Reduced Risk of Parkinson’s Disease in Users of Calcium Channel Blockers: A Meta-Analysis

Kapil Gudala, Raju Kanukula, and Dipika Bansal

Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, SAS Nagar, Punjab 160062, India

Correspondence should be addressed to Dipika Bansal; dipikabansal079@gmail.com

Received 30 July 2014; Accepted 15 January 2015

Copyright © 2015 Kapil Gudala et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Approximately 1% of the population over 60 years of age suffers from Parkinson’s disease (PD) which is a second most common chronic progressive neurodegenerative disorder in the elderly after Alzheimer’s disease [1]. It has been characterized clinically by three motor symptoms, which includes resting tremors, rigidity, and bradykinesia [2]. Pathology involved in PD is the loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and neuronal lewy bodies development. The results in the experimental therapies for treating PD were very limited [3]. A systematic review suggests that the centrally acting calcium channel blockers (CCBs) may have disease-modifying effects, and there were no drugs to prevent the disease or slow its progression [4].

Recent interest in antihypertensive drugs, especially CCBs, has been triggered by the belief that these medications, which inhibit nitric oxide, tumor necrosis factor-alpha, and interleukin-1 beta synthesis, thus reduce oxidative stress and the inflammatory response, which might be neuroprotective [5]. Experiments in animal models indicated that the voltage-gated calcium channel subtype Ca (V) 1.3 has a function in making neurons vulnerable to neurodegeneration [6].

Several observational studies have been conducted to examine the association between CCBs use and PD risk and have generated mixed results. Until now, no definite conclusion on this topic has been established. In the present meta-analysis, we examined the CCB use in relation to risk of PD.

2. Materials and Methods

2.1. Literature Search. Two authors independently performed the literature search by using MedLine (PubMed), EBSCO, and the Cochrane library databases up to March 2014. Search terms include “(((calcium channel blockers) OR antihypertensive agents) OR calcium antagonists) OR dihydropyridine calcium channel blockers) AND parkinson disease’ with limits of humans and English language. Titles and abstracts of the resulting articles had been examined to exclude irrelevant
studies. Full texts of remaining articles were read to extract information on the topic of interest. Bibliographies and citation sections of retrieved articles had been reviewed for additional pertinent studies.

2.2. Inclusion and Exclusion Criteria. The studies considered in this meta-analysis were all observational (cohort or case-control) studies that evaluated exposure to CCBs and risk of PD. Articles were excluded if they were reviews, letters to the editor without original data, editorials, case reports, or clinical trials. When there were multiple publications from the same population, only data from the most recent report were included in the meta-analysis and the remaining was excluded. Any discrepancies were addressed by a joint reevaluation of the original article.

2.3. Data Extraction. Two authors independently reviewed the primary studies to assess the appropriateness for inclusion in the present meta-analysis and data which has been extracted. The following information was extracted from each study: (i) first author’s last name, year of publication, and country of the population studied; (ii) study design; (iii) number of subjects and number of PD cases; (iv) effect estimates and 95% confidence intervals (CIs); (v) assessment of CCB exposure; (vi) PD assessment; and (vii) control for confounding factors by matching or adjustments, if applicable. We extracted the effect estimates that reflected the greatest degree of control for potential confounder.

2.4. Quality Assessment. Two authors using the Newcastle-Ottawa Scale (NOS) [7] assessed the quality of each study independently. The NOS consists of three parameters of quality: selection, comparability, and outcome/exposure and it assigns a maximum of four points for selection, two points for comparability, and three points for exposure/outcome. Therefore, 9 points altogether reflect the high quality and 7-8 points reflect medium quality and six or less points reflect low quality. Any discrepancies were addressed by a joint reevaluation of the original article with a third author.

2.5. Data Synthesis and Analysis. Because the risk of PD is low, the risk ratio (RR) in prospective cohort studies mathematically approximates the odds ratio [8], therefore permitting the combination of cohort and case-control studies. Publication bias was assessed using Egger’s regression asymmetry test [9, 10]. To assess the heterogeneity among studies, we used the Cochran Q and I² statistics; for the Q statistic, a P value <0.10 and for I², a value >50% was considered statistically significant for heterogeneity [11]. The primary measure pooled RR of PD from individual studies, calculated using the random-effects model (DerSimonian and Laird method) [12, 13], which accounts for heterogeneity among studies. All analyses were performed using Comprehensive Meta-Analysis software version 2. All statistical tests were two-sided and P < 0.05 was considered statistically significant, except otherwise specified.

The primary outcome in this meta-analysis was reported as RR with 95% CI of developing PD in CCB users. Subgroup analyses were performed according to (i) dihydropyridine calcium channel blockers (DiCCBs) versus non-DiCCBs; (ii) individual type of CCB; (iii) dose; (iv) duration; (v) study design (cohort and case-control); (vi) gender; and (vii) age group to examine the impact of these factors on the association. To evaluate the stability of our results, we also performed a one-way sensitivity analysis. The present work was performed in this meta-analysis as per the guidelines for the meta-analysis PRISMA [14].

3. Results

3.1. Search Results. A total of 626 articles were identified during the initial search (Figure 1). After screening the titles of 626 articles, 575 articles were excluded, as they were found irrelevant. Full text of 51 articles was collected and read. After detailed evaluation, 45 articles were found to be ineligible as there were reviews, editorials, case reports, and others which did not meet the inclusion criteria (Figure 1). A total of 6 studies were included for final analysis [15–20].

3.2. Study Characteristics. Six relevant studies were identified, including three cohort [15–17] and three case-control [18–20] studies involving a total of 27,67,990 subjects including 11,941 PD cases.

Three cohort studies involve [15–17] (Table 1) 27,48,578 participants with more than 2,06,000 CCB users out of which 6,182 were incident PD cases. Participants were followed up for 4 to 16 years and the studies have been published between 2009 and 2012. Pasternak et al. [15] study is a historical cohort study in being the biggest cohort among the three studies. Simon et al. [17] have done analysis by combining both the Nurses Health Study (NHS) and Health Professionals Follow-Up Study (HPFS). Louis et al. have reported the results of both cross-sectional and prospective analysis. However, present analysis has included only the prospective results of Louis et al. [16].

Three population-based case-control studies [18–20] (Table 2) involving 5,759 PD cases and 13,653 controls were published in between 2007 and 2010. All three studies are population-based studies, which assessed PD or CCB usage from national database or medical records or from pharmacy database.

3.3. Main Results. As a significant heterogeneity was found (P = 0.031; I² 54.6%), random-effects model was chosen over a fixed effects model. We found CCB use was associated significantly with decreased risk of PD compared with not using CCB (pooled RR, 0.81 (95% CI, 0.69–0.96)). The multivariable adjusted RRs of use of CCB and risk of PD for each study and grouped data of all studies are shown in Figure 2. Visual examination of the funnel plot revealed minimal asymmetry (data not shown), further confirmed by Egger’s test (P = 0.68) indicating little or no publication bias in our analysis.

3.4. Subgroup Analysis. Table 3 presents the results of subgroup analyses stratified by characteristics of study designs.
Table 1: Characteristics of cohort studies included in meta-analysis.

| Author, year (country)<sup>a</sup> | Cohort name | Cohort size | Follow-up period (start–end year) | Assessment of CCB use | Number of CCB users | Assessment of PD | Number of PD cases | Quality rating (NOC) |
|-----------------------------------|-------------|-------------|------------------------------------|-----------------------|---------------------|-----------------|------------------|---------------------|
| Pasternak et al. [15] 2012 (Denmark)<sup>a</sup> | NR | 25,732 | 8 (1998–2006) | Prescription drug registry | 2,028 | National patient registry | 5,711 | 9<sup>b</sup> |
| Simon et al. [17] 2010 (USA)<sup>a</sup> | Nurses Health study & Health Professionals Follow-Up Study | 1,713 | 16 (1986–2002) | Self-reported through structured questionnaire | 3,826 | Self-reported and after confirmed by medical records and physician | 421 | 7<sup>c</sup> |
| Louis et al. [16] 2009 (Spain)<sup>a</sup> | Neurological Disorder in Central Spain | 3,942 | 4 (1994–1998) | Self-reported | NR | Presence of any two cardinal signs and physician confirmed PD | NR | 8<sup>c</sup> |

<sup>a</sup>Country of study conducted.

<sup>b</sup>High quality.

<sup>c</sup>Moderate quality.

USA: United States of America, NR: not reported, CCB: calcium channel blockers, PD: Parkinson’s disease, and NOC: Newcastle-Ottawa Scale.
Table 2: Characteristics of case-control studies included in meta-analysis.

| Author, year (country) | Period of recruitment | Source of study population | Study size | Number of PD patients | Assessment of CCB usage | Assessment of PD | Quality rating (NOC) |
|------------------------|-----------------------|---------------------------|------------|-----------------------|------------------------|-----------------|---------------------|
| Ritz et al. [18] 2010 (Denmark) | 2001–2006 | Population based | 11,582 | 1,931 | National pharmacy database | Hospital register | 8c |
| Becker et al. [19] 2008 (UK) | 1994–2005 | Population based | 7,274 | 3,637 | General practice research database | General practice research database | 8c |
| Ton et al. [20] 2007 (USA) | 1992–2002 | Population based | 556 | 191 | Medical records | Medical records and cardinal signs | 9b |

*a Country of study conducted.
*b High quality.
*c Medium quality.

UK: United Kingdom, USA: United States of America, CCB: calcium channel blockers, PD: Parkinson's disease, and NOC: Newcastle-Ottawa Scale.
### Table 3: Overall effect estimates for Parkinson's disease and calcium channel blockers use according to study characteristics.

| Characteristic      | 𝑛  | Risk ratio (95% CI)    | 𝑃   | Heterogeneity | 𝐼² (%) Cochrane Q |
|---------------------|----|------------------------|-----|---------------|-------------------|
| All studies         | 6  | 0.81 (0.69–0.96)        | 0.014* | 54.6          | 0.031             |
| Study design        |    |                        |      |               |                   |
| Cohort              | 3  | 0.73 (0.64–0.84)        | <0.001* | 42.6          | 0.156             |
| Case-control        | 3  | 0.84 (0.68–1.04)        | 0.111  | 58.1          | 0.06              |
| Class of CCB        |    |                        |      |               |                   |
| DiCCB               | 4  | 0.80 (0.65–0.98)        | 0.032* | 72.9          | 0.011             |
| Non-DiCCB           | 2  | 0.70 (0.53–0.92)        | 0.013* | 0             | 0.546             |
| Gender              |    |                        |      |               |                   |
| Men                 | 3  | 0.85 (0.66–1.12)        | 0.243  | 53.1          | 0.118             |
| Women               | 3  | 0.67 (0.55–0.81)        | <0.001* | 0             | 0.919             |
| Sensitivity analysis|    |                        |      |               |                   |
| All studies except Pasternak et al. [15] | — | 0.85 (0.71–1.01) | 0.080* | NA            | NA                |
| All studies except Becker et al. [19] | — | 0.83 (0.68–1.01) | 0.071* | NA            | NA                |
| Quality             |    |                        |      |               |                   |
| High                | 2  | 0.70 (0.61–1.08)        | <0.001* | 0             | 0.774             |
| Medium              | 4  | 0.89 (0.72–1.09)        | 0.272  | 55.3          | 0.062             |

* 𝑃 value representing significant inverse association between CCBs use and Parkinson’s disease.

CCB: calcium channel blockers, DiCCB: dihydropyridine calcium channel blockers, and NA: not available.

CI: confidence interval.

---

**Figure 2**: Combined estimate of risk ratio and 95% confidence interval of Parkinson’s disease associated with calcium channel blockers use based on six studies (three case-control and three cohort) of 27,679,990 subjects including 11,941 PD cases. Squares indicate RR in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of horizontal lines represents the 95% CI. The shaded diamond indicates the combined RR and 95% CI (random-effects model).

A P value representing significant inverse association between CCBs use and Parkinson’s disease. When cohort studies were analyzed alone [15–17], the pooled RR was found to be 0.73 (95% CI, 0.64–0.84). Using case-control studies alone [18–20], we found that the pooled RR was 0.84 (95% CI, 0.68–1.04). We found a significant difference between studies according to study design, where cohort studies significantly showed decreased risk of PD in CCB users. Although the RR of case-control studies is nonsignificant but still the effect estimate is on lower side.

Both the classes of CCB, that is, DiCCB (0.80 (95% CI, 0.65–0.98) 𝑃 = 0.032) and non-DiCCB (0.70 (95% CI, 0.53–0.92) 𝑃 = 0.013), were found to be reducing the risk of PD.
We found a significant reduced risk of PD in females 0.67 (95% CI, 0.55–0.81) \( P = 0.243 \), in contrary to males 0.85 (95% CI, 0.66–1.12) \( P < 0.001 \). To test the robustness of our findings, we also performed a sensitivity analysis. To do this, the overall effect size was calculated by removing one study at a time. This analysis showed no significance variation when excluding the Pasternak et al. [15] study 0.85 (95% CI, 0.71–1.01) \( P = 0.080 \) and Becker et al. [19] study 0.83 (95% CI, 0.68–1.01) \( P = 0.07 \). Subgroup analysis revealed that use of nondihydropyridine CCBs was reported in only two studies [15, 19]. We found a significant reduced risk of PD in subgroup of nondihydropyridine CCBs users. The observed effect may explain that the protective role of CCBs in PD may not be limited to inhibition of voltage gated calcium channels [15]. A word of caution is necessary in interpretation of the analysis because sensitivity analysis by excluding study by Pasternak et al. [15] or Becker et al. [19] resulted in nonsignificant decrease in the RR of PD. The reason for this can be that these are two large well-conducted studies, which reported a decreased risk of PD in CCB users. These have a major contribution while pooling of effect estimates. Moreover subgroup analysis of high quality studies [15, 20] further suggested decreased risk of PD in CCB users, which further helps to conclude the usefulness of CCBs use in prevention of PD.

Several limitations of our study need to be addressed. Our analysis was restricted to articles in English language, which may have led to somewhat biased results. All the studies included were observational studies with different follow-up periods, and no standard definition of CCBs usage was there.

4. Discussion

In the past decade, the role of CCBs in reduction of PD has been understood increasingly. With the present pooled analysis of 6 observational studies, a 19% reduction in PD risk among CCBs users as compared to nonusers was observed. CCBs are one of the most important antihypertensive drugs. The present analysis demonstrated the potential neuroprotective role of CCBs in reducing the risk of PD.

The etiopathogenesis of PD is complex. It involves \( \alpha \)-synuclein deposition, dysfunction of protein turnover, and mitochondrial dysfunction leading to neuronal loss via excitotoxicity, calcium overload, and apoptosis [21]. Factors that potentiate pathological \( \alpha \)-synuclein aggregation include posttranslational modifications, oxidative stress, and raised intracellular calcium ion [22, 23]. In vitro culture models showed that transient increases of intracellular calcium induce cytoplasmic \( \alpha \)-synuclein aggregates [23, 24]. In addition to the intracellular calcium overload, oxidative stress cooperatively promotes \( \alpha \)-synuclein aggregation. By blocking the influx of calcium, CCBs can prevent or stop the progression of PD [23]. Dopaminergic neurons in substantia nigra possess L-type voltage gated calcium channels L.3 for their pacemaker activity [25]. Kang et al. reported that, by selectively antagonizing Ca (V) L-type channels, one could provide a solution for diminishing cell loss in PD with minimal side effects [26]. This provides a potential therapeutic target, by using drugs that modulate the amount of free Ca\(^{2+} \) in the cell. An array of CCBs are approved by USFDA to treat hypertension which could be tried to lessen the increase in intracellular Ca\(^{2+} \) seen in aged neurons in patients at high risk of developing PD based on family history.

Evidence on association between hypertension and risk of PD is conflicting. Prospective studies [27–29] showed an increased risk of PD in hypertensive patients. Some speculative mechanisms include untreated chronic hypertension which may lead to ischemic cerebrovascular lesions, increased oxidative stress, and modulation of central renin-angiotensin system (RAS) leading to PD [27]. It is not clear that whether lowering blood pressure has any role in reducing the risk of PD. The observed effect of decreased risk of PD in CCB users is assumed primarily by its neuroprotection action and not due to reduction of blood pressure in patients with hypertension.

Other antihypertensive drugs were also studied as potential agents to prevent or to stop progression of PD. In vitro and few in vivo studies have shown the role of agents modulating the RAS such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [30]. Angiotensin type II when binds to the angiotensin type 1 receptor (AT1) activates the nicotinamide adenine dinucleotide phosphate oxidase complex, thus providing a major source of oxidative stress. In addition, activation of the AT1 receptor stimulates the NF-B signal transduction pathway which facilitates the synthesis of inflammatory mediators, which cause inflammation and later cell death. Thus ARBs and ACEIs act by modulating the oxidative stress and inflammation at the level of dopaminergic neurons in substantia nigra and basal ganglia. This makes them potential future targets to prevent or to stop progression of PD [30].

In our subgroup analysis, we found more pronounced reduced risk in women among CCBs users 0.67 (0.55–0.81, \( P = 0.243 \)) as compared to men 0.85 (0.66–1.12, \( P < 0.001 \)). These results are well coincided with the results published by Becker et al. [19]. Our study results were found to be significantly affected by study design, which might possibly be due to large sample size in cohort studies [15–17] as compared to case-control studies [18–20]. The definition of CCBs use in cohort and case-control studies is different. Moreover, none of the studies except study by Pasternak et al. [15] provided data regarding individual type of CCBs, duration, and dose. They emphasized on the protective association of amlodipine and felodipine with reduced risk of PD. They also concluded that individuals using high doses of amlodipine were at lower risk compared to those using standard dose. However, similar correlation was not observed in case of felodipine and nifedipine. Moreover, the results were nonconclusive because of low sample size.

Subgroup analysis revealed that use of non-dihydropyridine CCBs was reported in only two studies [15, 19]. We found a significant reduced risk of PD in subgroup of non-dihydropyridine CCBs users. The observed effect may explain that the protective role of CCBs in PD may not be limited to inhibition of voltage gated calcium channels [15].
The specific role of individual drugs and doses was also not possible because of nonreporting in the studies. Our analysis suggests that CCBs may have protective role in PD. However, future prospective studies with larger sample size are required to understand the effect of individual CCBs at various dose and duration of use.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**

[1] L. M. de Lau and M. M. Breteler, "Epidemiology of Parkinson's disease," *The Lancet Neurology*, vol. 5, no. 6, pp. 525–535, 2006.

[2] M. Göttlich, T. F. Münte, M. Heldmann, M. Kasten, J. Hagenah, and U. M. Kräm er, "Altered resting state brain networks in Parkinson's disease," *PLoS ONE*, vol. 8, no. 10, Article ID e77336, 2013.

[3] J. M. Beitz, "Parkinson's disease: a review," *Frontiers in Bioscience (Scholar Edition)*, vol. 6, pp. 65–74, 2014.

[4] K. Rees, R. Stowe, S. Patel et al., "Anti-hypertensive drugs as disease-modifying agents for Parkinson's disease: evidence from observational studies and clinical trials," *Cochrane Database of Systematic Reviews*, no. 11, Article ID CD008535, 2011.

[5] Y. Li, X. Hu, Y. Liu, Y. Bao, and L. An, "Nimodipine protects dopaminergic neurons against inflammation-mediated degeneration through inhibition of microglial activation," *Neuropharmacology*, vol. 56, no. 3, pp. 580–589, 2009.

[6] M. J. Hurley, B. Brandon, S. M. Gentleman, and D. T. Dexter, "Parkinson's disease is associated with altered expression of Ca$_2$-1 channels and calcium-binding proteins," *Brain*, vol. 136, no. 7, pp. 2077–2097, 2013.

[7] Ottawa Hospital Research Institute, "The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses," 2011, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[8] J. Zhang and K. F. Yu, "What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes," *The Journal of the American Medical Association*, vol. 280, no. 19, pp. 1690–1691, 1998.

[9] F. Song, T. A. Sheldon, A. J. Sutton, K. R. Abrams, and D. R. Jones, "Methods for exploring heterogeneity in meta-analysis," *Evaluation and the Health Professions*, vol. 24, no. 2, pp. 126–151, 2001.

[10] M. Egger, G. D. Smith, M. Schneider, and C. Minder, "Bias in meta-analysis detected by a simple, graphical test," *British Medical Journal*, vol. 315, no. 7109, pp. 629–634, 1997.

[11] J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring inconsistency in meta-analyses," *British Medical Journal*, vol. 327, no. 7414, pp. 557–560, 2003.

[12] R. DerSimonian and N. Laird, "Meta-analysis in clinical trials," *Controlled Clinical Trials*, vol. 7, no. 3, pp. 177–188, 1986.

[13] R. DerSimonian and R. Kacker, "Random-effects model for meta-analysis of clinical trials: an update," *Contemporary Clinical Trials*, vol. 28, no. 2, pp. 105–114, 2007.

[14] "PRISMA check list," http://www.prisma-statement.org/2.1.2%20-%20PRISMA%202009%20Checklist.pdf.

[15] B. Pasternak, H. Svanström, N. M. Nielsen, L. Fugger, M. Melbye, and A. Hviid, "Use of calcium channel blockers and Parkinson's disease," *American Journal of Epidemiology*, vol. 175, no. 7, pp. 627–635, 2012.

[16] E. D. Louis, J. Benito-León, and F. Bermejo-Peura, "Anti-hypertensive agents and risk of Parkinson's disease, essential tremor and dementia: a population-based prospective study (NEDICES)," *Neuroepidemiology*, vol. 33, no. 3, pp. 286–292, 2009.

[17] K. C. Simon, X. Gao, H. Chen, M. A. Schwarzschild, and A. Ascherio, "Calcium channel blocker use and risk of Parkinson's disease," *Movement Disorders*, vol. 25, no. 12, pp. 1818–1822, 2010.

[18] B. Ritz, S. L. Rhodes, L. Qian, E. Schernhammer, J. H. Olsen, and S. Friis, "L-type calcium channel blockers and Parkinson disease in Denmark," *Annals of Neurology*, vol. 67, no. 5, pp. 600–606, 2010.

[19] C. Becker, S. S. Jick, and C. R. Meier, "Use of antihypertensives and the risk of Parkinson disease," *Neurology*, vol. 70, no. 16, pp. 1438–1444, 2008.

[20] T. G. N. Ton, S. R. Heckbert, W. T. Longstreth Jr. et al., "Calcium channel blockers and β-blockers in relation to Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 13, no. 3, pp. 165–169, 2007.

[21] J. B. Schulz, "Mechanisms of neurodegeneration in idiopathic Parkinson's disease," *Parkinsonism and Related Disorders*, vol. 13, no. 3, pp. S306–S308, 2007.

[22] V. M.-Y. Lee and J. Q. Trojanowski, "Mechanisms of Parkinson's disease linked to pathological alpha-synuclein: new targets for drug discovery," *Neuron*, vol. 52, no. 1, pp. 33–38, 2006.

[23] K. Vekrellis and L. Stefanis, "Targeting intracellular and extracellular alpha-synuclein as a therapeutic strategy in Parkinson's disease and other synucleinopathies," *Expert Opinion on Therapeutic Targets*, vol. 16, no. 4, pp. 421–432, 2012.

[24] C. Lo Bianco, J.-L. Ridet, B. L. Schneider, N. Déglon, and P. Aeberscher, "α-synucleinopathy and selective dopaminergic neuron loss in a rat lentiviral-based model of Parkinson's disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 16, pp. 10813–10818, 2002.

[25] C. S. Chan, J. N. Guzman, E. Ilijić et al., "'Rejuvenation' protects neurons in mouse models of Parkinson's disease," *Nature*, vol. 447, no. 7148, pp. 1081–1086, 2007.

[26] S. Kang, G. Cooper, S. F. Dunne et al., "CaV1.3-selective L-type calcium channel antagonists as potential new therapeutics for Parkinson's disease," *Nature Communications*, vol. 3, p. 1146, 2012.

[27] C. Qiu, G. Hu, M. Kivipelto et al., "Association of blood pressure and hypertension with the risk of Parkinson disease: the national FINRISK study," *Hypertension*, vol. 57, no. 6, pp. 1094–1100, 2011.

[28] K. C. Simon, H. Chen, M. Schwarzschild, and A. Ascherio, "Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease," *Neurology*, vol. 69, no. 17, pp. 1688–1695, 2007.

[29] A. Paganini-Hill, "Risk factors for Parkinson's disease: the Leisure world cohort study," *Neuroepidemiology*, vol. 20, no. 2, pp. 118–124, 2001.

[30] B. Mertens, P. Vanderheyden, Y. Michotte, and S. Sarre, "The role of the central renin-angiotensin system in Parkinson's disease," *Journal of the Renin-Angiotensin-Aldosterone System*, vol. 11, no. 1, pp. 49–56, 2010.