Spring 5-15-2022

Antioxidant Synergy of the Glutathione Pathway and Incidence of Parkinson's Disease: A Systematic Review

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Abstract

Background: The etiopathogenesis dopaminergic neuron dysfunction of Parkinson's Disease (PD) has not been clearly established. Oxidative stress is a commonly proposed causative mechanism for this dysfunction as variations in antioxidant intake have been observed between older adults with and without PD. The objective of this systematic review was to evaluate the synergistic relationship between antioxidant micronutrients of the glutathione pathway and the incidence of PD in older adults.

Methods: This systematic review evaluated the relationship between the intake of vitamins C, D, and E, and selenium, riboflavin and niacin and incidence of PD according to PRISMA guidelines. Four electronic databases (Medline (PubMed), CINAHL, Web of Sciences and SCOPUS) were reviewed, most recently on April 12, 2022. Risk of bias was assessed and reported for each study utilizing respective Joanna Briggs Institute (JBI) Quality Review Checklist for Case Control Studies and Cohort Studies, and Risk of Bias in Systematic Reviews (ROBIS) to assess systematic reviews and meta-analyses. Inclusion criteria were assessment of usual intake of above antioxidants, population of interest was idiopathic PD, and exclusion criteria were assessing population with mean age less than 50 years old, or deemed poor quality of evidence

Results: A total of 31 studies were included in the final review after evaluating final inclusion/exclusion criteria. Vitamin D revealed the most prominent relationship with incidence of PD, with 18 of 19 studies identifying a negative relationship between intake and incidence, while results were largely inconclusive for vitamins E and C. There were no studies for selenium, riboflavin or niacin that met criteria for the current study.

Discussion: These results suggest that there is an associated dietary aspect comprising risk of PD. Vitamin D may mitigate risk of PD through mechanisms independent of the glutathione pathway. The influence of the glutathione redox pathway with respect to risk of PD requires further exploration given limitations in available research on many aspects of this pathway in isolation or in a synergistic pattern. Other limitations of these studies are that the studies are primarily retrospective in nature rather than prospective or longitudinal studies.
Other: There was no funding to support this study. This systematic review is registered with PROSPERO under registration number CRD42021268660.

Keywords: Parkinson's Disease, antioxidants, oxidative stress

ANTIOXIDANT SYNERGY OF THE GLUTATHIONE PATHWAY AND INCIDENCE OF PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

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May 2022

Acknowledgements:

I would like to thank Dr. Lynn Brann for her guidance through each stage of the research process. My research partner, Ligeng (Ray) Xiong, was instrumental in completing the review. Additionally, I would like to thank other members of my thesis committee, Dr. Margaret Voss and Dr. Sudha Raj for their direction and expert feedback.

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Introduction

Idiopathic Parkinson's Disease (PD) is the second most common neurodegenerative disorder (1). First described by Dr. James Parkinson in 1817 as a "shaking palsy", it is an irreversible, progressive condition with little known regarding the origin of its pathology (2). The condition has motor (predominantly tremor, rigidity and bradykinesia), and non-motor phenomena (cognitive dysfunction, fatigue) resulting from the loss of dopaminergic neurons of the basal ganglia (3). Neurological conditions are the leading cause for disability worldwide with the fastest growing pathology being PD (4). Between 1990 and 2015 the incidence of PD globally increased by 118% and with a growing aging population, it is expected to continue increasing in numbers (4).

PD is progressive and long-term therapies come with diminished efficacy as the disease progresses(5). Identification of modifiable risk factors for PD may allow for recommendations to reduce the incidence of PD. Individuals may present with prodromal symptoms of PD up to 12-14 years prior to diagnosis (1). The early identification of those with prodromal symptoms and intervention to mitigate modifiable risk factors may be used to avoid translation to fulminant PD.

Oxidative stress is a systemic theme of balancing involving three areas of metabolic interaction: detoxification from antioxidants, pro-oxidant exposure causing increased oxidative stress, and chronic inflammation resulting from a pro-oxidative state. If the availability of antioxidants cannot meet the demand of oxidation-reduction (redox) cycling of pro-oxidants, then oxidative stress results and, subsequently, systemic inflammation accumulates (6). The increase in systemic inflammation then in turn further contributes to more metabolically pro-oxidative state and further difficulty in maintaining a sufficient supply of antioxidant activity. With the etiopathogenesis of PD, a cycle of neuronal destruction is the result of oxidative stress

from a cycle of conformational change of alpha-synuclein which promotes its aggregation in neuronal tissue and increasing lipid peroxidation (7).

While strictly studying the diet, many studies evaluate a somewhat arbitrary group of micronutrients and other dietary factors in isolation (i.e. increase in "X" and separate increase in "Y" micronutrients are associated with effect "Y" without accounting for "Z" micronutrient). However, the human diet is complex and has numerous interactions which cannot be considered in such a reductionist view. Synergistic effects and complex interactions between dietary components exist and create a variety of outcomes based upon the abundance or deficiency of other micronutrients. The intake of compounds of various oxidative or redox potential is on a spectrum and states of excess and deficiency are not mutually exclusive from one another; one may have both patterns of long-term intake of pro-oxidant compounds and antioxidants. Viewing antioxidant intake in groups related to their metabolic function is a practice that is not commonly viewed in nutrition literature.

Glutathione is a tripeptide of pivotal importance to a complex redox-cycling reaction that reduces oxidative stress. The cycle is comprised of three separate redox loops that are interconnected and interdependent upon one another. The redox cycles within the glutathione reduction pathway are based upon redox reactions of vitamin E, vitamin C, and glutathione with several cofactors and coenzymes involved. Primary antioxidant micronutrients involved in antioxidant redox cycling include the following: vitamins E, C, selenium, riboflavin, and niacin. Glutathione peroxidase is an essential enzyme that catalyzes the oxidation of glutathione from its reduced state and selenium is an essential cofactor for its function. Glutathione reductase, with its cofactor riboflavin, is the enzyme which returns glutathione to is reduced form, allowing it to initiate the redox cycle once again. Niacin is a precursor to the terminal electron receptor of the

pathway, nicotinamide adenine dinucleotide. Vitamin D is not directly involved in the redox cycling directly, however vitamin D bioavailability is dependent upon glutathione status (8). Antioxidant therapy has been proposed as an intervention to help attenuate the progression of PD by intervening in the effect of oxidative stress (9).

This systematic review sought to explore the differences in intake of selected antioxidant micronutrients of the glutathione redox pathway to evaluate for possible synergistic mechanisms. This synergistic perspective was distinct from prior body of systematic reviews as intake of these micronutrients is not functionally in isolation and should not be considered as such when evaluating influence of risk of incidence. The objective of this review was to identify patterns of dietary intake of these selected antioxidants of the glutathione antioxidant pathway in older adults with PD compared to those without PD.

Methodology

Search Strategy

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10). Medline (PubMed), CINAHL, Web of Sciences and SCOPUS were evaluated by a single reviewer (CY) with search terms to identify studies under consideration. Initial search terms included were “Parkinson’s Disease” OR “Parkinsons Disease” AND “antioxidants” or “vitamin D”, or “vitamin C”, “Vitamin E”, or “selenium”, or “riboflavin”, or “niacin” (Table 1). “Antioxidant” was only utilized for the title search; all other search terms were carried through the entirety of the search protocol. Synonymous terms were allowed to be included as an equivalent result within the database search generator, as well as upon interpretation of studies. Equivalent terms included alpha-tocopherol and vitamin E, riboflavin, and vitamin B2, niacin and vitamin B3, ascorbic

acid, ascorbate, and vitamin C, and hydroxyvitamin-D and vitamin D. Selected micronutrients directly interact within the glutathione reductase pathway with limited involvement in other antioxidant redox cycles. Vitamin D was also included within this study due to its direct connection with the glutathione pathway as its bioavailability is dependent upon glutathione (8). The intake and effect of each antioxidant micronutrient independently and in setting of other micronutrient intakes were included if reported in the study.

A single reviewer (CY) completed the title search to ensure that each title met search term criteria. Abstract review was completed by the same reviewer who completed the title search (CY) and included studies that assessed intake of antioxidants of interest with respect to incidence of PD. Relationship between intake and incidence for this study was defined as a comparison in levels of intake between individuals who do or do not have PD, or usual intake of those who develop PD compared to those who remain free of pathology. Two independent reviewers, a subject matter expert (CY) and a non-subject matter expert (LX), conducted the full-text review independently to determine applicability to full-text review and potential themes. Any discordance in results between the two reviewers was advanced to a tertiary reviewer (LB) who evaluated any discrepancy and determined the outcome for studies meeting final criteria for inclusion after discussion and consensus with the two primary reviewers. There was no inclusion of automation tools.

Incidence of PD was the primary outcome factor that was evaluated for the purpose of our study. Studies that evaluated an alternative primary outcome but included data consistent with our outcome measures and inclusion/exclusion criteria were included for evaluation in our study. Determination of differences in risk of incidence was defined as different levels of intake between the two groups, or as determined by odds ratio (OR), hazard ratio (HR), or risk ratio

(RR). Other notation of differences in intake was observed by noting whether significant differences in level of intake was noted between the PD and control groups. Studies were ultimately categorized based upon the antioxidant assessed within the study and may have been included in more than one category based upon if more than one micronutrient was investigated.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were outlined in Table 2. Full text of each article needed to be available in English to the reviewers for evaluation. For this study, Parkinson's Disease referenced Primary Idiopathic Parkinson's Disease only as opposed to Parkinsonism which may be from other causes such as adverse medication effect or cerebral ischemic events.

Exclusion criteria removed studies that evaluated populations of participants with secondary parkinsonism related to causes such as vascular parkinsonism and medication-related side effects. This was done as these alternate forms of Parkinsonism are of distinct provoked etiologies rather than due to a progressive neurodegenerative condition. Investigational studies primarily investigating specifically genetically associated or early onset PD were not included as this pathology is the result of factors that are likely distinct from the idiopathic neurodegenerative presentation (11). Given that many clinicians do not test for genetic predisposition, studies primarily investigating individuals under the age of 50 years old were not included in this study to increase likelihood that the process was related to neurodegenerative PD as opposed to alternative mechanisms contributing to early onset PD (11). If the age range of study participants was not explicitly defined or in part included individuals younger than 50 years of age, the presented mean age was required to be at least one standard deviation above established cutoff age of 50 years. If the standard deviation was not presented with the mean,

then mean age alone was be used with the established cutoff of 50 years old for evaluation for inclusion.

We completed a thorough review of the literature and were unable to find any studies that specifically investigated the influence of the intake of antioxidant micronutrients, from a synergistic perspective, on risk of developing PD. Peer-reviewed manuscripts from any date were included up to the time of the review (July 2021) and this was not classified as an update to a review given its novelty. The usual intake of each micronutrient had to be quantified by biospecimens validated for usual intake or use of dietary assessment tools assessing usual intake. Acceptable biospecimen data were serum vitamin D or E. Data assessing dietary intake that cannot be used to determine usual intake, being one to two days of 24-hour food recall or food diary/record, or serum selenium, riboflavin, niacin, and vitamin C were not included in this study. If a study included data regarding some components of usual intake, and others without accepted assessment of usual intake, the data regarding usual intake were included and the remainder was excluded from the study.

Oxford Centre for Evidence Based Medicine (OCEBM) criteria were utilized to assess quality of evidence and any studies classified as level 4 or 5 evidence were not included in this review (11). For the present study, level 4 evidence of poorly conducted case-control studies was be noted as deemed as such if a "no" or "unclear" response was achieved when assessing question 1 of the Joanna Briggs Institute (JBI) Case-Control Checklist tool for quality review which stated "were the groups comparable other than the presence of disease in cases or the absence of disease in controls" (14). Aside from these parameters, studies were not strictly excluded based on quality of evidence or risk of bias.

Data Extraction and Interpretation

The following data from each study were obtained: author, year of publication, sample size, population of interest, study design, micronutrient(s) of interest, method of assessment of dietary intake, data regarding risk of developing PD or differences in dietary intake between PD and control groups, and, if present, variables that were adjusted for in statistical analysis. Results were used to generate themes summarizing interactions between various levels of intake of selected antioxidant micronutrients reported in the literature with how these are associated with risk of developing PD. There were no assumptions made regarding missing or unavailable data. The available data regarding relationship between intake of each antioxidant and incidence of PD was presented in whatever manner is presented within the study including but not limited to p-values, odds ratios (OR), hazard ratios (HR), and risk ratios (RR). Aggregate data analysis and determination of heterogeneity were not completed for the purpose of this study given variable data representation within included studies.

Risk of bias was assessed for each study by a single reviewer. Systematic reviews and meta-analyses were assessed via Joanna Briggs Institute Critical Appraisal Tools for Quality Review Checklists for Case-Control (Appendix 1) and Cohort studies (Appendix 2) and Risk of Bias in Systematic Reviews (ROBIS) assessment (Appendix 3) (14–16). Risk of bias and quality review outcomes were presented for each study. The composite of the quality of cumulative evidence was assessed according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was noted (17). This study was registered with PROSPERO under registration number CRD42021268660.

Results

A flow diagram of studies documenting the selection process is shown in Figure 1 in appendices. A total of 1,011 studies were included in the initial title review, which was

conducted from July 19, 2021 through July 22, 2021. Titles were evaluated with duplicate studies removed and to prompt evaluation of 407 titles for relevance with search terms. Three additional studies were excluded due to one pair of retraction notice and associated study, and an unmatched retraction notice. The primary study associated with the unmatched retraction notice did not populate within our study, therefore only the notice was present. The 404 studies were assessed for relevance with discussing incidence of PD and intake of antioxidants with 330 were excluded as they were not felt to be relevant. For these remaining 74 publications, 43 studies were excluded from final inclusion: 39 studies did not meet criteria based on inclusion/exclusion criteria, and an additional 4 studies were excluded following completion of quality review. A total of 16 studies were brought before a third-party reviewer during the full-text review where a collaborative discussion took place regarding which studies to include or exclude. All parties agreed on the included studies with minimal discourse required. After final discourse was reached 31 studies were yielded for data analysis and interpretation. Studies were reviewed again on April 12, 2022 with no further updates to the included body of literature.

The distribution of study type of included studies were as follows: 21 case-control studies (18–38), 3 cohort studies (39–41), 4 meta-analyses (42–45), and 3 systematic review/meta-analyses (46–48). Table 3 presented basic study characteristics of primary studies and overall relationship with risk of PD and table 4 outlined specific data, level of significance, control variables, and interpretation of reported effect. Table 5 outlines the results of systematic reviews and meta-analyses. Of the included primary research studies conducted, 14 studies reviewed exclusively biospecimen data (18–23,27–30,33,34,36,37,41), seven studies utilized food frequency questionnaires (semi-quantitative or otherwise not specified) (24–26,38,38–40), one study utilized both serum analysis and a semi-quantitative FFQ (35), one study utilized a Health

Habits and History Questionnaire to assess dietary intake 20 years ago (31), and one study utilized a "structured ad hoc interview" approach (32).

Studies were performed around the world, most prominently represented by seven studies completed in East Asia(25,26,36,37,37,37,38). North America(24), Europe (30,32,33,39,41), Western Asia and Northern Africa (21,34) were each represented by several studies, however the remainder of African populations and South American populations were not represented in any of the included studies. None of the studies reported assessing patients while they were institutionalized, whether acutely or in long-term care.

Vitamin D was the most frequently investigated micronutrient included in the study (n=19) (25–27,33–36,38,44–48). Nearly all researchers found a significant negative association between vitamin D intake and risk of PD in 18 of 19 studies (18–21,23,28–30,33–36,38,41,44–47). All reported ORs for vitamin D were significant and ranged from 0.58 – 4.17 (18,26,35,38,44,46). Thirteen studies reported strongly significant values of $p \leq 0.01$(18–20,23,28–30,33,34,36,38,41,47). Most of the studies (n=12) assessing vitamin D intake did so with serum 25-hydroxyvitamin D assessment for at least a portion of the assessment method (18–21,23,28–30,33–36,41).

Vitamin E was investigated by ten studies (22,24,25,27,31,32,37,39,40,43). Vitamin E influence revealed a less consistent relationship with incidence of PD when compared to that of vitamin D, with five studies (25,32,39,42,43) having reported an inverse association between intake and rate of PD and the remaining studies showed no association. There is a possible relationship with decreased risk of PD with higher intake of vitamin E. There were no patterns noted in association with vitamin E intake on risk of PD when assessed as whole intake, division into quartiles of level or intake, or by assessment method (serum or dietary questionnaires).

Vitamin C was evaluated by six studies (24,25,31,39,40,43). Vitamin C showed a relationship between PD and level of intake in only two of these reported studies (31,39). These two studies revealed trending towards or "borderline" significance. This effect remained consistent when level of intake was stratified into quartiles or if whole intake was assessed between groups. There were no studies that met all necessary study criteria for assessment of the relationship between PD and riboflavin, selenium or niacin. A complete representation of the data from each study was represented in table 4 of appendices for further review.

Quality of evidence for case-control (table 6) and cohort studies (table 7) and risk of bias assessment for systematic reviews and meta-analyses (table 8-12) were presented in the appendices. Risk of bias of systematic reviews and meta-analyses were low for included studies when assessed by ROBIS. Common findings of the case-control studies were that cases and controls were not appropriately matched, and the data did not identify or account for confounding variables for data analysis. All three of the cohort studies included failed to address incomplete data or strategies to address loss of follow-up in the methodology. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) overall quality of evidence was determined to be "low" given predominantly associative effects, large volume of case-control studies, exclusively observational studies, and variability of results (17).

Discussion

The objective of this study was to assess the relationship between micronutrients of the glutathione redox pathway and the influence of the incidence of PD. Our findings reported a commonly observed inverse association between vitamin D intake and risk of PD. The current systematic review revealed a more inconsistent association with vitamin E and PD. Researchers were unable to identify any relationship between vitamin C intake and incidence of PD. This

suggested that the glutathione redox pathway may not be strongly associated with incidence of PD. It is difficult to have definitively excluded the possible influence of the glutathione pathway on the risk of PD without having data surrounding riboflavin, niacin, and selenium. The lack of available data surrounding patterns of usual intake of these micronutrients and PD revealed a knowledge gap in the literature.

The negative association between vitamin D and incidence of PD being revealed in nearly all studies assessing the relationship suggests the possibility that a mechanism independent of glutathione pathway may be at work in this inverse relationship. A multitude of mechanisms have been proposed to explain this mitigating effect ranging from genomic effects including vitamin D receptor polymorphisms, to non-genomic measures such as effect on prostaglandins, nitric oxide synthase and low-voltage sensitive calcium channels (49). Antioxidant-based mechanisms including calcitriol are suggested to promote sensitivity of monocytes in the substantia nigra to produce superoxide dismutase and increase oxidative capacity (49). Many of the proposed mechanisms appeared to be independent of the function of the involvement of vitamin D in the glutathione pathway by increasing bioavailability of glutathione.

The inconsistent response of vitamin E with respect to PD incidence warrants further investigation to explain this variability. This suggested a possibility that some of the results of these studies may be due to random error and would require further investigation or a larger pool of studies to assess realistic effect size. The inconsistent presentation may be related to error from small volume of studies yielded for this antioxidant. There are no clear discrepancies related to assessment methods used, populations investigated, or other components of methodologies that would clearly explain the variability in results. Given these inconsistencies,

the relationship between vitamin E intake and the incidence of PD remains unclear. Given that vitamin E appeared to have a more prevalent effect on PD risk than vitamin C we may consider mechanisms aside from the glutathione pathway as the function of vitamin C and E are interconnected in this cycle. Vitamin E has been suggested to play a protective role in maintaining the blood brain barrier to potentially mitigate risk of PD in a mechanism independent of the glutathione redox pathway by inhibiting 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (50).

There were no studies that met criteria for inclusion of selenium, riboflavin or niacin on the basis of criteria established for this review. This suggests the possibility that the current criteria were too stringent for sufficient inclusion of studies relating to these markers, or possible need for differing search terms to expand included manuscripts. A limited quantity of studies was apparent on initial search for each of these antioxidants, which may also suggest that there is a paucity of research conducted regarding these micronutrients and risk of PD.

A puzzling finding is that seven studies evaluated in the full-text review process assessed the serum and/or cerebrospinal fluid (CSF) levels of selenium as it pertains to PD(51–57). Neither of these biospecimens are validated for the assessment of usual intake of selenium. Upon evaluation of these studies, it is found that some association may exist between levels of serum and CSF samples of selenium and incidence of PD, although this remains inconclusive. This warrants further investigation as to whether CSF selenium levels may be validated for usual intake, or further studies may utilize validated dietary assessment tools to identify association of deficiency of selenium with PD diagnosis. CSF levels of vitamin E were also assessed in excluded studies which may also be warranted for further evaluation as a potential marker of usual intake with its relevance to incidence of PD studies (58).

Many of the studies were case-control studies, a lower quality of evidence in comparison to more longitudinal style assessments to monitor onset of PD. However, with these case-control studies it would have provided a greater body of information to assess the overall nutritional composition of diets with one another (i.e. PD is associated with states of deficiency of vitamin E and C, but not with deficiency of vitamin E and normal intake of vitamin C). This would have provided a more realistic assessment of the dietary interactions of antioxidants as it pertains to a natural diet. This would also have been beneficial in anticipating the influence of whether a deficiency of antioxidants or increased pro-oxidative metabolic demands are favored in the risk of developing PD. All nutritional assessment tools evaluated observational, retrospective dietary analysis rather than any sort of longitudinal or intervention-based approach. Given neurodegenerative nature of the condition, a stronger emphasis on prospective cohort studies may be beneficial to obtain a more scientifically rigorous level of evidence on the matter.

For this study, we generated what was felt to be an applicable, logical interpretation of incidence as it pertained to the current body of literature. This definition is not necessarily one that allowed for causal interpretation of the evidence. Given the nature of primarily retrospective, observational studies, we were unable to report if any change in risk of developing PD is truly from mitigating the risk of developing the condition, or if it causes delayed onset of the condition beyond the study parameters. We are unable to identify incidence prevalence given the time frame of many of these studies and lack of predictive modeling included within our study.

An additional limiting factor lies in the nutritional demands and difference in dietary composition if evaluating individuals who have PD at various points in disease process. Individuals with PD have a higher resting metabolic rate and have greater caloric expenditure as

a result (59). Many of the studies did not clearly report if the PD group was advanced PD which would increase likelihood of including patients with dementia or oropharyngeal dysphagia. Many of these studies did not specify the level of disability that was allowable within the sample population.

This systematic review was not without limitations. This systematic review did not present restrictions on the method of diagnosis of case participants leaving some potential for diagnostic bias and inconsistent reporting between clinicians. Other limitations include the narrow scope of micronutrient inclusion for this study in addition to the limited output for some micronutrients and no result for three of the antioxidants of interest. This suggests that our search criteria may have been restrictive, or our inclusion/exclusion criteria may have been too stringent. The influence of the microbiome was not included in this study as this scope requires formal independent review. The microbiome may be in close relationship with level of oxidative stress and is a tertiary influence on the outcomes related to patterns of micronutrient intake(60). This study only included studies that the full-text was publicly available to the reader in English. It is possible that articles in other languages or not available to the researchers may have met our eligibility criteria but were unable to be fully evaluated. Additional limitations of the current review involved the lack of specification of the type of data that was permitted for presentation in the study; the variable data presentation restricted the ability to perform aggregate analyses to gain further understanding of the data.

Other limitations of some of the included studies involve the subjective nature of many forms of dietary questionnaires to gain information regarding patterns of intake (61). Most questionnaires were completed in self-reported measures which are particularly subject to impaired accuracy based on participant reporting bias. One such study included self-reporting of

data from 20 years prior making it particularly susceptible to reporting bias (31). This is an acceptable limitation that is inherent to much of nutrition research. Many studies evaluated a wide range of participants and while they did not specifically investigate genetically associated PD, it is possible that some of the individuals with onset at younger age may have had undiagnosed genetically predisposed PD, therefore the decision was made to not include any studies including any individuals less than 50 years of age. This systematic review included components from both dietary and supplemental intake of micronutrients to obtain a more realistic ideal of what nutritional composition of that individual is in vivo, however the differential metabolic functioning of supplements remains intertwined with the results of the current data.

Implications

The intended outcome of this study was to provide information that can guide various practitioners to mitigate the risk of onset in older adults to reduce the risk of developing PD. The consideration of oxidative stress with respect to micronutrient intake ideally would be actively assessed by the nutrition community and become a formal portion of the Assessment, Diagnosis, Intervention, and Monitoring/Evaluation (ADIME) assessment to mitigate the risk of older adults developing PD if a more formal framework stratifying risk and intake is revealed. A theoretical formal recommendation regarding level of intake will not be able to be established from the findings of this review as findings were not conclusive and necessitate further research to elucidate the relationship more clearly between patterns of dietary intake and incidence of PD.

Conclusion

Upon assessment of the entire body of literature regarding the association between risk of PD and intake of antioxidants of the glutathione pathway (vitamins C, D, E, and niacin,

riboflavin, and selenium) it was found that vitamin D revealed the most prevalence in the literature and the most consistent inverse relationship between risk and intake. Results of vitamin C and E did not reveal a clear relationship, or lack thereof between intake and incidence of PD, the effect is largely inconclusive. The search did not yield any result for niacin, riboflavin or selenium. Vitamin D intake, either through dietary measures or supplementation, appears to be protective in incidence of onset of PD from an observational standpoint. Medical practitioners and dietitians may benefit from recommending routine vitamin D assessment and supplementation as needed in the elderly population but we cannot definitely report whether this would be associated with decreased risk of PD without further interventional or longitudinal-based studies. The relationship between the antioxidants of the glutathione redox pathway and risk of PD is not clear at this time given the lack of available data surrounding several of the antioxidants. Further research should be conducted to evaluate the association between level of intake of these micronutrients and incidence of PD.

Other Information

There are no financial disclosures for this study. The author does not report any conflicts of interest. This review is registered through PROSPERO. An update to the review protocol was completed after initial approval of the research proposal of this systematic review with input from subject matter experts.

Appendices

Table 1. Title Search Terms

Column A	"AND"	**Column B**
Parkinson's Disease		Vitamin D
Parkinsons Disease		Vitamin C
		Vitamin E
		Niacin
		Riboflavin
		Selenium
		Antioxidant(s) – title search only

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Full-text in English available to reviewers • Diagnosis of Primary/Idiopathic Parkinson's Disease as outcome of interest • Explore long-term intake patterns of micronutrients of interest (usual intake assessed via validated biospecimens or diet history questionnaires) • Reporting some association of level of intake with respect to risk of developing PD or differences between the PD and control population • Age of participants ≥50 years old (or mean age ≥50 + 1SD, if reported)	• Secondary Parkinsonism (drug-induced, extra-pyramidal parkinsonism) • Studies primarily investigating individuals ≤50yo (or if mean +1SD ≤50 if range partially includes ≤50) • Secondary literature (except systematic review or meta-analysis as above) • Non-human studies (animal models, in vivo/in vitro cellular/molecular research) • CBEM evidence levels 4 or 5 • Investigating population with genetic predisposition to PD or early onset PD

Table 3. Characteristics of Primary Research Studies

Study (author/year)	Study Type	Sample Size Case:Control (+PD, -PD)	Demographic of Interest	Specific Qualities of PD Group	Nutrient Assessment Tool	Effect on PD
Ahangar (2018) (18)	CC	50:50	Age≥60yo		25(OH)D	VD (-)
Ding (2013) (19)5/12/22 5:25:00 PM	CC	388:273	Harvard Biomarker Study, age >21yo, MMSE >21	"early stage of PD"	25(OH)D-3	VD (-)
Evatt (2008) (20)	CC	100:99	PD DX		25(OH)D	VD (-)
Fahmy (2020) (21)	CC	50:50	Age 45-70yo, Egyptian population		25(OH)D-3	VD (-)
Foy (1999) (22)	CC	41:41	MMSE >25, UK population		Serum VE	VE (+/-)
Gezen-Ak (2017) (23)	CC	382: 242	No family history of PD, Turkish population	Use of dopamine therapy	25(OH)D	VD (-)
Knekt (2010) (41)	CO	(+PD 50 -PD 3,123)	Mini-Finland Health Survey, Finnish population		25(OH)D	VD (-)
Logroscino (1996) (24)	CC	110:287	Community dwelling in NYC		SQ- FFQ	VE (+/-) VC (+/-)
Miyake_AOx (2011) (25)	CC	249:368	Japanese population	Within 6 years of disease onset	SQ- DHQ	VE (-) VC (+/-)
Miyake_VitD (2011) (26)	CC	249:368	Japanese population	Within 6 years of disease onset	SQ- DHQ	VD (+/-)
Nicoletti (2001) (27)	CC	54:93	Italian population		Serum VE	VE (+/-)
Ozturk (2016) (15)	CC	115:117	55-85yo, Turkish population	H&Y staging ≤4	25(OH)D	VD (-)
Ozturk (2020) (28)	CC	124:116	50-80yo, Turkish population		25(OH)D	VD (-)
Petersen (2014) (30)	CC	121:235	Faroese population	Within 6 years of diagnosis	25(OH)D	VD (-)
Scheider (1997) (31)	CC	57:50	White, male, 40-79yo		Health Habits and History Questionnaire	VE (+/-) VC (+)

Schirinzi (2019) (32)	CC	100:100	Italian population		"Structured ad hoc interview"	VE (-)
Sleeman (2017) (32)	CC	145: 94	UK population	"Newly diagnosed PD"	25(OH)D	VD (-)
Soliman (2019) (34)	CC	25:25	Egyptian population	Established in outpatient neurology clinic	25(OH)D	VD (-)
Wang (2016) (35)	CC	201:199	Chinese population	"Newly diagnosed" PD patients	25(OH)D , SQ- FFQ	VD (-)
Yang (2017) (39)	CO	(+PD 1,329 -PD 83,445)	Swedish Mammography Cohort and Cohort of Swedish Men, Swedish population		FFQ	VE (-) VC (-)
Ying (2020) (40)	CO	(+PD 544 -PD 59,703)	Singapore Chinese Health Study, Chinese population		SQ-FFQ	VE (+/-) VC (+/-)
Yoon (2015) (36)	CC	81:52	South Korean population		25(OH)D	VD (-)
Yuan (2000) (37)	CC	26:26	Taiwanese population	Stable symptoms on levodopa therapy, community dwelling	Serum VE	VE (+/-)
Zhu (2014) (38)	CC	209: 210	Chinese population		SQ-FFQ	VD (-)

CC=Case Control; CO=Cohort Study; PD DX = No additional demographic criteria regarded for patients, study completed in USA; 25(OH)D = Serum 25-hydroxyvitamin D; VE = Vitamin E; VC=Vitamin C; VD=Vitamin D; (+)=Positive association between levels and PD incidence; (+/-) = No change in risk of PD; (-) =Negative association between levels and PD incidence; +PD=Diagnosed with PD; -PD=Not diagnosed with PD; FFQ=Food Frequency Questionnaire; DHQ=Diet History Questionnaire; 24-HR=24-Hour Dietary Recall; SQ=Semi-quantitative

Table 4. Effect of Micronutrient Intake on Risk of Parkinson's Disease

Study	OR, RR, HR	95% CI	p-value [IQR, if sole value reported]	Variables in risk adjustment	Interpretation of findings
Vitamin D					
Ahangar (18)	OR=4.17*	1.371-12.71	P=0.012*	Age, gender, education	Mean serum vitamin D significantly lower in PD than control
Ding (19)			P=0.032* P=0.0034*	Age, sex, race, vitamin D supplementation	Mean serum total vitamin D significantly lower in PD than control Mean serum vitamin D3 significantly lower in PD than control
Evatt (20)			P=.01* P=0.008*		Vitamin D mean was significantly lower in PD than control. Vitamin D deficiency and insufficiency significantly more prevalent in PD than control
Fahmy (21)			P=0.029*		Mean serum vitamin D3 significantly lower in PD than control
Gezen-Ak (23)		13.3-16.0*	p<0.001*	Age, sex, season adjusted, sporadic PD status	Mean serum vitamin D significantly lower in PD than control
Knekt (41)	RR=0.3*	0.14-0.80*	P=0.006*	Age, sex, BMI, leisure-time, physical activity, smoking, education, marital status,	Inverse association between serum vitamin D level and PD

				alcohol consumption, month of blood draw	
Lv (62)	OR=1.5* OR=2.2*	-33.5 to -0.2 1.1-2.0 1.5-3.4			PD subjects have lower levels of vitamin D compared to controls Patients with vitamin D insufficiency had increased risk of PD Patients with vitamin D deficiency had increased risk of PD
Miyake_VitD (26)	Q2: OR=0.65 Q3: OR=0.83 Q4: OR=0.82	Q2: 0.38-1.09 Q3: 0.50-1.37 Q4: 0.46-1.47	P=0.69	Age, sex, region of residence, pack-years smoking, years of education, BMI, dietary intake of cholesterol, glycemic index, vitamin E, beta-carotene, vitamin B6, caffeine, iron, alcohol	There was no significant association between level of intake of vitamin D and incidence of PD
Ozturk_2016 (29)			Males and females p<0.001* Males p=0.008 Females p=0.004*		Mean serum vitamin D significantly lower in PD than control for both males and females Vitamin D deficiency and insufficiency significantly more prevalent in PD than control for both males and females
Ozturk_2020 (28)			P<0.001* P=0.038*		Mean serum vitamin D significantly lower in PD than control

					Mean serum vitamin D significantly lower in early PD than control
Petersen (30)			P<0.001* P=0.038*		Mean serum vitamin D significantly lower in PD than control Mean serum vitamin D significantly lower in early PD than control
Rimmelzwaan (47)			P<0.00001*		Serum vitamin D levels are lower in PD than in control group
Shen (44)	OR=2.08* OR=1.29*	1.63-2.65 1.10-1.51			Vitamin D deficiency increased risk of PD Vitamin D insufficiency increases risk of PD
Sleeman (33)			P=0.005* P=0.002*		Mean vitamin D levels are lower in PD compared to controls at baseline Mean vitamin D levels are lower in PD compared to controls at 18 months
Soliman (34)			P=0.001* P<0.001*		Vitamin D mean was significantly lower in PD than control Vitamin D deficiency significantly more prevalent in PD than control
Wang (63)	Q1: OR=1* Q2: OR=10.668* Q3: OR=10.656*	Q1 1 Q2: 0.373, 1.197 Q3: 0.356, 1.209	P=0.04*	Age, sex, BMI, smoking, alcohol use, vitamin D intake, education	Vitamin D mean was significantly lower in PD than control

	Q4: 0 OR=1.499*	Q4 (0.268, 0.930)			
Yoon (36)			P=0.01* P=0.02*		Vitamin D mean was significantly lower in PD than control Vitamin D deficiency significantly more prevalent in PD than control
Yan Zhao (45)		-2.44 to -0.21			PD patients had lower levels of vitamin D compared to healthy control groups
Zhu (38)	OR=0.538*	0.301-0.960	P=0.011*	Age, sex, education, BMI, alcohol use, smoking	At highest quartile of intake, a negative association between vitamin D intake and PD is observed
Vitamin E					
Etminan (+) (43)	Moderate intake RR=0.81* High intake RR=0.78*	Moderate intake 0.67-0.98 High intake 0.57-1.06			Moderate intake of vitamin E decreases risk of developing PD High intake of vitamin E decreases risk of developing PD
Foy (22)			[PD[IQR 21.0-42.0 Control IQR 20.0-32.0]		No significant difference between serum vitamin E between PD and control
Logroscino (+) (64)			P=0.81		Vitamin E intake was not associated with PD
Miyake_AOx (+) (25)	Q2: OR=0.49 Q3: OR=0.41	Q2: 0.29-0.81 Q3: 0.24-0.71	P=0.009	Age, sex, region of residence, pack-years smoking, years of education, BMI, dietary	Vitamin E at in quartiles Q2, Q3, Q4 of intake are significantly preduced

	Q4: OR=0.45	Q4: 0.25-0.70		intake of cholesterol, total dairy products, coffee, and dietary glycemic index	incidence of PD compared to Q1 level of intake
Nicoletti (27)			P=0.359		No significant difference between vitamin E intake in PD and controls
Scheider (+) (31)	OR=1.18	0.47-2.98		Age, education, smoking, rural living, total energy intake	No reduction in PD risk associated with higher vitamin E risk
Schirinzi (32)	OR=1.022*	0.999-1.045	P<0.05	Age, gender	Vitamin E intake is directly associated with control status (risk reduction of PD with higher vitamin E intake)
Yang (+) (39)	HR=0.69* HR=0.91*	0.52-0.90 0.93	P=0.02* P=0.02*	Smoking status, intake of alcohol, coffee, BMI, highest level of education, multivitamin supplementation, total energy intake	Inverse association between dietary intake of vitamin E and risk of PD in women at highest quartile Inverse association between dietary intake of vitamin E and risk of PD in men (when assessed as continuous variable per 1.2 mg/day intake)
Ying (+) (40)	HR=1.23 (highest quartile of intake)	0.90-1.70	P=0.38	Age at recruitment, yar of interview, sex, dialect group, level of education, daily energy intake, BMI, cigarette smoking, black tea intake, caffeine intake, cholesterol intake, monounsaturated fat intake	No clear association between intake of vitamin E and PD

Yuan (37)			p>0.001		No significant difference between serum vitamin E between PD and controls
Vitamin C					
Etminan (+) (43)	Moderate intake: RR=1.02 High intake: RR=1.00	Moderate intake: 0.87-1.18 High intake: 0.80-1.24			No significant benefit to PD risk reduction with diets moderate or high in vitamin C
Logroscino (+) (24)			P=0.78	Age, sex, race, education, total energy (calories)	Vitamin C intake was not associated with PD
Miyake_AOx (+) (25)			P=0.95	Age, sex, region of residence, pack-years smoking, years of education, BMI, dietary intake of cholesterol, total dairy products, coffee, and dietary glycemic index	There is no significant association between quartiles of intake of vitamin C and incidence of PD
Scheider (+) (31)	OR=1.48	0.67-3.29		Age, education, smoking, rural living, total energy intake	Trend towards higher PD risk with increasing intake of Vitamin C
Yang (+) (39)	HR=0.77	0.58-1.03	P=0.04*	Smoking status, intake of alcohol, coffee, BMI, highest level of education, multivitamin supplementation, total energy intake	Vitamin C intake is inversely associated with PD risk in women at borderline significance at highest quartile of intake (borderline significance)
Ying (+) (40)	HR=1.30 (highest quartile of intake)	1.01-1.67	P=0.10	Age at recruitment, yar of interview, sex, dialect group, level of education, daily energy intake, BMI,	No clear association between intake of vitamin C and PD

				cigarette smoking, black tea intake, caffeine intake, cholesterol intake, monounsaturated fat intake	

*=significant finding ($p<0.05$)
(+)=Present in multiple sections
HR=Hazard Ratio; OR=Odds Ratio; RR=Relative Risk; Q=Quartile; PD=Parkinson's Disease

Table 5. Systematic Review/Meta-Analysis Report of Antioxidant Intake and Association with Risk of Parkinson's Disease

Author (Year)	**Study Type**	**Total Studies (#)**	**Effect on PD**
Chang (2021) (42)	MA	13	VE (-) VC (+/-)
Etminan (2005) (43)	MA	8	VE (-) VC (+/-)
Lv (2014) (46)	SR/MA	7	VD (-)
Rimmelzwaan (2016) (47)	SR/MA	8	VD (-)
Shen (2015) (44)	MA	7	VD (-)
Yan Zhao (2013) (45)	MA	6	VD (-)
Zhou (2019) (48)	SR/MA	8	VD (-)

VC = Vitamin C; VD = Vitamin D; SR = Systematic Review; MA = Meta-Analysis; (+) Direct Association; (-) Indirect Association

Table 6. Joanna Briggs Institute (JBI) Case Control Study Critical Appraisal Results

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Include
Ahangar (18)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ding (19)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Evatt (20)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Fahmy (21)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Foy (22)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Gezen-Ak (23)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
King (65)	N	Y	U	Y	Y	N	N	Y	Y	U	N
Logroscino (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Miyake_AOx (25)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Miyake_VitD (26)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Molina (58)	N	Y	Y	Y	Y	N	N	Y	Y	Y	N
Murakami (66)	U	N	Y	Y	Y	Y	Y	Y	Y	Y	N
Nicoletti (27)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Ozturk_2016 (29)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Ozturk_2020 (28)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Petersen (30)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Scheider (31)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Schirinzi (32)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Sleeman (33)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Soliman (34)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Van den Bos (67)	U	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wang (35)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yoon (36)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Yuan (37)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Zhu (38)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y=Yes N=No U=Unclear

Table 7. Joanna Briggs Institute (JBI) Cohort Study Critical Appraisal Results

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Include
Knekt (41)	Y	Y	Y	Y	Y	Y	Y	Y	N	U	Y	Y
Yang (39)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y

Ying (40)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y

Table 8. Risk of Bias in Systematic Review (ROBIS) Critical Appraisal of Systematic Review/Meta-Analyses Responses: Domain 1

	Q1.1	Q1.2	Q1.3	Q1.4	Q1.5	Concerns
Chang (42)	Y	Y	Y	PY	PY	Low
Etminan (43)	PY	PY	PN	NI	PN	High
Lv (46)	Y	Y	Y	Y	NI	Low
Rimmelzwaan (47)	Y	Y	PY	Y	Y	Low
Shen (44)	Y	Y	Y	Y	Y	Low
Yan Zhao (45)	Y	Y	Y	Y	Y	Low
Zhou (48)	Y	Y	Y	Y	Y	Low

Table 9. Risk of Bias in Systematic Review (ROBIS) Critical Appraisal of Systematic Review/Meta-Analyses Responses: Domain 2

	Q2.1	Q2.2	Q2.3	Q2.4	Q2.5	Concerns
Chang(42)	Y	Y	Y	NI	Y	Low
Etminan (43)	Y	Y	Y	Y	Y	Low
Lv (46)	Y	Y	Y	NI	Y	Low
Rimmelzwaan (47)	Y	Y	Y	Y	Y	Low
Shen (44)	Y	Y	Y	Y	Y	Low
Yan Zhao (45)	Y	Y	Y	Y	Y	Low
Zhou (48)	Y	Y	Y	Y	Y	Low

Table 10. Risk of Bias in Systematic Review (ROBIS) Critical Appraisal of Systematic Review/Meta-Analyses Responses: Domain 3

	Q3.1	Q3.2	Q3.3	Q3.4	Q3.5	Concerns
Chang(42)	Y	Y	Y	Y	Y	Low
Etminan (43)	PN	Y	Y	PY	PY	High
Lv (46)	Y	Y	Y	Y	Y	Low
Rimmelzwaan (47)	Y	Y	Y	N	N	Unclear
Shen (44)	Y	Y	Y	N	N	Unclear
Yan Zhao (45)	Y	Y	Y	N	N	Unclear
Zhou (48)	Y	Y	Y	Y	Y	Low

Table 11. Risk of Bias in Systematic Review (ROBIS) Critical Appraisal of Systematic Review/Meta-Analyses Responses: Domain 4

	Q4.1	Q4.2	Q4.3	Q4.4	Q4.5	Q4.6	Concerns

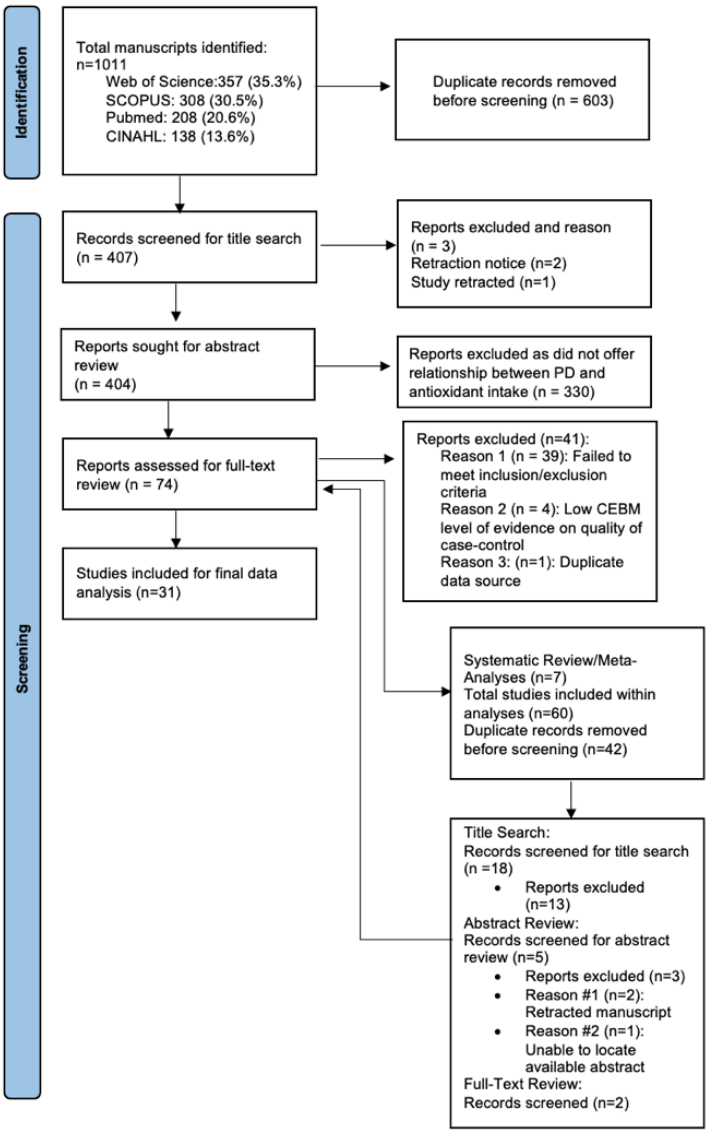
Chang (42)	Y	Y	Y	Y	Y	Y	Low
Etminan (43)	Y	Y	Y	Y	Y	Y	Low
Lv (46)	Y	Y	Y	Y	Y	Y	Low
Rimmelzwaan (47)	Y	Y	Y	Y	Y	N	Low
Shen (44)	Y	Y	Y	Y	YY	Y	Low
Yan Zhao (45)	Y	Y	Y	Y	Y	Y	Low
Zhou (48)	Y	Y	Y	Y	Y	Y	Low

Table 12. Risk of Bias in Systematic Review (ROBIS) Critical Appraisal of Systematic Review/Meta-Analyses Responses: Overall Risk of Bias in Review

	A	B	C	Risk Level
Chang (42)	Y	Y	Y	Low
Etminan (43)	PY	Y	Y	Low
Lv (46)	Y	Y	Y	Low
Rimmelzwaan (47)	PY	Y	Y	Low
Shen (44)	Y	Y	Y	Low
Yan Zhao (45)	Y	Y	Y	Low
Zhou (48)	Y	Y	Y	Low

Y=Yes, PY=Probably yes, PN=Probably no, N=No, NI=No information

Figure 1. Flow Chart Documenting Screening Process



Appendix 1. Joanna Briggs Institute (JBI) Critical Appraisal for Case Control Studies Tool

JBI Critical Appraisal Checklist for Case Control Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☐	☐	☐	☐
2. Were cases and controls matched appropriately?	☐	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☐	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☐	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☐	☐	☐	☐
6. Were confounding factors identified?	☐	☐	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	☐	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix 2. Joanna Briggs Institute (JBI) Critical Appraisal for Cohort Studies Tool

JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were confounding factors identified?	☐	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
11. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix 3. Risk of Bias in Systematic Reviews (ROBIS) Tool

ROBIS: Tool to assess risk of bias in systematic reviews

Phase 1: Assessing relevance (Optional)

ROBIS is designed to assess the risk of bias in reviews with questions relating to interventions, aetiology, diagnosis and prognosis. State your overview/guideline question (target question) and the question being addressed in the review being assessed:

Intervention reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Intervention(s):		
Comparator(s):		
Outcome(s):		

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Exposure(s) and comparator(s):		
Outcome(s):		

For DTA reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients):		
Index test(s):		
Reference standard:		
Target condition:		

For prognostic reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients:		
Outcome to be predicted:		
Intended use of model:		
Intended moment in time:		

Does the question addressed by the review match the target question?	YES/NO/UNCLEAR

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding methods used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review	RISK: LOW/HIGH/UNCLEAR
Rationale for risk:	

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

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Curriculum Vitae

Ms. Chelsea Yager, PA-C
200 Tamarack St. Liverpool, NY 13088
(C): 315-404-0442 (E): ccyager1@gmail.com

Licenses/Certificates:

- National Commission of Certification of Physician Assistants (NCCPA) Board Certified
- Current New York State Physician Assistant License
- Current DEA license

Employment Summary:

Physician Assistant, Neurology St. Joseph's Hospital Health Center
September 2019-Present Syracuse, NY

Practice in neurology full-time in a moderate-sized urban community hospital and associated outpatient clinic. This is presently a hybrid position with a 50:50 inpatient:outpatient distribution. I am responsible for follow-up assessments and initial consultations while working at the hospital as well as responding to all neurological emergencies, including attending and directing code stroke evaluations. I also work in our outpatient clinic to assess, diagnose, and treat non-emergent neurological conditions, including appropriately ordering and following up on patient testing and triages.
Applicable Skills:

- Proficient in management of neurologic care in acute, emergency department setting, hospitalized patients on medical floors, and treatment of neurologic conditions of patients in intensive care units (medical/surgical and cardiovascular ICUs)
- Creation and implementation of both diagnostic and treatment plans from a consultant standpoint to provide guidance to primary treatment team.
- Responding to stroke codes to emergently evaluate patient as potential candidate for alteplase and/or mechanical thrombectomy interventions. I respond to and run the stroke code, connecting with attending neurologist over the phone, or update and collaborate with attending when he/she reaches bedside. During this process, I order appropriate emergent diagnostic testing, and offer/administer available stroke intervention or pursue alternate medical intervention as appropriate.
- Interpretation and assessment of imaging modalities of the brain and spine including but not limited to contrasted and non-contrasted CT, CTA, MRI, MRA, MRV.
- Participate in stroke and neurology department quality improvement measures to optimize patient care and implement hospital education and initiatives via multiple committees
- Treat patients with conditions including but not limited to various forms of stroke, seizure, encephalopathy, headache disorders, spinal cord injuries, peripheral nerve injuries, myasthenia gravis and post-cardiac arrest care
- Aid in the learning process for family medicine residents and medical students through formal education, teaching physical examination techniques, and patient interaction.

- Created the neurology education curriculum for rotating residents and students.
- Create asynchronous learning options for continuing education (CE) credits for non-provider member so the stroke team including PM&R department and nursing to maintain DNV accreditation
- Serve as formal preceptor for family nurse practitioner students and mentorship for pre-PA students to provide clinical experience
- Skill to work in diverse multicultural environment in a refugee city, always prioritizing patient understanding and learning and respecting the belief systems of others without assumption

Physician Assistant, Urgent Care River Hospital
March 2021-Present Alexandria Bay, NY

Applicable Skills:

- Provide non-emergent treatment to acute conditions in ages 18 months and older
- Conduct physical examination and obtaining appropriate diagnostic testing as indicated
- Competent in procedures including the following: Simple interrupted sutures, glue adhesion, fish hook removal, foreign body removal, fluorescein staining, cast and splint application, X-ray interpretation, read PPDs

Nutritionist I Cornell Cooperative Extension
May 2016-September 2016 Norwich, NY

Direct Support Professional Liberty Resources
July 2014-December 2016 Binghamton/Syracuse, NY

Education:

Syracuse University Syracuse, NY
Master of Science, Nutrition Science and Dietetics
May 2022
Thesis: A Systematic Review of Antioxidant Synergy and Incidence of Parkinson's Disease

Clarkson University Potsdam, NY
Master of Science, Physician Assistant Studies
May 2019

Binghamton University, SUNY Vestal, NY
Bachelor of Science in Integrative Neuroscience, Molecular Track
May 2014

Certifications:

- Basic Life Support (BLS) through American Heart Association
- Advanced Cardiovascular Life Support (ACLS) through American Heart Association
- National Institute of Health Stroke Scale (NIHSS)

- Certification in Progress: Ketogenic Nutrition Specialist through American Nutrition Association

Professional Training:

- Focused Assessment with Sonography for Trauma (FAST) Examination Training
- Fundamentals of Critical Care Support course completion (Society of Critical Care Medicine)
- Alteplase Administration Certification (August 2021)
- Neurology for the Advance Practice Provider through AAN
- Child Abuse and Maltreatment Mandated Reporter Training
- Heads-Up Concussion Training
- Training Course in Progress: Adult Hospital Medicine Boot Camp through AAPA
- Certification in Progress: Ketogenic Nutrition Specialist through American Nutrition Association

Professional Associations:

- American Academy of Neurology
  October 2019-Present
- American Academy of Physician Assistants (AAPA)
  January 2017-2019
- New York State Society of Physician Assistants (NYSSPA)
  January 2017-2019

Honors and Awards:

- NYSSPA Scholarship Recipient (2017)
- Pi Alpha National Honor Society for Physician Assistants (2019)

Departmental, Community and Professional Service

- Webinar Panelist: Managing Energy and Fatigue During Quarantine, American Pakistan Foundation, April 2020
- Stroke and COVID community education, St. Joseph's Hospital Media Marketing via Facebook Live, September 2020
- Stroke Steering Committee, St. Joseph's Hospital, September 2019 - present
- Stroke Committee, St. Joseph's Hospital, September 2019 - present
- Students Without Borders Medical Mission Trip, Nicaragua, Trip Coordinator , Clarkson University, March 2019
- Students Without Borders Medical Mission Trip, Nicaragua, Clarkson University, March 2018

Research:

Published Manuscripts: and Abstracts

1. Boolani, A., **Yager, C.**, Smith, M., Mondal, S., Sathiyakumar, T., Senarathna, D., Teymouri, S., Vogel-Rosbrook, C., Alvarez, J, Taladay, P., Martin R., 43 State Mental Energy Influences Posture During Vision-Occluded States, *Age and Ageing*, 48(4), December 2019, Pages iv9–iv12, https://doi.org/10.1093/ageing/afz164.43

2. Roy, M., Boolani, A., **Yager, C.**, Teymouri, S., Vogel-Rosbrook, C., Taladay, P., & Martin, J. (2021). INFLUENCE OF OBTAINING RECOMMENDED SLEEP DURATION ON SINGLE-TASK GAIT IN HEALTHY ADULTS: 411. *Medicine & Science in Sports & Exercise*, *53*(8S), 130.
3. Devereaux, C., **Yager, C.** A., Pickett, A. C., Smith, M. L., Martin, J., & Boolani, A. (2021). Predictors of Feelings of Anxiety in Graduate Allied Health Students-An Exploratory Study. *Journal of Allied Health*, *50*(2), 73E-77E.
4. **Yager, C**., & Saada, F. (2020). Innovative Mutli-Approach Therapy for Treatment of Extrapontine Myelinolysis (4769).
5. Mahoney, G., Martin, J., Martin, R., **Yager, C.,** Smith, M. L., Grin, Z., ... & Boolani, A. (2021). Evidence that feelings of energy and fatigue are associated differently with gait characteristics and balance: an exploratory study. *Fatigue: Biomedicine, Health & Behavior*, *9*(3), 125-138.
6. Boolani, A., **Yager, C.,** Reid, J., Lackman, J., & Smith, M. L. (2021). Correlates of depressive mood among graduate-level allied health students: An exploratory study examining trait energy and fatigue. *Journal of American College Health*, 1-12.
7. Stark, M., **Yager, C.,** Taladay, P., Teymouri, S., Alvarez, J., Vogel-Rosbrook, C., ... & Boolani, A. (2020). Manifestation of Anxiety in Gait. *The FASEB Journal*, *34*(S1), 1-1.
8. Boolani, A., Yager, C., Smith, M. L., Mondal, S., Sathiyakumar, T., Senarathna, D., ... & Martin, R. State Mental Energy Influences Posture During Vision-Occluded States.

Manuscripts Under Review:

1. Martin, J., Huang, H., Johnson, R., Yu, L., Jansen, E., Martin, R., **Yager, C.,** Boolani, A. Association between self-reported sleep quality and single-task gait in young adults: A study using machine learning. *Gait & Posture.*
2. Nesshover, L., Carpenter, Sampieri, S., Keefer, J., **Yager, C.,** Pickett, A., Smith, M., Boolani, A. A short report examining the relationship between trait energy and fatigue and feelings of depression in young healthy adults. *International Journal of Psychiatry.*

Manuscripts Under Preparation:

1. **Yager, C.,** Panarites, A., Boolani, A. A systematic review of the most commonly theorized reasons for changes in gait and postural control in patients with Alzheimer's Disease.
2. **Yager, C.,** Boolani, A. Neurological Manifestations of SARS-CoV-2 Infection: A Pilot Study.

Peer Reviewed Scientific and Professional Presentations:

1. LaFay, V., Martin, J., Johnson, R., **Yager, C.,** Boolani, A. Does sleep quality influence gait? An exploratory study in a young, healthy population. American Physical Therapy Association (APTA) Combined Sections Meeting 2021, Orlando, Florida. Abstract accepted

2. **Yager, C**. Saada, F. Innovative Mutli-Approach Therapy for Treatment of Extrapontine Myelinolysis. Poster presentation at American Academy of Neurology 2020, Toronto, ON, Canada. (online platform)
3. Stark, M., **Yager, C**., Taladay, P, Teymouri, S., Alvarez, J., Vogel-Rosbrook, C., Martin, R., Boolani, A. Manifestation of Anxiety in Gait. Experimental Biology 2020, San Diego, CA (Conference cancelled)
4. Boolani, A., **Yager, C.,** Smith, M., Monday, S., Sathiyakumar, T., Senarathna, D., Teymouri, S., Vogel-Rosbrook, C., Alvarez, J., Taladay, P., Martin, R. (2019). State Mental Energy Influences Posture During Vision-Occluded States. Presented at the World Congress on Falls and Postural Stability, December 4-7, 2019, Kuala Lumpur, Malaysia.
5. Senarathna, S, Sathiyakumar, T., **Yager, C.,** Taladay, P, Li, R., Sur, S., Mondal, S., Boolani, A. Multivariate study to determine the postural correlates of trait mental and physical energy and fatigue. Poster session at Clarkson University Spring Research & Project Showcase (RAPS), April, 2019.
6. Robertson, B., Lewis, S., Vashishtha, A., **Yager, C.**, Taladay, P., Mondal, S., Boolani, A. Gait associations with trait moods: Energy and Fatigue. Poster session at Clarkson University Spring Research & Project Showcase (RAPS), April, 2019.
7. **Yager, C.,** Bradley, D., Caruso, J., Boolani, A. The manifestation of anger in walking gait. Poster session at Clarkson University Spring Research & Project Showcase (RAPS), April, 2019.
8. Roy, M., Boolani, A., Yager, C., Teymouri, S., Vogel-Rosbrook, C., Taladay, P., Martin, J. Influence of Obtaining Recommended Sleep Duration on Single-Task Gait in Healthy Adults. American College of Sports Medicine. June 2021.

Grant Activity:

1. Alzheimer Society Research Program
    - Amount requested- $100,000 (Canadian)
    - November 2019
    - PI- Nick Bellissimo, Co-PI- A.Boolani, Co-applicant- **C. Yager**
    - Effect of high versus low glycemic response breakfast meals on glycemic response, amylin, insulin, amyloid-beta 40 and 42 concentrations on cognitive performance in adults with mild cognitive impairments
    - Not funded
2. Retirement Research Foundation
    - Amount requested- $248,669
    - November 2019
    - PI- Nick Bellissimo, Co-PI- A.Boolani, Co-applicant- **C. Yager**
    - Effect of a 45-day high versus low glycemic response breakfast meals on glycemic response, amylin, insulin, amyloid-beta 40 and 42 concentrations on cognitive performance in adults with mild cognitive impairments and those without
    - Not funded