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Onset and progression factors in Parkinson's disease: A systematic review

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ABSTRACT

Current research has identified several factors thought to be associated with the onset and progression of Parkinson's Disease (PD); however, whether certain factors contribute to or are protective against PD remains unclear. As such, a systematic search of the literature was performed using variations of MeSH and keyword search terms to identify and summarize systematic reviews and primary studies pertaining to factors associated with the onset and progression of PD. Factors referred to both traditional risk factors and prodromal markers. The following databases were searched: MEDLINE, MEDLINE In-Process, EMBASE, PsycINFO, Scopus, Web of Science, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Dissertations & Theses, AARP AgeLine, and PDGene. A quality assessment of included systematic reviews was completed using the validated Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool. Data extraction targeted reported factors, risk estimates, and 95% confidence intervals (CI). Findings identified -+ +reviews of sufficient quality reporting factors for PD onset, and no systematic reviews reporting factors for PD progression. In addition, 93 primary articles were identified, of which, 89 articles addressed factors related to PD onset and 4 articles addressed factors related to the PD progression. Pesticide exposure, rural living, well-water drinking, and farming occupation were consistently found to be positively associated with the onset of PD. Moreover, family history and polymorphisms to key genes were also found to be positively associated with the onset of PD. Conversely, coffee consumption, cigarette smoking, and some polymorphisms were consistently found to be negatively associated with the onset of PD. Urate was the only identified factor linked to the progression of PD; it was mostly found to be negatively associated with PD. In sum, the evidence was systematically found and summarized in the literature pertaining to factors related to the onset and progression of PD.

1. Introduction

Parkinson's disease (PD) is a common neurological condition, affecting 1 in 300 Canadians (Parkinson Post, 2005). It is particularly prevalent in the elderly as the incidence increases with age (de Lau et al., 2004). In Western Europe's 5 most and the world's 10 most populous nations, the number of individuals with PD over the age of 50 years was 4.1 and 4.6 million in 2005 respectively, and is expected to nearly double by 2030 – 8.7 and 9.3 million respectively (Dorsey et al., 2007). PD is a complex disorder with several subtypes that are classified according to genetic involvement, time of onset, and presence of dementia. Onset may be sporadic or familial, early or late, and with or without dementia (Crosiers et al., 2011; Spatola and Wider, 2014; Wider and Wszolek, 2007). PD is associated with a disorganization of the circuitry of the basal ganglia, which is caused by the loss of dopaminergic neurons

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in the substantia nigra (Bartels and Leenders, 2009). Physically, this results in timing and scaling problems when the affected individual performs bodily movements (Bartels and Leenders, 2009). The common cardinal motor features of PD include resting tremor, bradykinesia, rigidity, postural instability, stooped posture, and freezing of gait (Savitt et al., 2006). Also, as many as 40% of patients with PD have cognitive impairment or dementia (Shulman et al., 2001; Braak et al., 2006). Together, these motor and nonmotor features contribute largely to functional difficulties; thereby, affecting the individual's ability to perform activities of daily living (Weintraub et al., 2004), and eventually increase morbidity and mortality (Savitt et al., 2006). As such, individuals with PD have an increasing need for social and medical care resulting in a potentially large economic burden for them, their families, and their care partners (Hindle, 2010).

Current research has identified several factors associated with PD; however, whether certain factors contribute to or are protective against PD remains unclear. The purpose of this study was to systematically identify literature pertaining to select factors associated with the onset and progression of PD. We targeted factors relating to biology, socioeconomics, environment, psychosocial issues, lifestyle, comorbid conditions, and genetics. We sought to provide a comprehensive review of current literature pertaining to these factors in order to provide a basis for policy makers to identify and implement appropriate measures that will mitigate the burden of PD in Canada.

2. Materials and methods

The methods utilized have been provided in detail (Hersi et al., 2017), and hence are only briefly described herein. Our study had two stages. Stage one included a systematic search of existing systematic reviews and *meta*-analyses, while stage two included a systematic search of primary studies (case-control, cohort, and cross-sectional).

2.1. Locating systematic reviews and meta-analyses: stage one

2.1.1. Identification of studies

To identify eligible systematic reviews and *meta*-analyses, searches of the following electronic databases were executed, modified appropriately to that used by the central research office in Ottawa following extensive consultation with local library staff at the University of Toronto: MEDLINE (1946 to September Week 3 2012), MEDLINE In-Process (September 28, 2012), EMBASE (1980 to 2012 Week 39), PsycINFO (1806 to September Week 4 2012), Scopus (1960 to October 1 2012), Web of Science (1899 to October 1 2012), Cochrane Database of Systematic Reviews (until September 2012), and CINAHL (1981 to September 2012). Variations of MeSH and keyword search terms were used that related to PD; its risk factors; progression of the disease; and study type such as systematic review and *meta*-analysis. Refer to Supplementary material I for the complete Medline search strategy.

2.1.2. Inclusion criteria

To be included, eligible studies had to meet all of these inclusion criteria: published in English or French; involved human subjects only; systematic review or *meta*-analysis; evaluated at least one risk factor in relation to the onset or progression of PD; and provided at least one risk estimate.

2.1.3. Study selection

Two raters independently screened all unique citations (titles and abstracts) for eligibility using DistillerSR software (DistillerSR, Evidence Partners, Ottawa, Canada). Full articles for all eligible citations were then assessed for inclusion by the same two independent raters. Discrepancies between raters were resolved by consensus.

2.1.4. Quality assessment

Two raters independently evaluated the quality of selected systematic reviews and *meta*-analyses using the validated Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) tool (Shea et al., 2007) in the DistillerSR software. Reviews that scored low (three or less) were excluded, while reviews that scored moderate (between four and seven) or high (greater than eight) were included in this review. Discrepancies with AMSTAR scores were resolved by consensus with a third rater. Refer to the Methodology paper by Hersi et al. (2017) for the AMSTAR tool.

2.1.5. Data collection

Two raters independently extracted the data for the included systematic reviews and *meta*-analyses using the DistillerSR software. The data extracted included methodological design details such as, years of capture, databases utilized, risk factor(s), risk estimates, whether or not publication bias was addressed by the authors, and whether or not a heterogeneity test had been performed for pooled data.

2.2. Locating primary studies: stage two

2.2.1. Identification of studies

To identify eligible primary articles, the following electronic databases were searched, once again modified appropriately to that used by the central research office in Ottawa following extensive consultation with local library staff at the University of Toronto: MEDLINE (1946 to February Week 1 2012), MEDLINE In-Process (February 09, 2012), EMBASE (1980 to 2012 Week 05), PsycINFO (1806 to February Week 1 2012), Scopus (1960 to February 14, 2012), Web of Science (1899 to February 14, 2012), Cochrane Library (Until February 2012), CINAHL (1981 to February 2012), ProQuest Dissertations & Theses (1997 to February 10, 2012), and AARP Ageline (1978 to February 10, 2012). Refer to Supplementary material II for our complete Medline search strategy.

A systematic search was performed using variations of MeSH and keyword search terms to identify primary studies pertaining to factors associated with the onset and progression of PD. Search terms included factors that might be associated with risk of PD onset and/or progression; namely factors pertaining to biological, lifestyle, socioeconomic, environmental, and psychosocial issues, as well as co-morbidities. Additionally, only articles that used an observational study design were included. Articles utilizing randomized control design were excluded, as this review was not targeting pharmacological and/or clinical treatment factors.

2.2.2. Inclusion criteria

To be included, eligible articles had to meet all of the following inclusion criteria: published in English or French; involved human subjects only; evaluated at least an onset and, or progression factor; case-control or cohort or cross-sectional study; and provided at least one risk estimate.

2.2.3. Study selection

The liberal accelerated method was utilized (Hersi et al., 2017). One reviewer screened the titles and abstracts of all search results, as well as screened all full articles of included studies. A second