



Review

Occupational exposure to pesticides and Parkinson's disease: A systematic review and meta-analysis of cohort studies

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ABSTRACT

Objectives: To systematically review available cohort studies and estimate quantitatively the association between occupational exposure to pesticides and Parkinson's disease (PD).

Methods: Studies were identified from a MEDLINE search through 30 November 2011 and from the reference lists of identified publications. Relative risk (RR) estimates were extracted from 12 studies published between 1985 and 2011. Meta-rate ratio estimates (mRR) were calculated according to fixed and random-effect meta-analysis models. Meta-analyses were performed on the whole set of data and separate analyses were conducted after stratification for gender, exposure characterisation, PD cases identification, geographic location, reported risk estimator and cohort study design.

Results: A statistically significant increased risk of PD was observed when all studies were combined (mRR = 1.28; 95% confidence interval [CI]: 1.03–1.59) but there was a high heterogeneity and inconsistency among studies. The highest increased risks were observed for studies with the best design, i.e. reporting PD diagnosis confirmed by a neurologist (mRR = 2.56; CI: 1.46–4.48; $n = 4$), for cohort studies reporting incidence of PD (mRR = 1.95; CI: 1.29–2.97; $n = 3$) as well as for prospective cohorts (mRR = 1.39; CI: 1.09–1.78; $n = 6$). A significant increased risk was also seen for banana, sugarcane and pineapple plantation workers (mRR = 2.05; CI: 1.23–3.42; $n = 2$).

Conclusions: The present study provides some support for the hypothesis that occupational exposure to pesticides increases the risk of PD.

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Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; HWE, healthy worker effect; mRR, meta-rate ratio estimate; PD, Parkinson's disease; PMR, proportional mortality ratio; PR, prevalence ratio; RR, relative risk; SHR, standardized hospitalization (for PD) ratio; SMR, standardized mortality ratio; 95% UI, 95% uncertainty interval.

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1. Introduction

Parkinson's disease (PD, primary parkinsonism) is a movement disorder which develops as a result of the degeneration of dopaminergic neurons in the substantia nigra. PD is the most frequent adult neurodegenerative disorder after Alzheimer's disease (Olanow and Tatton, 1999). It is clinically characterised by 4 cardinal signs: bradykinesia (slow movements), chronic progressive rest tremor, rigidity and postural instability. "Parkinsonism" refers to PD symptoms that are components of syndromes that include other signs or symptoms that are not characteristic of PD (Wirdefeldt et al., 2011). The term "parkinsonism" is typically used for syndromes with known aetiology, such as ischemic injuries, exposure to toxins or neuroleptic medications.

PD is principally a disease of ageing, with a peak age of onset between 60 and 65 years although young-onset (upper limit arbitrarily restricted to 40 years of age) as well as juvenile (before the age of 21 years) PDs are also reported (Paviour et al., 2004; Schrag and Schott, 2006). Overall, incidence rates for PD in studies that reported results for all age groups ranged between 1.5 and 22 per 100,000 person-years (Wirdefeldt et al., 2011). The frequency of PD varies across the world with higher prevalence and incidence rates in European (von Campenhausen et al., 2005) and North American populations (Wright Willis et al., 2010) and with a men/women ratio of 1.5 (Taylor et al., 2007).

The etiology of PD remains largely unknown but is likely to be multifactorial resulting from both genetic and environmental factors as recently reviewed by Wirdefeldt et al. (2011). The main risk factor is clearly age. Identified genetic risk factors are rare and account for only a small percentage of PD cases (Wood-Kaczmar et al., 2006). Several environmental exposures influencing the risk of PD have been identified (Tanner, 2010). Factors inversely associated with PD include cigarette smoking, coffee/caffeine intake, high uric acid levels and anti-inflammatory drug use. Less well-established inverse associations with PD include high cholesterol levels, statin use, high dietary vitamin B6, and night shift work. Factors associated with an increased risk of PD include pesticide exposure, head trauma, certain occupations and milk consumption (Tanner, 2010).

Studies on the relation between pesticides and PD were triggered by the description of parkinsonism in drug users exposed to 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) shown to cause degeneration of dopaminergic neurons in animals (Bove et al., 2005; Langston et al., 1983) as well as by the similarity between the chemical structure of MPP⁺ (1-methyl-4-phenylpyridinium; the toxic metabolite of MPTP) and that of the bipyridylum herbicides (e.g. paraquat and diquat) (Elbaz et al., 2009). A large body of epidemiologic literature exists concerning pesticides and PD, most of them relying on a case-control design. However, evidence of an increased risk of PD associated with exposure to pesticides remains inconsistent. Case-control studies were combined in three meta-analyses (Priyadarshi et al., 2000, 2001; van der Mark et al., 2012) and reviewed in details by several authors including Li et al. (2005), Brown et al. (2006), Wirdefeldt et al. (2011). These authors concluded that the weight of evidence of an association between pesticide exposure and PD exists but is insufficient for concluding to a causal relationship. A potential for recall bias has been suggested to explain, at least partially, the association between pesticide exposure and PD in case-control studies (Rugbjerg et al.,

2011). During the last ten years, several studies with a cohort design focusing on occupational exposure to pesticides have been published, offering an opportunity to reduce the possible influence of recall bias. Two descriptive reviews of 4 and 5 cohort studies concluded to a possible association between pesticide exposure and PD and to the need of further research (Brown et al., 2006; Wirdefeldt et al., 2011). In the meta-analysis of van der Mark et al. (2012), using restrictive study selection criteria, a substratification of four cohort studies resulted in a non statistically significant increased risk of PD.

The purpose of the present study was to perform a comprehensive systematic review and meta-analysis focusing on published cohort studies on the association between occupational pesticide exposure and PD, including studies published very recently and not included in the previous systematic reviews and meta-analyses. The aim is to enhance our understanding of the potential involvement of such exposures in the aetiology of PD as well as to identify specific risk factors.

2. Materials and methods

2.1. Study identification and selection

2.1.1. Study identification

Publications were identified by a search on MEDLINE (National Library of Medicine, Bethesda, MD) conducted for the period 1966 to 30th November 2011 using various combinations of the following key words: pesticide(s), herbicides, insecticides, fungicides, occupation, occupational, farmers, agriculture, horticulture, pesticide applicators, manufacturing workers, Parkinson, Parkinsonism, Parkinsonian, cohort study, prospective, retrospective, historical with no restriction of publication date. The reference lists of the relevant publications identified were checked for additional studies. The search was limited to studies published in English in the open literature in peer-reviewed journals. All titles or abstracts were screened to determine the suitability of the publication.

2.1.2. Study selection

A publication was considered eligible for further review if (1) it referred to workers occupationally exposed to pesticides (farmers, pesticide applicators, workers engaged in the manufacture of pesticides and others such as horticulturists, greenhouse workers, gardeners, ...), (2) if the outcome included Parkinsonian disorders or associated diseases (referenced as Parkinson's disease, Parkinsonism) and (3) if the publication presented original data from a cohort design. Studies reporting prevalence ratios and referring to past exposure and past or current diagnosis were regarded as historical cohort studies. Excluded studies were those published in a non-English language, experimental studies, or studies focusing only on genetic data. Proportional mortality ratio (PMR) studies were excluded mainly due to ambiguities in interpreting results. We also excluded studies providing no Parkinson's disease cases or insufficient data to determine an estimator of relative risk (RR) for PD and its confidence interval (CI). The systematic review and identification of eligible studies was performed by VMFG.

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