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Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands

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ABSTRACT

Background: Exposure to pesticides has been linked to Parkinson's disease (PD), although associations between specific pesticides and PD have not been well studied. Residents of rural areas can be exposed through environmental drift and volatilization of agricultural pesticides.

Objectives: Our aim was to investigate the association between lifetime environmental exposure to individual pesticides and the risk of PD, in a national case-control study.

Methods: Environmental exposure to pesticides was estimated using a spatio-temporal model, based on agricultural crops around the residential address. Distance up to 100 m from the residence was considered most relevant, considering pesticide drift potential of application methods used in the Netherlands. Exposure estimates were generated for 157 pesticides, used during the study period, of which four (i.e. paraquat, maneb, lindane, benomyl) were considered *a priori* relevant for PD.

Results: A total of 352 PD cases and 607 hospital-based controls were included. No significant associations with PD were found for the a priori pesticides. In a hypothesis generating analysis, including 153 pesticides, increased risk of PD was found for 21 pesticides, mainly used on cereals and potatoes. Results were suggestive for an association between bulb cultivation and PD.

Conclusions: For paraquat, risk estimates for the highest cumulative exposure tertile were in line with previously reported elevated risks. Increased risk of PD was observed for exposure to (a cluster of) pesticides used on rotating crops. High correlations limited our ability to identify individual pesticides responsible for this association. This study provides some evidence for an association between environmental exposure to specific pesticides and the risk of PD, and generates new leads for further epidemiological and mechanistic research.

1. Introduction

Parkinson disease (PD) is an idiopathic neurodegenerative disease, which is second most prevalent worldwide after Alzheimer's Disease. Decreased motor function is one of the main symptoms, caused by the progressive degeneration of dopaminergic neurons in the substantia nigra, resulting in dopamine deficiency (Wirdefeldt et al., 2011). Motor symptoms become apparent when roughly 30% of dopaminergic neurons are lost, but several non-motor symptoms have been reported to precede motor symptoms and PD diagnosis by several years to decades (Tolosa and Pont-Sunyer, 2011; Pont-Sunyer et al., 2015). Research indicates that PD is associated with aging and gender, and familial aggregation studies support the role of genetics. However, these genetic factors appear to be mainly associated with early-onset PD (Martin et al., 2011). Environmental factors have been suggested as potentially involved in the etiology of PD, especially for older-onset PD cases (Wirdefeldt et al., 2011).

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Pesticides are one of the exposures frequently linked to PD. Occupational exposure to pesticides has rather consistently been associated with an increased risk of PD, and a meta-analysis found a 60% increased risk for being ever exposed (van der Mark et al., 2012). Besides occupational exposure to pesticides, several studies also investigated environmental residential exposure to pesticides, utilizing spatial data on agricultural land-use in geographic information systems (GIS) and data on pesticide use (Nuckols et al., 2007; Brody et al., 2002). Although environmental exposure to pesticides is expected to be lower than exposure in occupational settings, the number of potentially exposed individuals will be higher, including possibly more susceptible subgroups (e.g. children, elderly, subjects with preexisting conditions and poor health). Positive associations between environmental exposure to pesticides and PD risk have been reported, although these studies are mainly limited to the USA (California) (Wang et al., 2014; Costello et al., 2009). Only few epidemiological studies have investigated the association between exposure to individual pesticides and PD.

The Netherlands is unique in terms of dense agriculture and a high population density and a substantial part of the general population therefore may be exposed to (low) concentrations of pesticides in the environment originating from agricultural applications. We have previously developed a spatio-temporal model for the Netherlands to estimate environmental pesticide exposure at the residential addresses, going back to 1961 (Brouwer et al., 2017).

In the current study, we extend on previous work by studying the association between PD risk and residential exposure to pesticides in a European setting, focusing both on pesticides previously suggested to be potentially associated with PD, and a broad screen of pesticides used in the Dutch agricultural sector from 1961 to 2010. This work is part of a large hospital-based case-control study on PD in the Netherlands (van der Mark et al., 2014a).

2. Methods

2.1. Cases and controls

Details of the case-control study have been described previously (van der Mark et al., 2014a). In brief, cases and controls were recruited in five hospitals, covering four regions of the Netherlands, between 2010 and 2012 (Fig. 1). Patients with a first PD diagnosis between January 2006 and December 2011 were considered and their medical files were reviewed by a neurologist to confirm case diagnosis. Controls were selected from patients attending the same neurology departments between January 2006 and December 2011 for non-neurodegenerative symptoms (i.e. median nerve neuropathy; International Classification of Diseases, 10th revision (ICD-10) G56.0 and G56.1, ulnar nerve neuropathy; ICD-10 G56.2, thoracic and lumbar disc disease; ICD-10 G55.1, G54.3 and G54.4, and sciatica; ICD-10 M54.3 and M54.4). The idiopathic PD cases and controls were matched based on hospital, sex, age and visiting date (within 3 years). The participation rate among eligible cases was 45% and 35% among controls, resulting in a total of 444 cases and 876 controls. The study was approved by the medical ethics committee of the University Medical Centre Utrecht, The Netherlands.

2.2. Data collection

Trained interviewers administered a questionnaire to cases and controls during a telephone interview. Data was collected on demographics, medical history, diet, lifestyle factors such as smoking or alcohol consumption, and the personal use of pesticides in and around the home (van der Mark et al., 2014b). Furthermore, a complete occupational and residential history was obtained. The residential history listed all addresses the participant lived at for over a year, and the first and last year the participant inhabited each address. These addresses were geocoded by matching them to the building coordinates in the cadastral Registry of Addresses and Buildings (BAG) (Kadaster, 2015). If there was no match in the BAG, the addresses were geocoded to the density weighted midpoint of the corresponding 6-digit, 5-digit or 4-digit postal code area. Of the addresses of participants included in the analytical dataset for the current study (n = 4552), 3779 (83%) could be matched to the building coordinates in the BAG, 248 (5%) were geocoded at the 6-digit postal code level, 313 (7%) at the 5-digit postal code level, 62 (1%) at the 4-digit postal code level. A total of 150 addresses (3%) could not be geocoded.

2.3. Environmental pesticide exposure

We used a previously developed spatio-temporal model to assign environmental pesticide exposure to residential addresses (Brouwer et al., 2017). Here, we combined land-use datasets, containing information on the type of crop cultivated per 25 by 25 m grid cell, with agricultural census data and historical crop-specific pesticide use estimates generated by experts (i.e. probability and frequency of use). For the period 1961 to 1989, land-use datasets providing information on 'arable or bare land' (HGN) were available. For 1990 onward, available datasets contained more detailed crop information (e.g. potatoes, cereals, beets, bulbs, orchards and maize). The area likely treated with specific pesticides within circular rings around the residential addresses was estimated, serving as proxy for environmental pesticide exposure.

For the current study we considered pesticide exposures originating from crop cultivation within 100 m to be most relevant in terms of exposure probability and intensity. In the Netherlands, pesticide treatments have been predominantly conducted using ground-based sprayers. Drift of pesticides is highest within the first few meters from the field (Wolters et al., 2008; Rautmann et al., 2001) and decreases exponentially from there. Furthermore, drift reducing measures have been implemented in the Netherlands in 2000. Therefore, we report primarily on pesticide exposures based on crop cultivation within 100 m of the residence, split up in two distance categories: 0–50 m and > 50–100 m. Results on larger distances (i.e. > 100–500 m and > 500–1000 m) can be found in Appendix B.

Exposure estimates were generated for 157 pesticides that had previously been reported to be used in the Netherlands since 1961 (Brouwer et al., 2014). It was decided to start the exposure assessment at 1961 as this year corresponded to the first available land-use dataset (1960) and the collected historical pesticide use data (Brouwer et al., 2014). In addition, this period coincides with the rapid increase in the development and use of chemical pesticides and the implementation of pesticide legislation in the Netherlands in 1962.

Environmental exposure to a specific pesticide was defined by the agricultural surface area (hectares (ha)) likely treated with that pesticide within the specified distances. Participants were classified as ever or never exposed, and cumulative exposure (ha-years treated) was calculated for the period 1961 until the year preceding case-diagnosis. For controls, exposure was calculated until the year before the diagnosis year of the matched case. If a participant moved, or had multiple addresses for another reason during 1 year, the exposure estimates of the addresses were averaged. Given the lack of consensus for different pesticides on the most relevant biological mechanisms and time windows of exposure in relation to PD onset or disease progression, we decided a priori to present the results for unlagged exposures.

2.4. Selection of pesticides

Given the large number of pesticides in our dataset and the potential for multiple testing, a first priority selection was made based on a priori indications for an association with PD. The pesticides paraquat, maneb, lindane and benomyl were selected, based on previously reported significant associations with PD in the epidemiological literature (at least two studies). The herbicide paraquat, which first received attention due to the structural similarities with the parkinsonism inducing compound