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

Maartje Brouwer[a], Anke Huss[a], Marianne van der Mark[a], Peter C.G. Nijssen[b], Wim M. Mulleners[c], Antonetta M.G. Sas[d], Teus van Laar[e], Geert R. de Snoo[f], Hans Kromhout[a,1], Roel C.H. Vermeulen[a,g,*,1]

[a] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[b] Department of Neurology, St. Elisabeth Hospital, Tilburg, The Netherlands
[c] Department of Neurology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands
[d] Department of Neurology, Vlietland Hospital, Schiedam, The Netherlands
[e] Department of Neurology, University Medical Center Groningen, Groningen, The Netherlands
[f] Institute of Environmental Sciences, Leiden University, Leiden, The Netherlands
[g] Julius Centre for Public Health Sciences and Primary Care, Utrecht University Medical Centre, Utrecht, 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).

* Corresponding author at: Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, P.O. Box 80.178, 3584 TD Utrecht, The Netherlands.
E-mail address: r.c.h.vermeulen@uu.nl (R.C.H. Vermeulen).
[1] Shared last authorship.

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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

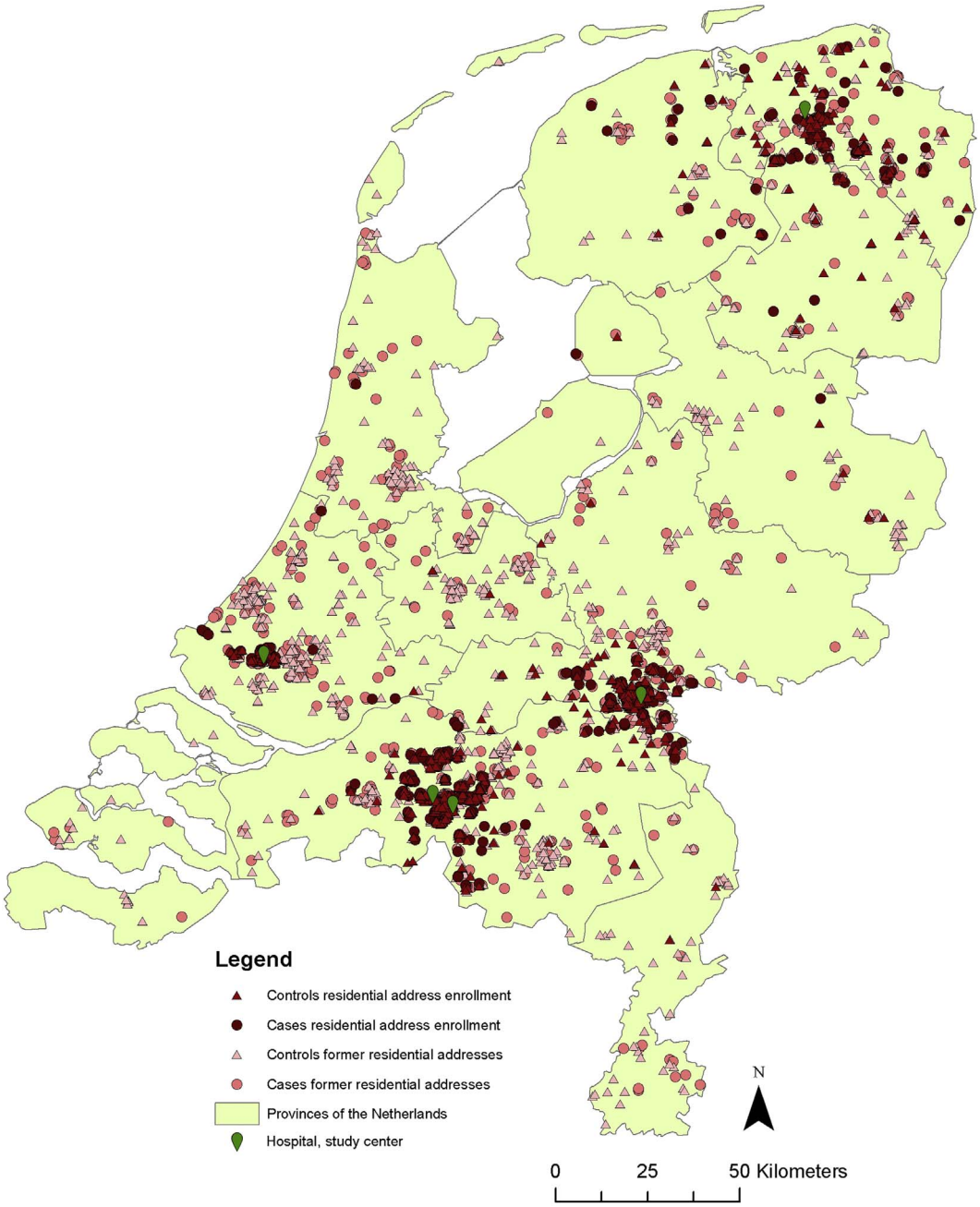

Fig. 1. The location of the five participating hospitals in the case-control study, the participants' residential address at enrollment and past residential addresses from 1961 onward.

MPTP (Langston et al., 1983), has been associated with increased PD risk in several studies (Tanner et al., 2011; Kamel et al., 2007). Organochlorine insecticides are persistent and accumulate in the human body, and lindane has been detected in higher concentrations in the brains and serum of PD patients (Corrigan et al., 2000; Richardson et al., 2011). Also fungicides, such as maneb and benomyl, have been reported to be associated with PD (Costello et al., 2009; Fitzmaurice et al., 2013). These four pesticides were the primary focus of our analysis. The remaining 153 pesticides were investigated in exploratory analyses.

2.5. Statistical analysis

Participants who were missing > 50% of their residential history were excluded (n = 17), as well as participants who were ever employed in a job with a high occupational exposure to pesticides (n = 201), according to a job-exposure matrix (JEM) assignment (Matheson et al., 2005). One case had missing data for one of the covariates and was removed. A total of 352 cases and 607 individually matched controls remained in the analytical dataset used in this study.

We used SAS V9.2 (SAS Institute Inc., Cary, North Carolina, USA) to calculate odds ratios (ORs) and 95% confidence intervals (CI) using conditional logistic regression analyses. Results are reported for exposure estimates based on three distance categories: 0–100 m, stratified into 0–50 m and > 50–100 m. Participants unexposed to the pesticide of interest, in the distance category analyzed, were considered as the reference category. This reference category is however not truly unexposed to pesticides, as participants may be exposed to other pesticides within the same distance category, or exposed to the same pesticide in a larger distance category. Participants exposed in 0–50 m, but not within > 50–100 m, were excluded from the reference group in the latter analysis. Cumulative exposure was categorized based on the

tertiles of the exposure distribution among the control participants. Risk estimates were only calculated if five or more cases were exposed in a particular exposure category. If fewer than five cases or controls were left in the unexposed reference category, the unexposed participants were merged with the lowest tertile of the exposed participants and considered as reference group.

The analyses were adjusted for potential confounders: pack years of smoking (5 categories), time since cessation (5 categories), occupational attainment (4 categories), low occupational pesticide exposure in the JEM (Matheson et al., 2005), home pesticide use, family history of PD and the percentage of low income inhabitants in the neighborhood (3 categories). The primary analysis focused on the four a priori selected pesticides: paraquat, maneb, lindane and benomyl. In a second, hypothesis-generating analysis, the remaining 153 pesticides for which data was available, were investigated.

Correlations between pesticide exposures were investigated using the spearman rank correlation coefficient. Clustering of pesticide exposures was additionally assessed by a principal component analysis (PCA) in order to reduce the number of analyses and look at use-patterns in relation to PD-risk. Noteworthy findings from the complete analysis, defined as those pesticides that showed significant elevated risk estimates and a significant trend over the categorical cumulative exposure risk estimates, were explored further in a number of sensitivity analysis, along with the four a priori pesticides. These sensitivity analyses were restricted to exposures estimated for 0–100 m around the residence, to reduce the amount of analyses. First, the exposure assessment was restricted to the period with higher quality agricultural land-use data (1990 onward). Second, exposure with lag-times of 5, 10 and 15 years was considered. Third, the analysis was corrected for the percentage of time spent in highly urbanized areas (> 1500 addresses/km^2) to assess potential residual confounding, as non-exposed participants may have lived in more urban areas than the exposed participants. Fourth, participants who were classified as ever-employed in a job with low occupational exposure to pesticides according to the JEM, were excluded. In addition, we assessed the association between crop cultivation and PD risk, split into different decades of exposure, to obtain more insight in potentially relevant time windows of exposure.

3. Results

In accordance with the known higher prevalence of PD among men, we observed a higher percentage of male PD cases (63%). The median age at diagnosis was 67 years (Table 1). As previously described, cases were more often never-smokers, and those who did smoke smoked less and quitted earlier (van der Mark et al., 2014a). Furthermore, cases more often had white-collar jobs and lived in neighborhoods with a smaller percentage of low income inhabitants than controls. A family history of PD occurred significantly more frequently among cases, while controls more frequently applied pesticides in and around the home themselves.

Exposure prevalence and ORs of the four a priori selected pesticides are shown in Table 2. The majority of participants were ever-exposed to paraquat, lindane and/or maneb within a 100 m distance around the residence, while only 6.8% of cases was ever-exposed to benomyl. The ORs for being ever-exposed to any of these four pesticides were not significantly deviant from unity. Although highest risk estimates were observed in the highest exposure category for all a priori selected pesticides, none of these ORs were statistically significant and there was also no significant trend over the increasing cumulative exposure categories. However, when a lag-time of 10 or 15 year was considered, the OR for the highest tertile of exposure to paraquat increased to OR 1.53 (1.00–2.33) and OR 1.60 (1.05–2.44), respectively (Appendix A, Table A1). For lindane, being ever-exposed during the period for which LGN data was available (≥ 1990, roughly the last 20 years preceding case diagnosis), was associated with an OR of 1.95 (1.07–3.56). For paraquat, non-significant elevated risks were found for being exposed during this same recent time window (Appendix A, Table A2). When investigating exposure to these pesticides during specific decades, the highest tertile of cumulative exposure to paraquat and lindane during the period 1991–2000 was associated with an increased risk of 3.42 (1.04–11.32) and 4.95 (1.20–20.46) respectively. This latter analysis was based on few exposed participants, however (data not shown). Risk estimates were not affected by an additional correction for the percentage of lifetime spend in highly urbanized areas, nor by removing participants classified as ever-exposed to pesticides during any occupation held (data not shown).

In the complete analysis, where the remaining 153 pesticides were included, significant elevated ORs were found for exposure within 100 m to 21 pesticides, as well as significant trends over the cumulative exposure categories (Appendix B). These were the fungicides (n = 7) anilazine, carbendazim, cymoxanil, fenpropimorph, pencycuron, prochloraz and triadimenol, the herbicides (n = 10) chlorotoluron, dinoterb, fluazifop, fluroxypyr, isoproturon, mcpa, mecoprop, metobromuron, metribuzin and monolinuron, the growth regulator (n = 1) chlormequat and the insecticides/fumigants (n = 3) 1,3-dichloropropene, metam-sodium and oxamyl (Table 3). Being ever-exposed to these pesticides within 100 m around the residence resulted in significant elevated ORs for nine pesticides, for example an OR of 2.62 (95% CI 1.33–5.16) for being ever-exposed to anilazine. Overall, the highest ORs were found for the highest tertile of cumulative lifetime exposure, and the ORs for this highest exposure tertile were generally higher for exposure within 50 m, than in > 50–100 m distance. These 21 pesticides had in common that they were mainly used on potatoes and cereals, and for most of them, their (reported) use peaked after 1980. None of the sensitivity analyses changed the results for these 21 pesticides significantly.

Correlations between these 21 pesticide exposures were high. For cumulative exposure within 100 m, the median spearman correlation coefficient was 0.63 (range 0.36–1.00). A heatmap showing these correlations graphically, can be found in Appendix A (Fig. A1). For all pesticides investigated (n = 157), the median spearman correlation coefficient of exposures within 100 m was 0.14 (range − 0.10–1.00) (data not shown).

In addition, potential clustering of pesticide exposures in the complete dataset was investigated using a PCA analysis. This analysis revealed 14 clusters with an Eigenvalue > 1. Two of these clusters were related to PD risk (Appendix A, Table A3, A4). The first cluster comprised a number of pesticides used on bulbs, but was unstable due to the low number of participants exposed to bulb cultivation within 100 m (0.4%). However, ever-exposure to bulbs in > 100–500 m was associated with a significant increased risk of OR 2.30 (95% CI 1.02–5.18) (Appendix A, Table A5). The second cluster consisted of a number of pesticides used on cereals and potatoes. When we investigated exposure to these crops per time period, we observed increased risk of PD associated with exposure to cereals and potatoes (i.e. rotating crops) during the periods 1981–1990 and 1991–2000. The highest tertile of cereal cultivation within 100 m in the period 1981–1990 was associated with OR 2.01 (95% CI 1.17–3.47). In the period 1991–2000, the same participants were exposed to potatoes and cereals, resulting in an OR of 1.67 (95% CI 0.95–2.94) for ever-exposure for both crops (Appendix A, Table A6).

4. Discussion

In our primary analysis we observed no significant associations between lifetime environmental exposure to four a priori selected pesticides (i.e. paraquat, maneb, lindane and benomyl) within 100 m from the residence and the risk of PD. The elevated ORs in the highest cumulative exposure tertiles can be seen as suggestive, however, as well as the significant associations found between cumulative exposure to paraquat and lindane and PD, when considering specific time windows of exposure. In a second, hypothesis generating analysis, including

Table 1
General characteristics of cases and controls.

	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	OR (95% CI)[a]
Men, N (%)	220 (62.5)	385 (63.4)	
Age at interview, median (range)	69 (37–89)	69 (38–89)	
Age at diagnosis, median (range)	67 (36–88)		
Year of case diagnosis			
2010–2011	94 (26.7)		
2008–2009	131 (37.2)		
2006–2007	127 (36.1)		
Cigarette smoking			
Never smoked	163 (46.3)	157 (25.9)	Reference
> 0–7.8 pack-years	64 (18.2)	113 (18.6)	0.55 (0.37, 0.80)
> 7.8–17.6 pack-years	58 (16.5)	112 (18.5)	0.50 (0.34, 0.73)
> 17.6–29.4 pack-years	33 (9.4)	114 (18.8)	0.28 (0.18, 0.44)
> 29.4–103 pack-years	34 (9.7)	111 (18.3)	0.30 (0.19, 0.46)
Time since quitting smoking			
Never smoked	163 (46.3)	157 (25.9)	Reference
Still smoking	21 (6.0)	116 (19.1)	0.17 (0.10, 0.29)
1–17 years	43 (12.2)	113 (18.6)	0.37 (0.24, 0.55)
18–31 years	61 (17.3)	117 (19.3)	0.50 (0.34, 0.73)
32–53 years	64 (18.2)	104 (17.1)	0.59 (0.41, 0.87)
Occupational attainment			
High-skilled white-collar worker	162 (46.0)	253 (41.7)	Reference
Low-skilled white-collar worker	75 (21.3)	133 (21.9)	0.88 (0.62, 1.24)
High-skilled blue-collar worker	67 (19.0)	117 (19.3)	0.89 (0.62, 1.28)
Low-skilled blue-collar worker	48 (13.6)	104 (17.1)	0.72 (0.49, 1.07)
Low occupational pesticide exposure[b]			
No	329 (93.5)	562 (92.6)	Reference
Yes	23 (6.5)	45 (7.4)	0.87 (0.52, 1.47)
Family history of PD			
No	292 (83.0)	563 (92.8)	Reference
Yes	60 (17.0)	44 (7.2)	2.63 (1.74, 3.97)
Pesticide use in and around the home			
No	240 (68.2)	363 (59.8)	Reference
Yes	112 (31.8)	244 (40.2)	0.69 (0.53, 0.92)
Average percentage low income Inhabitants in the neighborhood			
23–40%	136 (38.6)	314 (35.3)	Reference
41–45%	138 (39.2)	222 (36.6)	0.98 (0.72, 1.32)
46–62%	78 (22.2)	171 (28.2)	0.72 (0.51, 1.01)

[a] Conditional logistic regression analysis.
[b] Occupational pesticide exposure assigned using a job exposure matrix (JEM).

exposures to 153 individual pesticides within 100 m of the residence, an association with PD risk was found for 21 pesticides. This group of correlated pesticides was mainly used on cereals and potatoes, and cultivation of these crops appeared to be associated with increased PD risk during distinct decades (1981–1990 and 1991–2000). Another signal came from a cluster of pesticides used on bulbs, but too few participants were exposed within 100 m of their residences for a reliable analysis. This observation was somewhat strengthened by the observation of a positive association between bulb cultivation within > 100-500 m of the residence and PD risk.

Our assessment of environmental exposure to pesticides did not depend on participants' recall of exposure, but utilized information on residential history and external data on agricultural land use and pesticide use back in time. We did not observe that recall of the residential history was differential between cases and controls, i.e. the amount of missing data and geocoding quality was similar between cases and controls. The far majority of residential addresses could be geocoded using the most precise data available, which were the building coordinates (83%). Instead of assigning crude pesticide exposure proxies (e.g. rural living or crop type), we estimated exposure to individual pesticides. In addition to investigating pesticides previously suggested to be potentially associated with PD, we performed a broad screen of 157 individual pesticides in total, reported to be used in the Dutch agricultural sector from 1961 to 2010. The exposure assessment extended back to 1961, which covers the majority of the participants' lifetime, although for most participants this did not include potential childhood exposures. However, the development and use of large volumes of synthetic chemical pesticides only started after the second world war in Europe, in part replacing the inorganic compounds used prior. Due to the relatively high spatial resolution of the underlying agricultural land-use data (25 by 25 m raster cells), different distance categories around the residence could be investigated to explore the effect of proximity to pesticide applications. All PD cases were hospital diagnosed and their records were confirmed by a neurologist. We therefore expect disease misclassification to have been minimal.

One of the main limitations of the current study is the relatively low specificity of the retrospective exposure assessment method used to assign pesticide exposure back in time, due to the underlying structure of the model and crop-exposure matrix, which assigns exposure based on probability of crop cultivation and pesticide use on the crop during a time period (Brouwer et al., 2017). Mixed exposures, co-occurring exposures to pesticide active ingredients, and close proximity to different (rotating) crops are a given in many agricultural settings (Kromhout and Heederik, 2005). However, the low specificity of the exposure assignment, resulting from multiple (rotating) crops cultivated in vicinity of the participants and the large number of pesticides potentially used on these crops over time, will have contributed to the high prevalence of exposures and high correlations observed, even in close proximity to crops. These high correlations limited our ability to investigate the association between exposure to specific pesticides and PD risk.

Table 2
The association between environmental exposure to a priori selected pesticides within 100 m around the residence, and the risk of Parkinson's Disease.

Pesticide (crops)	0–100 m			0–50 m			> 50–100 m[c]		
	PD cases (*n* = 352) n (%)	Controls (*n* = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (*n* = 352) n (%)	Controls (*n* = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (*n* = 352) n (%)	Controls (*n* = 607) n (%)	Adj. OR (95% CI)[a]
Paraquat (POT, BUL, ORC)									
Not exposed	171 (48.6)	285 (47.0)	Reference	230 (65.3)	401 (66.1)	Reference	171 (48.9)	283 (47.0)	Reference
Ever exposed	181 (51.4)	322 (53.0)	1.00 (0.73–1.36)	122 (34.7)	206 (33.9)	1.01 (0.73–1.38)	179 (51.1)	319 (53.0)	0.98 (0.72, 1.34)
Cumulative, T1	44 (12.5)	106 (17.5)	0.74 (0.47–1.16)	34 (9.7)	68 (11.2)	0.81 (0.49–1.34)	51 (14.6)	106 (17.6)	0.82 (0.53, 1.27)
Cumulative, T2	58 (16.5)	110 (18.1)	0.93 (0.61–1.40)	46 (13.1)	71 (11.7)	0.99 (0.63–1.56)	51 (14.6)	109 (18.1)	0.84 (0.55, 1.28)
Cumulative, T3	79 (22.4)	106 (17.5)	1.46 (0.95–2.23)	42 (11.9)	67 (11.0)	1.28 (0.79–2.07)	77 (22.0)	104 (17.3)	1.43 (0.93, 2.22)
p-Value for trend[b]			0.19			0.50			0.33
Lindane (POT, BEE)									
Not exposed	146 (41.5)	241 (39.7)	Reference	204 (58.0)	366 (60.3)	Reference	146 (42.0)	237 (39.6)	Reference
Ever exposed	206 (58.5)	366 (60.3)	0.96 (0.70–1.30)	148 (42.0)	241 (39.7)	1.06 (0.78–1.43)	202 (58.0)	361 (60.4)	0.93 (0.68, 1.26)
Cumulative, T1	56 (15.9)	121 (19.9)	0.82 (0.54–1.25)	39 (11.1)	80 (13.2)	0.78 (0.48–1.26)	55 (15.8)	121 (20.2)	0.74 (0.49, 1.14)
Cumulative, T2	75 (21.3)	125 (20.6)	0.96 (0.65–1.40)	52 (14.8)	82 (13.5)	1.10 (0.72–1.69)	71 (20.4)	123 (20.6)	0.89 (0.60, 1.32)
Cumulative, T3	75 (21.3)	120 (19.8)	1.11 (0.73–1.68)	57 (16.2)	79 (13.0)	1.32 (0.84–2.06)	76 (21.8)	117 (19.6)	1.21 (0.79, 1.84)
p-Value for trend[b]			0.66			0.26			0.53
Maneb (POT, CER, BUL, ORC)									
Not exposed	91 (25.9)	136 (22.4)	Reference	150 (42.6)	245 (40.4)	Reference	91 (25.9)	136 (22.5)	Reference
Ever exposed	261 (74.1)	471 (77.6)	0.86 (0.61–1.22)	202 (57.4)	362 (59.6)	0.97 (0.72–1.30)	260 (74.1)	468 (77.5)	0.86 (0.61, 1.22)
Cumulative, T1	82 (23.3)	155 (25.5)	0.83 (0.54–1.27)	64 (18.2)	120 (19.8)	1.01 (0.68–1.52)	81 (23.1)	155 (25.7)	0.79 (0.52, 1.21)
Cumulative, T2	71 (20.2)	161 (26.5)	0.69 (0.45–1.04)	57 (16.2)	123 (20.3)	0.74 (0.50–1.12)	73 (20.8)	158 (26.2)	0.74 (0.49, 1.12)
Cumulative, T3	108 (30.7)	155 (25.5)	1.23 (0.80–1.90)	81 (23.0)	119 (19.6)	1.24 (0.82–1.86)	106 (30.2)	155 (25.7)	1.19 (0.77, 1.85)
p-Value for trend[b]			0.62			0.75			0.60
Benomyl (BEE, CER, BUL)									
Not exposed	328 (93.2)	574 (94.6)	Reference	346 (98.3)	594 (97.9)	Reference	328 (93.2)	574 (94.6)	Reference
Ever exposed	24 (6.8)	33 (5.4)	1.48 (0.77–2.84)	6 (1.7)	13 (2.1)	0.80 (0.28–2.34)	24 (6.8)	33 (5.4)	1.48 (0.77, 2.84)
Cumulative, T1	5 (1.4)	11 (1.8)	1.28 (0.39–4.15)	1 (0.3)	5 (0.8)	n.c.	5 (1.4)	11 (1.8)	1.29 (0.40, 4.20)
Cumulative, T2	13 (3.7)	13 (2.1)	1.58 (0.65–3.88)	1 (0.3)	4 (0.7)	n.c.	13 (3.7)	12 (2.0)	1.75 (0.71, 4.29)
Cumulative, T3	6 (1.7)	9 (1.5)	1.54 (0.47–5.04)	4 (1.1)	4 (0.7)	n.c.	6 (1.7)	10 (1.6)	1.30 (0.42, 4.07)
p-Value for trend[b]			0.24			0.73			0.28

T1, first tertile of cumulative exposure (ha-years); T2, second tertile of cumulative exposure; T3, third tertile of cumulative exposure. Reported use of these pesticides on: POT, potatoes; BUL, bulbs; ORC, orchards; CER, cereals; BEE, beets; MAI, maize. Cutoffs of the cumulative exposure tertiles are based on the distribution of exposure to the pesticide among the controls within a specific distance category, therefore these vary between pesticides and distance categories. The results of larger distance categories (i.e. > 100–500 m and > 500–1000 m) can be found in Appendix B.

[a] Conditional logistic regression adjusted for pack years of smoking (5 categories), time since cessation (5 categories), occupational attainment (4 categories), low occupational pesticide exposure, family history of PD, home pesticide use and neighborhood income (3 categories).

[b] *P*-value for trend based on the categorical cumulative exposure variable.

[c] Participants with exposure to the pesticide within 0-50 m distance but not in > 50–100 m, are excluded from the > 50–100 m reference group.

One major critique on the use of GIS based exposure estimates in epidemiological studies is the general lack of validation (Chang et al., 2014). We found moderate to high correlations between our model estimates and pesticide concentrations measured in air and precipitation (Brouwer et al., 2017). This comparison was, however, limited to a small number of pesticides ($n = 11$) measured in 2000 and 2001, and model estimates based on crop cultivation in buffers > 500 m around the measurement locations, as these locations were originally placed away from direct agricultural pesticide sources to measure atmospheric transport of pesticides. Here, we report on pesticide exposures based on crop cultivation within 0–50 and > 50–100 m of the residential address. Direct droplet drift, volatilization and deposition in and around the residence will be the main route of exposure for neighboring populations. Drift of pesticides is highest within the first few meters from the field and decreases exponentially with increasing distance given the high dilution in air (Rautmann et al., 2001; FOCUS, 2008). Given the common methods of pesticide ground application in the Netherlands, we consider exposure from pesticide applications on crops further than 100 m away from the residence to be low and less relevant to study potential health effects. The overall participation rate in the case-control study was low (45% for cases and 35% for controls) which has limited the power of the study (van der Mark et al., 2014a). We have no indications, however, that cases and controls have chosen to participate differently on the basis of their (former) residences near specific agricultural parcels. We also found no clear difference in geographical spread between the (former) residences of the cases and controls, in relation to the recruitment hospitals. Exposures were estimated for the residential address only, as information on lifetime work addresses was not collected. Therefore, we might be misclassifying part of the total environmental pesticide exposure for some participants, as these may have spent a substantial amount of time at their workplace, also when pesticide applications took place. This misclassification will be non-differential however, and likely bias our results to the null.

Paraquat has been associated to PD in a number of occupational studies (Tanner et al., 2011; Kamel et al., 2007), but also environmental exposure at the residential address to a combination of paraquat and maneb, was reported to be associated with increased risk of PD (OR 1.75, 95% CI 1.13–2.73) (Costello et al., 2009). However, in the same study, exposure to paraquat or maneb alone, was not significantly associated with PD risk (OR 1.01, 95% CI 0.71–1.43 and OR 3.04, 95% CI 0.30–30.86, respectively). A subsequent study in the same population found exposure to paraquat within 500 m of both the workplace and the home to be associated with PD risk (OR 1.50, 95% CI 1.03–2.18), but not exposure to paraquat solely at one of these addresses (Wang et al., 2011). Also several other studies could not detect significant associations between paraquat exposure and PD risk (van der Mark et al., 2014b; Firestone et al., 2010). In our primary analyses we did not find a significant association between exposure to paraquat and PD. The highest risk estimate was found for the highest cumulative exposure category (OR 1.46, 95% CI 0.95–2.23), and the magnitude of effect was in line with risks reported in previous studies (Costello et al., 2009; Wang et al., 2011). However, we found no significant trend across

Table 3
The association between environmental exposure to pesticides within 100 m around the residence, and the risk of Parkinson's Disease; pesticides showing a significant trend in the hypothesis generating analysis (n = 21).

Pesticide (crops)	0–100 m			0–50 m			> 50–100 m[c]		
	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]
Anilazine (CER)									
Not exposed	328 (93.2)	584 (96.2)	Reference	344 (97.7)	596 (98.2)	Reference	328 (93.4)	583 (96.2)	Reference
Ever exposed	24 (6.8)	23 (3.8)	2.62 (1.33, 5.16)	8 (2.3)	11 (1.8)	2.24 (0.71, 7.02)	23 (6.6)	23 (3.8)	2.57 (1.30, 5.09)
Cumulative, T1	10 (2.8)	8 (1.3)	2.46 (0.89, 6.77)	2 (0.6)	4 (0.7)	n.c.	10 (2.8)	8 (1.3)	2.72 (0.99, 7.42)
Cumulative, T2	8 (2.3)	8 (1.3)	2.83 (0.86, 9.25)	3 (0.9)	5 (0.8)	n.c.	7 (2.0)	8 (1.3)	2.32 (0.71, 7.58)
Cumulative, T3	6 (1.7)	7 (1.2)	2.68 (0.77, 9.40)	3 (0.9)	2 (0.3)	n.c.	6 (1.7)	7 (1.2)	2.64 (0.75, 9.24)
p-Value for trend[b]			0.01			0.13			0.01
Carbendazim (BEE, CER, TUL, ORC)									
Not exposed	256 (72.7)	466 (76.8)	Reference	305 (86.6)	540 (89.0)	Reference	256 (72.9)	464 (76.7)	Reference
Ever exposed	96 (27.3)	141 (23.2)	1.36 (0.95, 1.95)	47 (13.4)	67 (11.0)	1.45 (0.89, 2.35)	95 (27.1)	141 (23.3)	1.34 (0.93, 1.91)
Cumulative, T1	21 (6.0)	47 (7.7)	0.88 (0.49, 1.58)	11 (3.1)	23 (3.8)	0.89 (0.40, 2.01)	23 (6.6)	47 (7.8)	0.95 (0.53, 1.69)
Cumulative, T2	38 (10.8)	48 (7.9)	1.50 (0.89, 2.52)	18 (5.1)	22 (3.6)	1.73 (0.81, 3.71)	36 (10.3)	48 (7.9)	1.42 (0.84, 2.39)
Cumulative, T3	37 (10.5)	46 (7.6)	1.93 (1.09, 3.43)	18 (5.1)	22 (3.6)	1.86 (0.91, 3.82)	36 (10.3)	46 (7.6)	1.82 (1.03, 3.23)
p-Value for trend[b]			0.02			0.05			0.03
Chlormequat (CER, ORC)									
Not exposed	252 (71.6)	462 (76.1)	Reference	303 (86.1)	538 (88.6)	Reference	252 (71.8)	460 (76.0)	Reference
Ever exposed	100 (28.4)	145 (23.9)	1.41 (1.00, 2.00)	49 (13.9)	69 (11.4)	1.45 (0.91, 2.32)	99 (28.2)	145 (24.0)	1.38 (0.97, 1.96)
Cumulative, T1	20 (5.7)	48 (7.9)	0.89 (0.49, 1.59)	16 (4.5)	23 (3.8)	1.33 (0.64, 2.77)	20 (5.7)	48 (7.9)	0.83 (0.46, 1.50)
Cumulative, T2	47 (13.4)	51 (8.4)	1.67 (1.03, 2.73)	16 (4.5)	24 (4.0)	1.22 (0.58, 2.59)	50 (14.2)	50 (8.3)	1.93 (1.17, 3.20)
Cumulative, T3	33 (9.4)	46 (7.6)	1.87 (1.03, 3.40)	17 (4.8)	22 (3.6)	1.92 (0.90, 4.11)	29 (8.3)	47 (7.8)	1.50 (0.82, 2.76)
p-Value for trend[b]			0.01			0.09			0.02
Chlortoluron (CER)									
Not exposed	260 (73.9)	479 (78.9)	Reference	309 (87.8)	545 (89.8)	Reference	260 (74.1)	477 (79.1)	Reference
Ever exposed	92 (26.1)	128 (21.1)	1.52 (1.06, 2.18)	43 (12.2)	62 (10.2)	1.49 (0.90, 2.48)	91 (25.9)	126 (20.9)	1.50 (1.04, 2.16)
Cumulative, T1	23 (6.5)	43 (7.1)	1.16 (0.65, 2.07)	13 (3.7)	21 (3.5)	1.24 (0.56, 2.74)	27 (7.7)	42 (7.0)	1.36 (0.78, 2.37)
Cumulative, T2	33 (9.4)	43 (7.1)	1.34 (0.77, 2.33)	7 (2.0)	21 (3.5)	0.63 (0.22, 1.80)	32 (9.1)	43 (7.1)	1.36 (0.77, 2.41)
Cumulative, T3	36 (10.2)	42 (6.9)	2.42 (1.34, 4.37)	23 (6.5)	20 (3.3)	2.69 (1.32, 5.48)	32 (9.1)	41 (6.8)	1.91 (1.04, 3.50)
p-Value for trend[b]			0.00			0.03			0.02
1,3-Dichloropropene (POT)									
Not exposed	323 (91.8)	575 (94.7)	Reference	341 (96.9)	591 (97.4)	Reference	323 (92.0)	574 (94.7)	Reference
Ever exposed	29 (8.2)	32 (5.3)	2.01 (1.09, 3.70)	11 (3.1)	16 (2.6)	1.54 (0.61, 3.87)	28 (8.0)	32 (5.3)	1.97 (1.06, 3.65)
Cumulative, T1	13 (3.7)	11 (1.8)	1.95 (0.79, 4.82)	2 (0.6)	6 (1.0)	n.c.	13 (3.7)	11 (1.8)	1.95 (0.79, 4.83)
Cumulative, T2	8 (2.3)	11 (1.8)	1.48 (0.52, 4.23)	2 (0.6)	5 (0.8)	n.c.	7 (2.0)	11 (1.8)	1.37 (0.46, 4.04)
Cumulative, T3	8 (2.3)	10 (1.6)	3.33 (0.97, 11.46)	7 (2.0)	5 (0.8)	4.95 (1.20, 20.46)	8 (2.3)	10 (1.7)	3.33 (0.97, 11.46)
p-Value for trend[b]			0.02			0.09			0.03
Cymoxanil (POT)									
Not exposed	282 (80.1)	503 (82.9)	Reference	319 (90.6)	556 (91.6)	Reference	282 (80.3)	502 (83.1)	Reference
Ever exposed	70 (19.9)	104 (17.1)	1.43 (0.95, 2.15)	33 (9.4)	51 (8.4)	1.37 (0.80, 2.37)	69 (19.7)	102 (16.9)	1.42 (0.94, 2.13)
Cumulative, T1	16 (4.5)	35 (5.8)	1.02 (0.51, 2.04)	8 (2.3)	17 (2.8)	0.82 (0.31, 2.16)	17 (4.8)	32 (5.3)	1.10 (0.56, 2.17)
Cumulative, T2	24 (6.8)	35 (5.8)	1.31 (0.71, 2.42)	12 (3.4)	18 (3.0)	1.41 (0.61, 3.27)	23 (6.6)	37 (6.1)	1.21 (0.66, 2.22)
Cumulative, T3	30 (8.5)	34 (5.6)	2.14 (1.12, 4.08)	13 (3.7)	16 (2.6)	2.23 (0.91, 5.49)	29 (8.3)	33 (5.5)	2.16 (1.12, 4.18)
p-Value for trend[b]			0.02			0.09			0.03
Dinoterb (POT, CER)									
Not exposed	252 (71.6)	460 (75.8)	Reference	303 (86.1)	534 (88.0)	Reference	252 (72.0)	458 (76.1)	Reference
Ever exposed	100 (28.4)	147 (24.2)	1.37 (0.96, 1.95)	49 (13.9)	73 (12.0)	1.33 (0.83, 2.12)	98 (28.0)	144 (23.9)	1.35 (0.94, 1.92)
Cumulative, T1	20 (5.7)	49 (8.1)	0.84 (0.46, 1.54)	12 (3.4)	25 (4.1)	0.90 (0.41, 1.95)	21 (6.0)	47 (7.8)	0.93 (0.52, 1.68)
Cumulative, T2	41 (11.6)	50 (8.2)	1.43 (0.85, 2.38)	17 (4.8)	22 (3.6)	1.33 (0.62, 2.86)	41 (11.7)	49 (8.1)	1.37 (0.82, 2.27)
Cumulative, T3	39 (11.1)	48 (7.9)	2.09 (1.20, 3.64)	20 (5.7)	26 (4.3)	1.85 (0.92, 3.72)	36 (10.3)	48 (8.0)	1.95 (1.11, 3.44)
p-Value for trend[b]			0.01			0.09			0.02

(continued on next page)

Table 3 *(continued)*

Pesticide (crops)	0–100 m			0–50 m			> 50–100 m[c]		
	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]
Fenpropimorph (CER)									
Not exposed	285 (81.0)	527 (86.8)	Reference	317 (90.1)	567 (93.4)	Reference	285 (81.4)	524 (86.8)	Reference
Ever exposed	67 (19.0)	80 (13.2)	1.82 (1.18, 2.80)	35 (9.9)	40 (6.6)	1.85 (1.06, 3.25)	65 (18.6)	80 (13.2)	1.75 (1.14, 2.71)
Cumulative, T1	17 (4.8)	27 (4.4)	1.52 (0.74, 3.11)	14 (4.0)	14 (2.3)	1.69 (0.75, 3.83)	16 (4.6)	28 (4.6)	1.28 (0.62, 2.64)
Cumulative, T2	26 (7.4)	27 (4.4)	1.58 (0.84, 2.97)	8 (2.3)	13 (2.1)	1.14 (0.42, 3.12)	29 (8.3)	26 (4.3)	1.86 (1.00, 3.44)
Cumulative, T3	24 (6.8)	26 (4.3)	2.79 (1.33, 5.89)	13 (3.7)	13 (2.1)	3.73 (1.34, 10.37)	20 (5.7)	26 (4.3)	2.34 (1.11, 4.95)
p-Value for trend[b]			0.00			0.02			0.00
Fluazifop-butyl (BEE, POT)									
Not exposed	281 (79.8)	503 (82.9)	Reference	311 (88.4)	550 (90.6)	Reference	281 (80.1)	501 (82.8)	Reference
Ever exposed	71 (20.2)	104 (17.1)	1.36 (0.92, 2.01)	41 (11.6)	57 (9.4)	1.38 (0.84, 2.27)	70 (19.9)	104 (17.2)	1.33 (0.90, 1.97)
Cumulative, T1	17 (4.8)	34 (5.6)	1.11 (0.56, 2.19)	20 (5.7)	18 (3.0)	1.75 (0.83, 3.66)	16 (4.6)	34 (5.6)	0.94 (0.47, 1.89)
Cumulative, T2	24 (6.8)	36 (5.9)	1.07 (0.59, 1.94)	8 (2.3)	21 (3.5)	0.61 (0.23, 1.59)	25 (7.1)	35 (5.8)	1.23 (0.68, 2.22)
Cumulative, T3	30 (8.5)	34 (5.6)	2.16 (1.15, 4.06)	13 (3.7)	18 (3.0)	1.96 (0.85, 4.53)	29 (8.3)	35 (5.8)	1.93 (1.03, 3.62)
p-Value for trend[b]			0.04			0.23			0.05
Fluroxypyr (CER, MAI)									
Not exposed	260 (73.9)	470 (77.4)	Reference	300 (85.2)	537 (88.5)	Reference	260 (74.1)	468 (77.4)	Reference
Ever exposed	92 (26.1)	137 (22.6)	1.37 (0.96, 1.94)	52 (14.8)	70 (11.5)	1.49 (0.96, 2.32)	91 (25.9)	137 (22.6)	1.34 (0.94, 1.91)
Cumulative, T1	19 (5.4)	46 (7.6)	0.81 (0.44, 1.50)	19 (5.4)	24 (4.0)	1.70 (0.85, 3.40)	18 (5.1)	46 (7.6)	0.75 (0.40, 1.40)
Cumulative, T2	42 (11.9)	46 (7.6)	1.85 (1.12, 3.05)	14 (4.0)	23 (3.8)	1.14 (0.53, 2.42)	43 (12.3)	46 (7.6)	1.89 (1.15, 3.10)
Cumulative, T3	31 (8.8)	45 (7.4)	1.45 (0.83, 2.55)	19 (5.4)	23 (3.8)	1.65 (0.81, 3.35)	30 (8.5)	45 (7.4)	1.40 (0.79, 2.48)
p-Value for trend[b]			0.03			0.11			0.04
Isoproturon (CER)									
Not exposed	259 (73.6)	476 (78.4)	Reference	306 (86.9)	545 (89.8)	Reference	259 (74.0)	473 (78.3)	Reference
Ever exposed	93 (26.4)	131 (21.6)	1.45 (1.01, 2.08)	46 (13.1)	62 (10.2)	1.53 (0.94, 2.49)	91 (26.0)	131 (21.7)	1.41 (0.98, 2.03)
Cumulative, T1	22 (6.3)	44 (7.2)	1.09 (0.61, 1.94)	14 (4.0)	21 (3.5)	1.24 (0.58, 2.67)	22 (6.3)	44 (7.3)	1.09 (0.61, 1.94)
Cumulative, T2	31 (8.8)	45 (7.4)	1.25 (0.73, 2.14)	14 (4.0)	21 (3.5)	1.26 (0.56, 2.86)	33 (9.4)	44 (7.3)	1.37 (0.79, 2.37)
Cumulative, T3	40 (11.4)	42 (6.9)	2.56 (1.40, 4.68)	18 (5.1)	20 (3.3)	2.30 (1.07, 4.96)	36 (10.3)	43 (7.1)	2.05 (1.12, 3.74)
p-Value for trend[b]			0.01			0.04			0.02
MCPA (CER, ORC)									
Not exposed	259 (73.6)	474 (78.1)	Reference	309 (87.8)	543 (89.5)	Reference	259 (73.8)	472 (78.3)	Reference
Ever exposed	93 (26.4)	133 (21.9)	1.47 (1.02, 2.11)	43 (12.2)	64 (10.5)	1.42 (0.86, 2.35)	92 (26.2)	131 (21.7)	1.45 (1.01, 2.08)
Cumulative, T1	24 (6.8)	43 (7.1)	1.20 (0.68, 2.11)	13 (3.7)	22 (3.6)	1.18 (0.54, 2.60)	25 (7.1)	43 (7.1)	1.22 (0.70, 2.13)
Cumulative, T2	37 (10.5)	47 (7.7)	1.51 (0.87, 2.59)	7 (2.0)	21 (3.5)	0.66 (0.23, 1.89)	36 (10.3)	45 (7.5)	1.61 (0.91, 2.83)
Cumulative, T3	32 (9.1)	43 (7.1)	1.86 (1.02, 3.38)	23 (6.5)	21 (3.5)	2.38 (1.20, 4.75)	31 (8.8)	43 (7.1)	1.63 (0.89, 2.98)
p-Value for trend[b]			0.02			0.05			0.04
Mecoprop (CER, ORC)									
Not exposed	266 (75.6)	485 (79.9)	Reference	312 (88.6)	548 (90.3)	Reference	266 (76.0)	482 (80.3)	Reference
Ever exposed	86 (24.4)	122 (20.1)	1.45 (1.00, 2.10)	40 (11.4)	59 (9.7)	1.43 (0.86, 2.40)	84 (24.0)	118 (19.7)	1.46 (1.00, 2.14)
Cumulative, T1	23 (6.5)	41 (6.8)	1.13 (0.65, 1.98)	7 (2.0)	21 (3.5)	0.70 (0.27, 1.79)	23 (6.6)	39 (6.5)	1.20 (0.68, 2.13)
Cumulative, T2	30 (8.5)	41 (6.8)	1.49 (0.82, 2.71)	17 (4.8)	19 (3.1)	1.84 (0.83, 4.09)	31 (8.9)	41 (6.8)	1.52 (0.84, 2.76)
Cumulative, T3	33 (9.4)	40 (6.6)	1.90 (1.06, 3.41)	16 (4.5)	19 (3.1)	1.92 (0.87, 4.26)	30 (8.6)	38 (6.3)	1.78 (0.97, 3.28)
p-Value for trend[b]			0.02			0.05			0.03
Metam-sodium (POT)									
Not exposed	281 (79.8)	503 (82.9)	Reference	319 (90.6)	556 (91.6)	Reference	281 (80.1)	502 (83.1)	Reference
Ever exposed	71 (20.2)	104 (17.1)	1.44 (0.96, 2.18)	33 (9.4)	51 (8.4)	1.42 (0.82, 2.47)	70 (19.9)	102 (16.9)	1.43 (0.95, 2.16)
Cumulative, T1	25 (7.1)	37 (6.1)	1.17 (0.65, 2.12)	12 (3.4)	16 (2.6)	1.16 (0.48, 2.81)	22 (6.3)	34 (5.6)	1.12 (0.60, 2.09)
Cumulative, T2	19 (5.4)	33 (5.4)	1.34 (0.69, 2.60)	8 (2.3)	19 (3.1)	1.12 (0.43, 2.89)	21 (6.0)	35 (5.8)	1.34 (0.71, 2.53)
Cumulative, T3	27 (7.7)	34 (5.6)	2.16 (1.10, 4.21)	13 (3.7)	16 (2.6)	2.31 (0.94, 5.69)	27 (7.7)	33 (5.5)	2.21 (1.13, 4.33)
p-Value for trend[b]			0.03			0.10			0.03

(continued on next page)

Table 3 *(continued)*

Pesticide (crops)	0–100 m			0–50 m			> 50–100 m[c]		
	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]	PD cases (n = 352) n (%)	Controls (n = 607) n (%)	Adj. OR (95% CI)[a]
Metobromuron (POT)									
Not exposed	305 (86.6)	549 (90.4)	Reference	331 (94.0)	574 (94.6)	Reference	305 (86.9)	547 (90.9)	Reference
Ever exposed	47 (13.4)	58 (9.6)	1.87 (1.14, 3.06)	21 (6.0)	33 (5.4)	1.50 (0.76, 2.97)	46 (13.1)	55 (9.1)	1.93 (1.17, 3.19)
Cumulative, T1	12 (3.4)	20 (3.3)	1.21 (0.54, 2.72)	5 (1.4)	10 (1.6)	0.84 (0.23, 3.06)	13 (3.7)	19 (3.2)	1.32 (0.60, 2.91)
Cumulative, T2	20 (5.7)	18 (3.0)	2.48 (1.18, 5.18)	8 (2.3)	13 (2.1)	1.58 (0.58, 4.31)	19 (5.4)	18 (3.0)	2.40 (1.14, 5.07)
Cumulative, T3	15 (4.3)	20 (3.3)	2.15 (0.93, 4.97)	8 (2.3)	10 (1.6)	2.24 (0.73, 6.83)	14 (4.0)	18 (3.0)	2.41 (0.99, 5.87)
p-Value for trend[b]			0.01			0.12			0.01
Metribuzin (POT)									
Not exposed	277 (78.7)	495 (81.5)	Reference	316 (89.8)	553 (91.1)	Reference	277 (78.9)	494 (81.8)	Reference
Ever exposed	75 (21.3)	112 (18.5)	1.43 (0.96, 2.12)	36 (10.2)	54 (8.9)	1.45 (0.85, 2.48)	74 (21.1)	110 (18.2)	1.42 (0.96, 2.11)
Cumulative, T1	21 (6.0)	37 (6.1)	1.18 (0.63, 2.23)	14 (4.0)	17 (2.8)	1.65 (0.72, 3.78)	21 (6.0)	36 (6.0)	1.20 (0.64, 2.26)
Cumulative, T2	26 (7.4)	39 (6.4)	1.33 (0.74, 2.39)	8 (2.3)	20 (3.3)	0.81 (0.32, 2.03)	22 (6.3)	37 (6.1)	1.19 (0.64, 2.21)
Cumulative, T3	28 (8.0)	36 (5.9)	1.97 (1.03, 3.74)	14 (4.0)	17 (2.8)	2.37 (0.98, 5.72)	31 (8.8)	37 (6.1)	2.09 (1.11, 3.95)
p-Value for trend[b]			0.03			0.13			0.03
Monolinuron (POT)									
Not exposed	281 (79.8)	503 (82.9)	Reference	319 (90.6)	556 (91.6)	Reference	281 (80.1)	502 (83.1)	Reference
Ever exposed	71 (20.2)	104 (17.1)	1.44 (0.96, 2.18)	33 (9.4)	51 (8.4)	1.42 (0.82, 2.47)	70 (19.9)	102 (16.9)	1.43 (0.95, 2.16)
Cumulative, T1	18 (5.1)	35 (5.8)	0.97 (0.50, 1.88)	12 (3.4)	17 (2.8)	1.32 (0.55, 3.17)	16 (4.6)	32 (5.3)	0.95 (0.48, 1.86)
Cumulative, T2	27 (7.7)	34 (5.6)	1.65 (0.89, 3.06)	9 (2.6)	18 (3.0)	1.08 (0.44, 2.67)	30 (8.5)	38 (6.3)	1.60 (0.89, 2.87)
Cumulative, T3	26 (7.4)	35 (5.8)	2.00 (1.03, 3.89)	12 (3.4)	16 (2.6)	2.13 (0.87, 5.24)	24 (6.8)	32 (5.3)	2.07 (1.01, 4.21)
p-Value for trend[b]			0.02			0.14			0.03
Oxamyl (POT)									
Not exposed	286 (81.3)	512 (84.3)	Reference	322 (91.5)	559 (92.1)	Reference	286 (81.5)	511 (84.9)	Reference
Ever exposed	66 (18.8)	95 (15.7)	1.45 (0.95, 2.22)	30 (8.5)	48 (7.9)	1.34 (0.76, 2.35)	65 (18.5)	91 (15.1)	1.50 (0.97, 2.31)
Cumulative, T1	18 (5.1)	31 (5.1)	1.08 (0.55, 2.15)	8 (2.3)	15 (2.5)	0.82 (0.32, 2.12)	16 (4.6)	30 (5.0)	0.97 (0.48, 1.94)
Cumulative, T2	26 (7.4)	32 (5.3)	1.55 (0.83, 2.88)	9 (2.6)	18 (3.0)	1.21 (0.48, 3.02)	26 (7.4)	32 (5.3)	1.70 (0.91, 3.18)
Cumulative, T3	22 (6.3)	32 (5.3)	1.90 (0.94, 3.84)	13 (3.7)	15 (2.5)	2.44 (0.98, 6.08)	23 (6.6)	29 (4.8)	2.19 (1.07, 4.47)
p-Value for trend[b]			0.04			0.11			0.02
Pencycuron (POT)									
Not exposed	282 (80.1)	503 (82.9)	Reference	319 (90.6)	556 (91.6)	Reference	282 (80.3)	502 (83.1)	Reference
Ever exposed	70 (19.9)	104 (17.1)	1.43 (0.95, 2.15)	33 (9.4)	51 (8.4)	1.37 (0.80, 2.37)	69 (19.7)	102 (16.9)	1.42 (0.94, 2.13)
Cumulative, T1	19 (5.4)	36 (5.9)	1.16 (0.60, 2.24)	11 (3.1)	17 (2.8)	1.13 (0.47, 2.71)	15 (4.3)	34 (5.6)	0.94 (0.47, 1.88)
Cumulative, T2	22 (6.3)	34 (5.6)	1.23 (0.66, 2.31)	8 (2.3)	17 (2.8)	0.97 (0.38, 2.50)	27 (7.7)	35 (5.8)	1.49 (0.83, 2.70)
Cumulative, T3	29 (8.2)	34 (5.6)	2.08 (1.10, 3.94)	14 (4.0)	17 (2.8)	2.43 (1.00, 5.90)	27 (7.7)	33 (5.5)	2.02 (1.02, 3.97)
p-Value for trend[b]			0.03			0.12			0.03
Prochloraz (CER, BUL)									
Not exposed	327 (92.9)	584 (96.2)	Reference	343 (97.4)	596 (98.2)	Reference	327 (93.2)	583 (96.2)	Reference
Ever exposed	25 (7.1)	23 (3.8)	2.70 (1.38, 5.28)	9 (2.6)	11 (1.8)	2.48 (0.82, 7.47)	24 (6.8)	23 (3.8)	2.65 (1.35, 5.21)
Cumulative, T1	10 (2.8)	7 (1.2)	2.68 (0.94, 7.62)	2 (0.6)	4 (0.7)	n.c.	10 (2.8)	7 (1.2)	2.96 (1.05, 8.37)
Cumulative, T2	8 (2.3)	9 (1.5)	2.54 (0.81, 7.96)	3 (0.9)	5 (0.8)	n.c.	7 (2.0)	9 (1.5)	2.11 (0.67, 6.67)
Cumulative, T3	7 (2.0)	7 (1.2)	2.94 (0.88, 9.84)	4 (1.1)	2 (0.3)	n.c.	7 (2.0)	7 (1.2)	2.90 (0.87, 9.70)
p-Value for trend[b]			0.01			0.08			0.01
Triadimenol (CER)									
Not exposed	323 (91.8)	575 (94.7)	Reference	341 (96.9)	591 (97.4)	Reference	323 (92.0)	574 (94.7)	Reference
Ever exposed	29 (8.2)	32 (5.3)	2.01 (1.09, 3.70)	11 (3.1)	16 (2.6)	1.54 (0.61, 3.87)	28 (8.0)	32 (5.3)	1.97 (1.06, 3.65)
Cumulative, T1	11 (3.1)	11 (1.8)	1.74 (0.68, 4.46)	2 (0.6)	7 (1.2)	n.c.	8 (2.3)	11 (1.8)	1.37 (0.49, 3.78)
Cumulative, T2	10 (2.8)	11 (1.8)	2.09 (0.81, 5.38)	3 (0.9)	4 (0.7)	n.c.	11 (3.1)	11 (1.8)	2.15 (0.85, 5.41)
Cumulative, T3	8 (2.3)	10 (1.6)	2.43 (0.74, 7.97)	6 (1.7)	5 (0.8)	n.c.	9 (2.6)	10 (1.7)	2.99 (0.90, 9.93)
p-Value for trend[b]			0.03			0.12			0.02

T1, first tertile of cumulative exposure (ha-years); T2, second tertile of cumulative exposure; T3, third tertile of cumulative exposure; MCPA, 2-methyl-4-chlorophenoxyacetic acid. Reported use of these pesticides on: POT, potatoes; BUL, bulbs; ORC, orchards; CER, cereals; BEE, beets; MAI, maize. Cutoffs of the cumulative exposure tertiles are based on the distribution of exposure to the pesticide among the controls within a specific distance category, therefore these vary between pesticides and distance categories. The results of larger distance categories (i.e. > 100–500 m and > 500–1000 m) can be found in Appendix B.

[a] Conditional logistic regression adjusted for pack years of smoking (5 categories), time since cessation (5 categories), occupational attainment (4 categories), low occupational pesticide exposure, family history of PD, home pesticide use and neighborhood income (3 categories).

[b] P-value for trend based on the categorical cumulative exposure variable

[c] Excluding participants with exposure in 0–50 m distance but not in > 50–100 m.

exposure categories. We did observe an increased risk for the highest cumulative exposure tertile in the lagged analyses, for both a 10 and 15 year exposure lag (OR 1.53, 95% CI 1.00–2.33 and OR 1.60. 95% CI 1.05–2.44, respectively). This finding suggests that the relevant etiological time window for paraquat exposure might be some years before PD diagnosis. However, when exposure was restricted to roughly the last 20 years before case diagnosis (1990 onward), also elevated risk estimates were found for paraquat compared to the primary analysis, contradicting the results of the lagged sensitivity analysis. We did not investigate combined exposure to paraquat and maneb, as these were highly correlated in our study (exposure in 0–100 m, median spearman correlation coefficient 0.89). Both pesticides had been reported to be used on the same crops during roughly the same time window, and all participants ever exposed to paraquat were also considered exposed to maneb. Therefore, the risk estimate for paraquat might reflect a combined exposure to paraquat and maneb, rather than an individual effect. For lindane, we observed a significant increased risk when we estimated cumulative exposure for the period 1990 onward, for which land-use data was available on the level of individual crops. Similarly, the OR for maneb and paraquat exposure were higher when we

restricted to this period. It is unclear however, if this change in estimates relates to the better quality input data (Brouwer et al., 2017), the more recent timing of exposure or higher cumulative exposure for those subjects who continued living in rural areas. Other studies found elevated concentrations of lindane in serum and brains of PD patients (Corrigan et al., 2000; Richardson et al., 2011), but only non-significant elevated OR have been found for occupational exposure to lindane in the current case-control study (OR 1.39, 95% CI 0.70–2.75) (van der Mark et al., 2014b) and the agricultural health study (OR 1.4 95% CI 0.8–2.5) (Kamel et al., 2007). For benomyl, Fitzmaurice et al. (2013) reported a significant association between environmental exposure within 500 m of the address of the workplace (so not occupational exposure) and PD (OR 1.97, 95% CI 1.29–3.02), but this was not observed for the residential address (OR 1.20, 95% CI 0.78–1.86). This latter risk estimate is in line to the risk we found for being ever exposed to benomyl within 100 m of the residential address (OR 1.48, 95% CI 0.77–2.84). For occupational exposure to benomyl, we previously found a significantly increased risk of PD in our case-control study (OR 2.47, 95% CI 1.05–5.78) (van der Mark et al., 2014b).

In the complete analysis, including the remaining 153 pesticides, we found significant increased risks for being exposed within 100 m around the residence, and significant trends over the cumulative exposure categories, for ten herbicides, seven fungicides, three nematicides/insecticides and one growth regulator. Evidence on plausible biological mechanisms and additional epidemiological data supportive of an association with PD are lacking for these pesticides, however. There was also no clear pattern in either chemical group or suspected mode of action, for these 21 pesticides. For some of the chemical groups these pesticides belong to, there are reports of neurodegenerative properties. For example, a number of azole fungicides have been reported to induce nonspecific inhibition of voltage-gated calcium channels resulting in modulation of intracellular Ca^{2+} (Heusinkveld et al., 2013). Also, dinitrophenol herbicides have been described for their neurotoxic effects (Heusinkveld et al., 2016). Most of these 21 pesticides were used on cereals or potatoes, and we found relatively high correlations between them (median spearman correlation coefficient 0.63, exposure in 0–100 m). These high correlations will in part be due to the inherent nature of pesticide application (i.e. multiple pesticides are used over a growing season), but also due to the retrospective exposure assessment method driven by crop cultivation and time period (Brouwer et al., 2017) We investigated the effect of crop cultivation in a separate analysis, and did find an association between cereal and/or potato cultivation in vicinity of the residence and the risk of PD for distinct decades (i.e. 1981–1990 and 1991–2000). Overall, we did not succeed in identifying individual pesticides driving the observed association with PD risk in this analysis, but merely identified a cluster of pesticides used on rotating crops during a specific time window, that might be related to PD risk. These associations may be driven by a single pesticide during a specific time window, but it could also be the result of exposure to a mixture of pesticides used in vicinity of the residences. Given the number of analyses performed, we cannot exclude that the described associations are false positives. As such, the results on these pesticides should be seen as hypothesis generating and will need further mechanistic and/or epidemiological evidence.

There are some indications, however, that the elevated risks observed in this study are rather reflecting a true effect of agricultural exposures on PD risk, than a chance finding. The risk estimates for the highest tertile of cumulative exposure were consistently higher for the majority of pesticides, and the ORs tended to be higher when considering crop cultivation within the smallest distance category (0–50 m) compared to larger distance. Furthermore, we found a significant increased risk of PD for those ever exposed to bulb cultivation within > 100–500 m of their residence (OR 2.30, 95% CI 1.02–5.18). The case-control study covered four main regions in the Netherlands, but no hospital participated in the North-Western part of the country, which is known for its intensive cultivation of flower bulbs. Pesticide use on flower bulbs is the highest in the Netherlands with on average 54.4 kg of pesticide active ingredients applied to each hectare of bulbs in 2012, followed by orchard crops with 26.3 kg/ha (Statistics Netherlands, 2012). Only few participants were ever exposed to bulb cultivation in vicinity of their residence, and we lacked power to reliably calculate risk estimates for bulb cultivation within 100 m. This specific crop and region should be given more attention in future studies on environmental pesticide exposure and health in the Netherlands.

5. Conclusions

In summary, we investigated the association between lifetime environmental exposure to individual pesticides and PD, in a hospital based case-control study in the Netherlands. Environmental exposure to four *a priori* selected pesticides was not significantly associated with PD risk, but for paraquat, risk estimates were in line with previously reported elevated risks. This study found increased risk of PD with exposure to (a cluster of) 21 pesticides mainly used on two rotating crops. High correlations between these pesticides limited our ability to identify individual pesticides responsible for this association. Due to limited evidence on biological plausibility and the potential for multiple testing issues, we cannot rule out chance findings and emphasize that results should be seen as hypothesis generating. However, this study does provide relevant leads for future research on pesticide exposure and PD risk, highlighting potentially relevant pesticides, crops and time periods of exposure.

Competition of financial interests

None declared.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary data

Supplementary data to this article (Appendix A and B) can be found online at http://dx.doi.org/10.1016/j.envint.2017.07.001.

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