (Parkinson disease OR Parkinson’s Disease OR PD)”

1B. Example Scopus and Cochrane Library Search Strategy:

- | | |
|-----------------------|--|
| 1. thiazolidinediones | 11. type 2 diabetes |
| 2. glitazones | 12. T2D |
| 3. pioglitazone | 13. Parkinson disease |
| 4. rosiglitazone | 14. Parkinson’s Disease |
| 5. troglitazone | 15. PD |
| 6. diabetes | 16. 1 or 2 or 3 or 4 or 5 |
| 7. diabetes mellitus | 17. 6 or 7 or 8 or 9 or 10 or 11 or 12 |
| 8. DM | 18. 13 or 14 or 15 |
| 9. type 1 diabetes | 19. 16 and 17 and 18 |
| 10. T1D | |

pertension, smokers, stroke, and head injury), the number of participants in the exposure group, the number of participants in the control group, and the outcome of interest in each group.

Risk of bias assessment

Two independent reviewers conducted a risk of bias assessment of the included studies using an appropriate and validated tool. The Newcastle-Ottawa Scale (NOS) served to gauge the quality of the observational studies included, which covered three areas of assessment: the selection of participants for the study, the comparability between groups, and the determination of outcomes in each study. Each study

could score anywhere from 0 to 9, with studies achieving a score of 7 or above being classified as good quality research [15].

Statistical analysis

The incidence of Parkinson’s Disease (PD), which was the primary outcome of interest in this study, was reported in the form of a risk ratio (RR) along with its 95% confidence interval (95% CI) by using the Mantel-Haenszel formula. The random-effect model was chosen in this study because heterogeneity was expected due to different participant characteristics, study design, and time points on which the follow-up was performed. Heterogeneity between studies was

695 Records identified through database searching

386 Europe PMC

193 Scopus

101 Medline

15 Cochrane Library

695 Records screened

668 Records excluded on the basis of title and abstract and duplicates removed

27 Full-text articles assessed for eligibility

15 Full-text articles excluded, with reasons

7 Were review articles

5 Not in human subjects

3 No outcome of interest

12 Studies included in qualitative synthesis

12 Studies included in quantitative synthesis (meta-analysis)

FIGURE 1. PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis

assessed using I-squared (I²) statistics where values <25%, 26-50%, and >50% were considered as low, moderate, and high heterogeneity, respectively [16]. A meta-regression using a random-effects model was conducted with a restricted-maximum likelihood, focusing on specific variables like age, gender, hypertension, smoking status, history of stroke, head injuries, and the duration of diabetes. This was done to explore the interactive effect of TZD use with these factors on the occurrence of PD. If over 10 studies were combined in the meta-analysis, a funnel plot was utilized to evaluate publication bias. All the analyses for this research were executed using the Review Manager 5.4 from Cochrane Collaboration and the Comprehensive Meta-Analysis 3 software.

RESULTS

Study selection and characteristics

The literature searching process on four databases resulted in a total of 695 studies. After removing the duplicates and screening the studies based on the titles/abstracts, 668 studies were excluded and leaving 27 studies for full-text assessment. Of these 27 studies, 15 studies were further excluded due to the following reasons: 7 studies were review articles, 5 studies were not done in human subjects, and 3 studies did not have data on the outcome of interest. Ulti-

mately, there were 12 studies [10-12,17-25] included in the review which encompassed a total of 2,039,618 patients with diabetes mellitus (Figure 1). Of these 12 studies, 11 studies were retrospective cohorts while the remaining 1 study was a case-control study. Four of the included studies came from Taiwan, two studies from the United Kingdom (UK), and one study each from Norway, the United States of America (USA), Austria, South Korea, Finland, and China. The mean follow-up time within the included studies ranged from 2.9 to 6.9 years. More details regarding the baseline characteristics of the included studies can be seen in Table 1.

Quality of study assessment

Based on the risk of bias assessment using the NOS tool, all included studies were having good quality, so they were considered worthy of being included in the meta-analysis (Table 2).

Incidence of Parkinson's Disease (PD)

Our meta-analysis based on 12 observational studies showed that the use of thiazolidinediones (TZD) as antidiabetic agents in patients with diabetes mellitus (DM) was associated with a lower risk of developing Parkinson's disease (PD) when compared with other antidiabetic agents (RR 0.75; 95%CI: 0.63

TABLE 2. Newcastle-Ottawa quality assessment of observational studies

First author, year	Study design	Selection ^a	Comparability ^b	Outcom ^c	Total score	Result
Brakedal B et al. [17] 2017	Cohort	***	**	***	8	Good
Brauer R et al. [18] 2015	Cohort	***	**	***	8	Good
Brauer R et al. [11] 2020	Cohort	***	**	***	8	Good
Chang YH et al. [19] 2021	Cohort	***	**	**	7	Good
Connolly JG et al. [20] 2015	Cohort	***	**	***	8	Good
Deischinger C et al. [21] 2021	Cohort	***	**	**	7	Good
Lin HL et al. [22] 2018	Cohort	***	**	***	8	Good
Rhee SY et al. [10] 2020	Cohort	***	**	***	8	Good
Sunnarborg K et al. [23] 2022	Cohort	***	**	**	7	Good
Tseng CH et al. [24] 2018	Cohort	***	**	**	7	Good
Wu HF et al. [25] 2018	Cohort	***	**	**	7	Good
Zhao H et al. [12] 2022	Cohort	***	**	***	8	Good

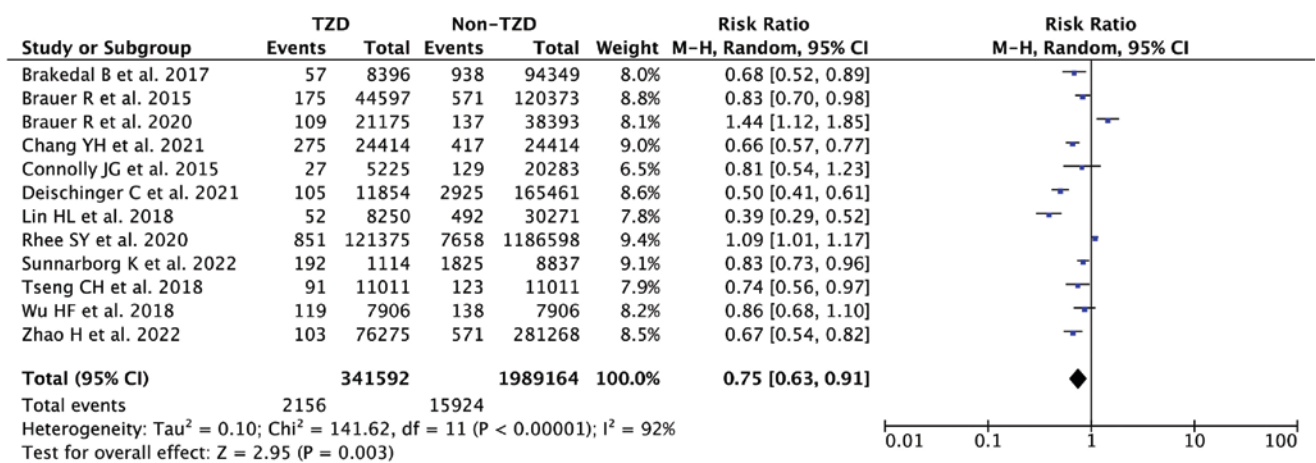
a(1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study

b(1) comparability of cohorts on the basis of design or analysis, (maximum two stars)

c(1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow up of cohorts

Supplementary TABLE 2. Results for the meta-regression models for incidence of Parkinson's Disease

Incidence of Parkinson's Disease					
Covariate	Coefficient	95% CI (min)	95% CI (max)	S.E.	p-value
Age	0.0181	-0.0189	0.0551	0.0189	0.3380
Gender	0.0004	-0.0236	0.0244	0.0122	0.9761
Hypertension	-0.0062	-0.0153	0.0030	0.0047	0.1849
Smokers	0.0081	-0.0029	0.0191	0.0056	0.1476
Stroke	-0.0188	-0.0713	0.0336	0.0267	0.4810
Head injury	0.0769	-0.1478	0.3015	0.1146	0.5025
Diabetes duration	-0.0570	-0.1549	0.0408	0.0499	0.2533

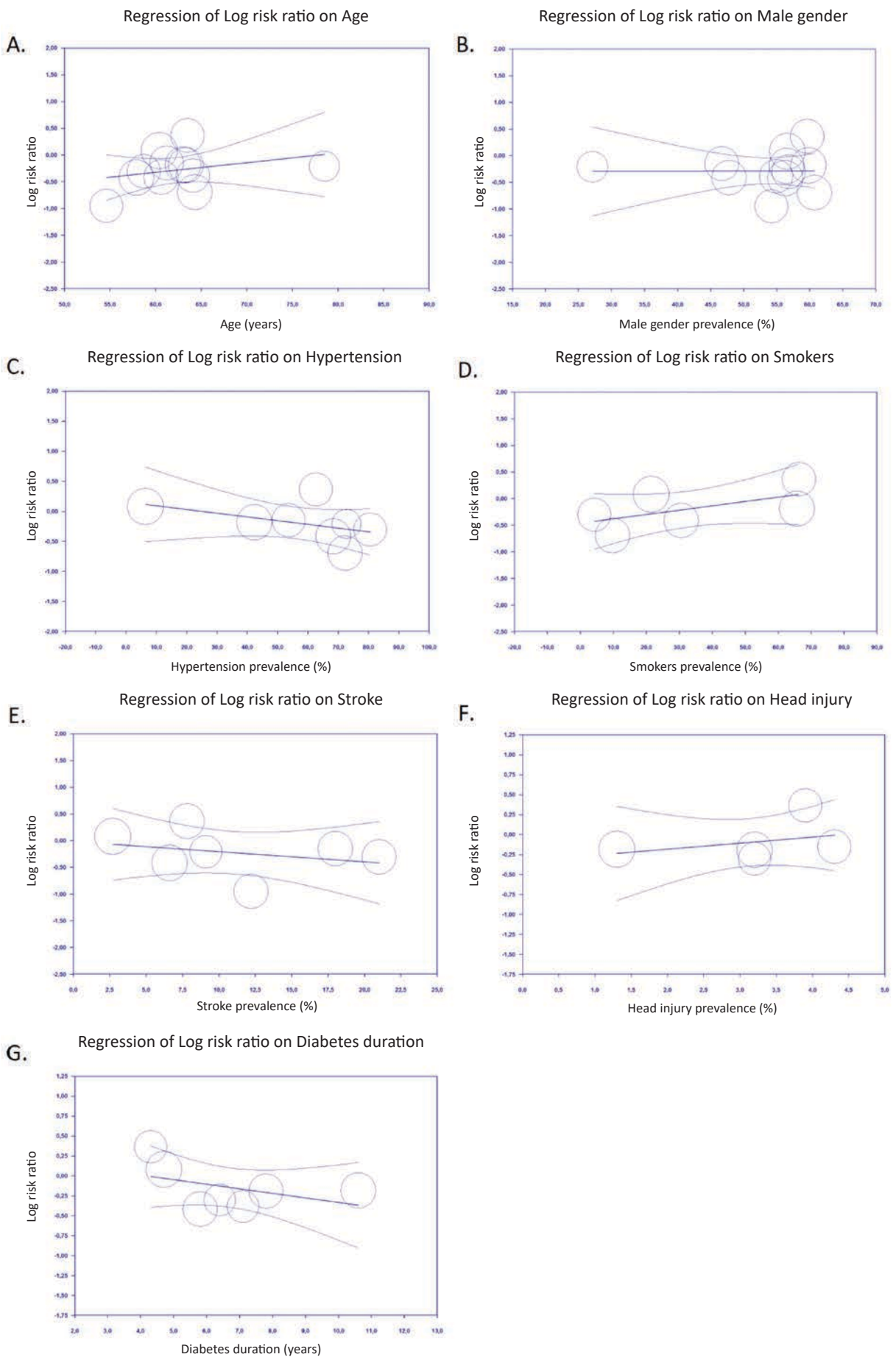
**FIGURE 2.** Forest plot that demonstrates the association between thiazolidinedione (TZD) use with the risk of Parkinson's Disease (PD) in patients with diabetes mellitus (DM)

- 0.91, p=0.003, I² = 92%, random-effect model) (Figure 2).

Meta-regression

Meta-regression was utilized to ascertain the risk factors that could potentially affect the correlation between the usage of thiazolidinedione (TZD) and the occurrence of Parkinson's Disease (PD). The

analysis indicated that the variation in PD occurrence among patients with diabetes mellitus who were on TZD therapy was not accounted for by established patient factors known to predict treatment outcomes, as detailed in Supplementary Table 2. From our meta-regression analysis, it was revealed that the incidence of PD in diabetes mellitus patients using TZD was not significantly influenced



SUPPLEMENTARY FIGURE 1. Bubble-plot for meta-regression. Meta-regression analysis showed that the association between thiazolidinedione (TZD) use and incidence of Parkinson’s Disease (PD) was not affected by age (A), gender (B), hypertension (C), smokers (D), stroke (E), head injury (F), nor diabetes duration (G)

by age ($p = 0.3380$) (Supplementary Figure 1A), gender ($p = 0.9761$) (Supplementary Figure 1B), hypertension ($p = 0.1849$) (Supplementary Figure 1C), smokers ($p = 0.1476$) (Supplementary Figure 1D), stroke ($p = 0.4810$) (Supplementary Figure 1E), head injury ($p = 0.5025$) (Supplementary Figure 1F), nor diabetes duration ($p = 0.2533$) (Supplementary Figure 1G).

Publication bias

We used Funnel plot analysis for the publication bias assessment. The resulting plot was fairly symmetrical when inverted for the incidence of Parkinson's Disease (refer to Figure 3), suggesting an absence of publication bias.

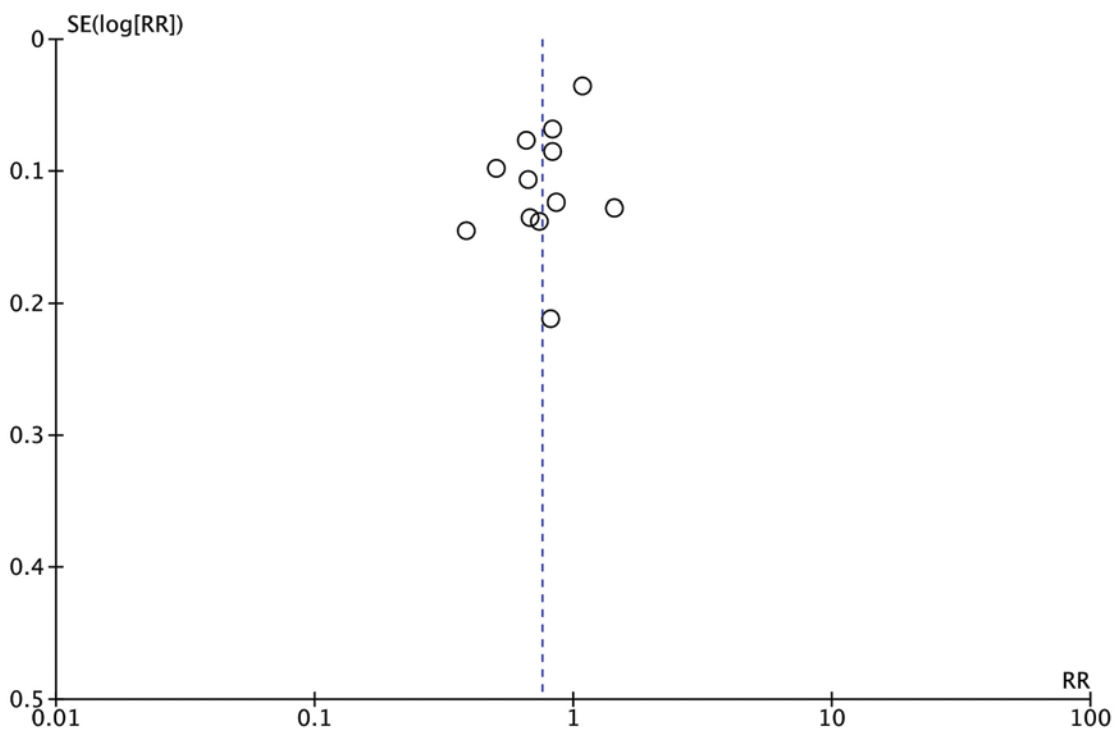


FIGURE 3. Relatively symmetrical inverted plot for the association between thiazolidinedione (TZD) use and risk of Parkinson's Disease (PD) which indicates no publication bias

DISCUSSION

Our meta-analysis from 12 observational studies has shown that the use of thiazolidinediones (TZD) as antidiabetic agents can reduce the risk of developing Parkinson's Disease (PD) in patients with diabetes mellitus (DM). Further regression analysis also showed that this relationship was generated independently and was not significantly influenced by other factors such as age, gender, hypertension, smokers, stroke, head injury, or diabetes duration.

Several hypotheses might explain why the use of TZD can reduce the risk of PD. One of the processes that underlie the occurrence of Parkinson's Disease (PD) is the presence of nerve damage mediated by microglia activation [26,27]. Thiazolidinediones

(TZD) may counter this mechanism by reducing astrogliosis and microglia activation [28]. Pioglitazone, one of the drugs which belong to TZD, can reduce the induction of cyclooxygenase-2 (COX-2), reduce the production of inducible nitric oxide (iNOS), and reduce phosphorylation of Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) so that the process of neuroinflammation in microglia can be inhibited [28-30]. Pioglitazone is also capable of inhibiting nuclear phosphorylation and translocation of the p65 subunit of nuclear factor- κ B (NF- κ B) where activation of NF- κ B itself contributes to the neurodegeneration seen in PD [28-30]. Two other drugs from the TZD class, namely rosiglitazone and troglitazone, are also able to produce neuroprotec-

tive effects on neurons and glia through inhibition of LPS-induced expression of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), iNOS, and COX-2 so that neuro-inflammatory processes can be reduced [28,31]. In addition to the anti-inflammatory effects on microglia, TZD is also able to produce anti-oxidant and anti-apoptotic effects on neurons which also play a significant role in the pathogenesis of PD [28]. TZD is able to induce the activity of the anti-oxidative enzyme superoxide dismutase (SOD) and catalase thereby protecting nerve cells from N-methyl-4-phenylpyridinium (MPP⁺)-induced cell death [28,32]. TZD is also able to increase the expression of anti-apoptotic BCL2 and reduce activation of Caspase-3 and BAX expression thereby preventing apoptosis of

nerve cells [33]. All of these mechanisms may explain the neuroprotective effect of TZD in preventing the incidence of PD.

The results of this study are in line with the previous meta-analysis by Hussain S et al. [34], which also showed that the use of thiazolidinediones (TZD) can reduce the risk of Parkinson's Disease (PD) in patients with diabetes. However, there are some significant differences between our current study with the previous study. The study by Hussain S et al. [34] only included a total of 5 studies with only 4 studies included in the final analysis, whereas in our study, there were a total of 12 studies (a 3-fold increase from the previous study) that were included in the final analysis, resulting in more solid evidence. Apart from that, in our current study, there is also an additional meta-regression analysis to identify several factors that could confound the relationship between TZD use and the risk of PD, something that was lacking in the previous study [34]. From the results of our regression analysis, it was found that the relationship between the use of TZD and reduced risk of PD was generated independently which was not significantly influenced by confounding factors such as age, gender, hypertension, smokers, stroke, head injury, or diabetes duration.

Our research still has some limitations. First, the evidence generated from our research only comes from observational studies which are very likely to be influenced by confounding factors as well as some biases, such as recall bias and information bias. In order to reduce the influence of confounding variables, a meta-regression analysis was performed. Additionally, there's notable variation in the study's outcome of interest, likely arising from varied follow-up times across studies and diverse baseline character-

istics of the studies' participants, such as the duration of diabetes and the period of TZD usage.

However, we believe that the results of our research can still have implications for clinical practice.

CONCLUSION

Our systematic review and meta-analysis showed that the use of thiazolidinediones (TZD) in patients with diabetes mellitus (DM) has a potential neuroprotective effect, potentially lowering the risk of Parkinson's Disease (PD). This advantageous impact of TZDs appears to be consistent regardless of patient characteristics like age, gender, or comorbid issues. Nonetheless, appropriate, and well-designed randomized clinical trials (RCTs) are still needed to validate the results of our study.

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Authors' contributions:

TIH and KCG concept the idea and design of the article. TIH analyzed the data of meta-analysis. KCG draft the manuscript. All authors read and approved the final manuscript.

Availability of data and materials: The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

REFERENCES

1. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA*. 2020 Feb 11;323(6):548-560. doi: 10.1001/jama.2019.22360.
2. Simon DK, Tanner CM, Brundin P. Parkinson Disease Epidemiology, Pathology, Genetics, and Pathophysiology. *Clin Geriatr Med*. 2020 Feb;36(1):1-12. doi: 10.1016/j.cger.2019.08.002.
3. Putri C, Hariyanto TI, Hananto JE, Christian K, Situmeang RFV, Kurniawan A. Parkinson's disease may worsen outcomes from coronavirus disease 2019 (COVID-19) pneumonia in hospitalized patients: A systematic review, meta-analysis, and meta-regression. *Parkinsonism Relat Disord*. 2021 Jun;87:155-161. doi: 10.1016/j.parkreldis.2021.04.019.
4. World Health Organization. Parkinson disease. 2022. Available from: <https://www.who.int/news-room/fact-sheets/detail/parkinson-disease>.
5. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol*. 2016 Nov;15(12):1257-72. doi: 10.1016/S1474-4422(16)30230-7.
6. Komici K, Femminella GD, Bencivenga L, Rengo G, Pagano G. Diabetes Mellitus and Parkinson's Disease: A Systematic Review and Meta-Analyses. *J Parkinsons Dis*. 2021;11(4):1585-96. doi: 10.3233/JPD-212725.
7. Liu W, Tang J. Association between diabetes mellitus and risk of Parkinson's disease: A prisma-compliant meta-analysis. *Brain Behav*. 2021 Aug;11(8):e02082. doi: 10.1002/brb3.2082.
8. Labandeira CM, Fraga-Bau A, Arias Ron D, Alvarez-Rodriguez E, Vicente-Alba P, Lago-Garma J, et al. Parkinson's disease and diabetes mellitus: common mechanisms and treatment repurposing. *Neural Regen Res*. 2022 Aug;17(8):1652-58. doi: 10.4103/1673-5374.332122.
9. Sergi D, Renaud J, Simola N, Martinoli MG. Diabetes, a Contemporary Risk for Parkinson's Disease: Epidemiological and Cellular Evidences. *Front Aging Neurosci*. 2019 Nov 8;11:302. doi: 10.3389/fnagi.2019.00302.
10. Rhee SY, Han KD, Kwon H, Park SE, Park YG, Kim YH, et al. Association Between Glycemic Status and the Risk of Parkinson Disease: A Nationwide Population-Based Study. *Diabetes Care*. 2020 Sep;43(9):2169-75. doi: 10.2337/dc19-0760.
11. Brauer R, Wei L, Ma T, Athauda D, Girges C, Vijaratnam N, et al. Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. *Brain*. 2020 Oct 1;143(10):3067-76. doi: 10.1093/brain/awaa262.
12. Zhao H, Zhuo L, Sun Y, Shen P, Lin H, Zhan S. Thiazolidinedione use and risk of Parkinson's disease in patients with type 2 diabetes mellitus. *NPJ Parkinsons Dis*. 2022 Oct 21;8(1):138. doi: 10.1038/s41531-022-00406-8.
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000 Apr 19;283(15):2008-12. doi: 10.1001/jama.283.15.2008.

14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71.
15. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003 Sep 6;327(7414):557-60. doi: 10.1136/bmj.327.7414.557.
17. Brakedal B, Flønes I, Reiter SF, Torkildsen Ø, Dølle C, Assmus J, et al. Glitazone use associated with reduced risk of Parkinson's disease. *Mov Disord*. 2017 Nov;32(11):1594-99. doi: 10.1002/mds.27128.
18. Brauer R, Bhaskaran K, Chaturvedi N, Dexter DT, Smeeth L, Douglas I. Glitazone Treatment and Incidence of Parkinson's Disease among People with Diabetes: A Retrospective Cohort Study. *PLoS Med*. 2015 Jul 21;12(7):e1001854. doi: 10.1371/journal.pmed.1001854.
19. Chang YH, Yen SJ, Chang YH, Wu WJ, Lin KD. Pioglitazone and statins lower incidence of Parkinson disease in patients with diabetes mellitus. *Eur J Neurol*. 2021 Feb;28(2):430-7. doi: 10.1111/ene.14542.
20. Connolly JG, Bykov K, Gagne JJ. Thiazolidinediones and Parkinson Disease: A Cohort Study. *Am J Epidemiol*. 2015 Dec 1;182(11):936-44. doi: 10.1093/aje/kwv109.
21. Deisinger C, Dervic E, Kaleta M, Klimek P, Kautzky-Willer A. Diabetes Mellitus is Associated with a Higher Relative Risk for Parkinson's Disease in Women than in Men. *J Parkinsons Dis*. 2021;11(2):793-800. doi: 10.3233/JPD-202486.
22. Lin HL, Lin HC, Tseng YF, Chao JC, Hsu CY. Association of thiazolidinedione with a lower risk of Parkinson's disease in a population with newly-diagnosed diabetes mellitus. *Ann Med*. 2018 Aug;50(5):430-6. doi: 10.1080/07853890.2018.1488083.
23. Sunnarborg K, Tiihonen M, Huovinen M, Koponen M, Hartikainen S, Tolppanen AM. Association between different diabetes medication classes and risk of Parkinson's disease in people with diabetes. *Pharmacoepidemiol Drug Saf*. 2022 Aug;31(8):875-882. doi: 10.1002/pds.5448.
24. Tseng CH. Pioglitazone Reduces Dementia Risk in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Analysis. *J Clin Med*. 2018 Sep 27;7(10):306. doi: 10.3390/jcm7100306.
25. Wu HF, Kao LT, Shih JH, Kao HH, Chou YC, Li IH, et al. Pioglitazone use and Parkinson's disease: a retrospective cohort study in Taiwan. *BMJ Open*. 2018 Aug 29;8(8):e023302. doi: 10.1136/bmjopen-2018-023302.
26. Carta AR, Pisanu A, Carboni E. Do PPAR-Gamma Agonists Have a Future in Parkinson's Disease Therapy? *Parkinsons Dis*. 2011;2011:689181. doi: 10.4061/2011/689181.
27. Gupta A, Dawson VL, Dawson TM. What causes cell death in Parkinson's disease? *Ann Neurol*. 2008 Dec;64 Suppl 2(0 2):S3-15. doi: 10.1002/ana.21573.
28. Ridder DA, Schwaninger M. In search of the neuroprotective mechanism of thiazolidinediones in Parkinson's disease. *Exp Neurol*. 2012 Dec;238(2):133-7. doi: 10.1016/j.expneurol.2012.08.012.
29. Xing B, Liu M, Bing G. Neuroprotection with pioglitazone against LPS insult on dopaminergic neurons may be associated with its inhibition of NF-kappaB and JNK activation and suppression of COX-2 activity. *J Neuroimmunol*. 2007 Dec;192(1-2):89-98. doi: 10.1016/j.jneuroim.2007.09.029.
30. Xing B, Xin T, Hunter RL, Bing G. Pioglitazone inhibition of lipopolysaccharide-induced nitric oxide synthase is associated with altered activity of p38 MAP kinase and PI3K/Akt. *J Neuroinflammation*. 2008 Jan 18;5:4. doi: 10.1186/1742-2094-5-4.
31. Luna-Medina R, Cortes-Canteli M, Alonso M, Santos A, Martínez A, Perez-Castillo A. Regulation of inflammatory response in neural cells in vitro by thiazolidinone derivatives through peroxisome proliferator-activated receptor gamma activation. *J Biol Chem*. 2005 Jun 3;280(22):21453-62. doi: 10.1074/jbc.M414390200.
32. Jung TW, Lee JY, Shim WS, Kang ES, Kim SK, Ahn CW, et al. Rosiglitazone protects human neuroblastoma SH-SY5Y cells against MPP+ induced cytotoxicity via inhibition of mitochondrial dysfunction and ROS production. *J Neurol Sci*. 2007 Feb 15;253(1-2):53-60. doi: 10.1016/j.jns.2006.11.020.
33. Martin HL, Mounsey RB, Mustafa S, Sathe K, Teismann P. Pharmacological manipulation of peroxisome proliferator-activated receptor γ (PPAR γ) reveals a role for anti-oxidant protection in a model of Parkinson's disease. *Exp Neurol*. 2012 Jun;235(2):528-38. doi: 10.1016/j.expneurol.2012.02.017.
34. Hussain S, Singh A, Baxi H, Taylor B, Burgess J, Antony B. Thiazolidinedione use is associated with reduced risk of Parkinson's disease in patients with diabetes: a meta-analysis of real-world evidence. *Neurol Sci*. 2020 Dec;41(12):3697-703. doi: 10.1007/s10072-020-04494-3.