ORIGINAL ARTICLE

Occupational exposures and Parkinson's disease mortality in a prospective Dutch cohort

Maartje Brouwer,[1] Tom Koeman,[1] Piet A van den Brandt,[2] Hans Kromhout,[1] Leo J Schouten,[2] Susan Peters,[3] Anke Huss,[1] Roel Vermeulen[1,4]

ABSTRACT

Objectives We investigated the association between six occupational exposures (ie, pesticides, solvents, metals, diesel motor emissions (DME), extremely low frequency magnetic fields (ELF-MF) and electric shocks) and Parkinson's disease (PD) mortality in a large population-based prospective cohort study.

Methods The Netherlands Cohort Study on diet and cancer enrolled 58 279 men and 62 573 women aged 55–69 years in 1986. Participants were followed up for cause-specific mortality over 17.3 years, until December 2003, resulting in 402 male and 207 female PD deaths. Following a case–cohort design, a subcohort of 5 000 participants was randomly sampled from the complete cohort. Information on occupational history and potential confounders was collected at baseline. Job-exposure matrices were applied to assign occupational exposures. Associations with PD mortality were evaluated using Cox regression.

Results Among men, elevated HRs were observed for exposure to pesticides (eg, ever high exposed, HR 1.27, 95% CI 0.86 to 1.88) and ever high exposed to ELF-MF (HR 1.54, 95% CI 1.00 to 2.36). No association with exposure duration or trend in cumulative exposure was observed for any of the occupational exposures. Results among women were unstable due to small numbers of high-exposed women.

Conclusions Associations with PD mortality were observed for occupational exposure to pesticides and ELF-MF. However, the weight given to these findings is limited by the absence of a monotonic trend with either duration or cumulative exposure. No associations were found between PD mortality and occupational exposure to solvents, metals, DME or electric shocks.

What this paper adds

- Different occupational exposures have been associated with an increased risk of Parkinson's disease (PD), but evidence from prospective cohort studies is limited.
- The Netherlands Cohort Study on Diet and Cancer is a large prospective cohort study with complete occupational histories up to baseline and 17.3 years of follow-up, enabling a comprehensive study on the association between different occupational exposures and PD mortality.
- This study found associations between PD mortality and exposure to pesticides and extremely low frequency magnetic fields, but neither association with exposure duration nor a trend in cumulative exposure was observed.
- No association between PD mortality and occupational exposure to solvents, metals, diesel motor emissions or electric shocks was found.
- This study does not support the hypothesis that the investigated occupational exposures increase PD mortality, although we cannot exclude that small risks may exist.

INTRODUCTION

Parkinson's disease (PD) is a progressive movement disorder which involves the degeneration of dopaminergic neurons in the substantia nigra, resulting in dopamine deficiency. PD is clinically characterised by decreased motor function: slow movements (bradykinesia), rigidity, postural instability and chronic progressive rest tremor.[1] Parkinsonism is a term used for conditions that share some or most of PD symptoms plus other symptoms not characteristic for PD, with often very distinct aetiology (eg, toxin exposure or ischaemic injury). PD is the second most common neurodegenerative disease following Alzheimer's disease (AD), and is estimated to have an incidence of about 160 per 100 000 person-years above 65 years of age,[2] but higher incidence rates may occur depending on study region, population and age range studied.[1] A sharp rise in incidence is seen after the age of 60 years,[3] although cases of early-onset PD (before 40 years of age) account for approximately 5–10% of all cases.[4] PD occurs more frequently in men than women, with an age-adjusted pooled male-to-female ratio of 1.5 (95% CI 1.2 to 1.7).[5]

The aetiology of PD is not well understood, but research indicates that both genetic and environmental factors are involved. Several genes related to PD have been identified and familial aggregation studies support the role of genetics.[6 7] However, these genetic factors are mainly associated with early-onset PD[4] and twin studies indicated that the environmental component is considerable for older-onset PD cases.[8 9] Epidemiological and toxicological studies have suggested a wide variety of environmental factors to be potentially involved in the aetiology of PD, including occupational and environmental exposures and lifestyle, such as smoking and diet.[1] Few consistent findings have emerged, with the exception of an inverse association between smoking and PD risk.[10]

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[1]Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[2]Department of Epidemiology, GROW School of Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands
[3]Department of Occupational Respiratory Epidemiology, School of Population Health, University of Western Australia, Perth, Western Australia, Australia
[4]Julius Centre for Public Health Sciences and Primary Care, Utrecht University Medical Centre, Utrecht, The Netherlands

Correspondence to
Maartje Brouwer, Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, PO Box 80.178, Utrecht 3584TD, The Netherlands; m.brouwer1@uu.nl

MB and TK contributed equally.

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A number of occupational exposures have been proposed as risk factors for PD. Epidemiological findings suggest a positive association between pesticide exposure and PD risk, but there is limited evidence on specific pesticides or groups of pesticides potentially involved.[11 12] Some solvents have shown neurotoxic effects in animal studies and case reports of parkinsonism have been described for exposure to solvents, such as n-hexane and methanol.[13] In addition, a recent meta-analysis indicated that exposure to solvents was associated with an increased risk of PD in case–control studies, although this was not found in the two cohort studies included in this meta-analysis.[14] For metals, neurotoxic effects have been described in toxicological studies and case reports suggest a possible association between exposure to metals, such as manganese and lead, and Parkinsonian symptoms or parkinsonism.[1] Although lead levels in the human bone have been related to PD,[15 16] the overall epidemiological evidence for an association between metal exposure and PD risk is limited. Studies suggesting a relation between traffic-related air pollution, to which diesel motor exhaust (DME) is an important contributor, and neurodegenerative diseases such as PD are emerging.[17] Other neurodegenerative diseases (ie, AD and amyotrophic lateral sclerosis (ALS)) have been associated primarily with electrical occupations rather than extremely low frequency magnetic field (ELF-MF) exposure and it has been hypothesised that this association may be related to electric shocks rather than to magnetic fields.[18 19] Few studies have reported on a positive association between occupational exposure to ELF-MF and PD,[20] but it is possible that electric shocks are involved as little knowledge exists regarding a potential association between electric shocks and PD. Data from prospective cohort studies are lacking for many of the occupational exposures listed above and evidence originating from case–control studies may suffer from methodological limitations, such as recall bias, when based on self-reported exposures or the inability to obtain a control group representative of the exposure distribution in the source population.

We examined the association between selected occupational exposures (ie, pesticides, solvents, DME, metals, ELF-MF and electric shocks) assigned through job-exposure matrices (JEMs) and PD mortality in a large population-based prospective cohort study in the Netherlands.[21]

MATERIALS AND METHODS

Population

The Netherlands Cohort Study on diet and cancer (NLCS) consists of 58 279 men and 62 573 women, aged 55–69 at enrolment in September 1986. The response rate of the study was 35.5% (34.5% among men and 36.6% among women). At baseline, participants completed a self-administered questionnaire on occupational history and other lifestyle factors such as smoking. A detailed description of the cohort study design can be found elsewhere.[21] In brief, basic demographic information was digitised for all cohort members from the first page of the questionnaire. Following a case–cohort design,[21 22] a subcohort of 5 000 participants (2411 men and 2589 women) was randomly selected from the total cohort to estimate the person-years accumulated in the entire cohort. After enrolment, information on the date of death was obtained from the Dutch Bureau of Genealogy (manually for September 1986 till October 1994, and through record linkage until 1999). Follow-up after 2000 occurred through automated linkage with the Dutch population registry. The cause of death (primary and secondary causes) was obtained from Statistics Netherlands (CBS). For both the subcohort and all incident deaths, the remaining questionnaire data was entered. The NLCS was approved by the institutional review boards of The Netherlands Organisation of Applied Scientific Research TNO (Zeist) and Maastricht University (Maastricht).

Case definition

At the time of this study, 17.3 years of follow-up was available (17 September 1986 to 31 December 2003). International Classification of Disease (ICD) codes 332.0 (ICD-9) and G20 (ICD-10) were used to identify PD deaths. Until 1996, ICD-9 was used. This was recoded into ICD-10 and from 1997 onwards, ICD-10 was used. Both primary and secondary PD deaths were considered as PD cases in this study.

Occupational exposures

The enrolment questionnaire covered the occupational history of the participants up to baseline. Participants were asked to provide detailed information for up to five occupations (job title, type of industry, time employed). Owing to the age at enrolment (55–69 years), the majority of the cohort was retired or otherwise not employed at baseline (78%). To each reported occupation, a job code was assigned using a Dutch coding system which was translated to International Standard Classification of Occupations (ISCO)-68 and ISCO-88 codes.[23] Four different JEMs were linked to these job codes to determine exposure to each of the selected occupational exposures. The ALOHA+JEM[23 24] was used to determine job-specific exposure to pesticides (ie, all pesticides, herbicides, insecticides and fungicides), solvents (ie, all solvents, aromatic solvent and chlorinated solvents) and metals. Exposure to DME was estimated using the DOMJEM.[25] ELF-MF exposure was determined with an adapted version of the ELF-MF JEM of Bowman *et al*.[26 27] Furthermore, risk of electric shocks at work was assigned with a newly developed shock-JEM based on electrical injury registration data.[28] The first three JEMs make use of a semiquantitative ordinal exposure scale, based on the intensity and prevalence of exposure within a job, with three exposure categories: not exposed (environmental background), low exposed and high exposed. These categories were assigned scores of 0, 1 and 4, respectively.[23] The shock-JEM has a similar structure but is based on the pooled accident rates of electric shocks, categorising jobs into low, medium and high risk (with assigned scores of 0, 1 and 4, respectively), based on the 75th and 90th centile of job-specific accident rates.[28] For 12% of both the cases and the subcohort, job descriptions were missing occupational history or the reported jobs could not be coded. For these participants, exposure was set to 'missing'. Jobs reported to be unpaid (ie, volunteer work) were regarded as 'unexposed'. If jobs overlapped in time, the overlapping years were divided equally between these jobs. For jobs where duration was missing (6% cases and 4% subcohort), an imputation was performed based on sex-specific average job durations in the cohort.[27]

Exposure metrics

For each of the selected exposures, several metrics were evaluated. First, being 'ever only low exposed' or being 'ever high exposed' in any of the reported jobs was evaluated. Second, the effect of exposure duration (per 10-year increase) was investigated, for low-exposed and high-exposed jobs combined. The third metric of interest was cumulative exposure up to baseline. The latter was calculated by summing the specific JEM scores (0, 1 or 4 for not exposed, low or high exposed, respectively) across all years and jobs in the occupational history, resulting in so called unit-years of exposure.

Statistical analysis

In this case–cohort study, cases were enumerated for the entire cohort, while the accumulated person-years for the entire cohort were estimated from the randomly sampled subcohort (n=5000). Person-years were calculated from baseline (ie, 17 September 1986) until death, loss to follow-up or end of follow-up (ie, 31 December 2003), whichever occurred first. HRs and corresponding 95% CIs for PD mortality were estimated using Cox proportional hazard models in STATA V.12 (Statacorp LP, College station, Texas, USA).[29 30] Attained age was used as the underlying time scale in the Cox models. SEs were estimated by using a robust covariance matrix estimator to account for the additional variance associated with the case–cohort study design.[31]

We considered the following covariates for inclusion in the models: smoking status (never, former and current smoker); body mass index (BMI; underweight: <18.5 kg/m^2, normal weight: 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2 and obese: >30.0 kg/m^2) non-occupational physical activity (30 min/day or less, >30–60 min/day, >60–90 min/day and more than 90 min/day); highest level of education attained (primary vocational, lower vocational, secondary and medium vocational and higher vocational); alcohol consumption (g/day, 5 categories); coffee consumption (g/day, 3 categories) and tea consumption (g/day, 3 categories). Variables with a p value<0.10 in a univariate model were combined in a multivariate model, after which a stepwise backward regression was applied retaining those variables with a p value<0.05. The final Cox proportional hazard models were corrected for smoking status, BMI and non-occupational physical activity. Being 'ever only low exposed' or 'ever high exposed' were analysed as categorical variables, using the unexposed participants (background exposure) as reference. Exposure duration was analysed as a continuous variable and the HRs are calculated per 10-year increase in duration. Cumulative exposure was analysed as a categorical variable, using background exposure (cumulative exposure of 0) as reference category and dividing those with a cumulative exposure higher than background in three categories based on the sex-specific tertiles of the exposed participants in the subcohort. A test for linear trend was performed based on the midpoints of the cumulative exposure tertiles. All analyses were stratified by sex and confounders were the same in all models.

The association between each occupational exposure and PD mortality was evaluated using a separate model adjusted for the selected confounders. Occupational exposures indicative of an association with PD mortality were subsequently combined pairwise in multiple exposure models to estimate their mutually adjusted effect. Four sensitivity analyses were performed. To investigate the effect of potential unknown exposures after enrolment, the analysis was first restricted to participants retired at enrolment who had a complete occupational history up to baseline. Participants who did not have any jobs that could be coded were considered as 'missing' in the main analysis, and in the second sensitivity analysis these participants were considered 'unexposed' to any of the occupational exposures. The third sensitivity analysis was restricted to those participants who ever had a paid job, leaving out the unemployed and housewives who had been regarded as 'unexposed' in the main analysis. Finally, a lag time of 20 years was implemented, excluding all exposures in the 20 years prior to death or end of follow-up, to have an equal effective lag time for both the cases and subcohort.

RESULTS

The mean follow-up time from baseline to death or administrative censoring was 14.6 years. A total of 465 men and 280 women died with PD during follow-up, of which 402 men (86%) and 207 women (74%) could be assigned occupational exposures and had complete confounder information. Of the 63 male PD cases excluded from the analysis, 34 (54%) missed data on their occupational exposures, 23 (37%) missed confounder data and 6 (10%) missed both. For the 73 excluded female cases, this was 44 (60%), 21 (29%) and 8 (11%), respectively. The male-to-female ratio for PD mortality in this study was 1.9. Of the subcohort, 2098 men (86% of total) and 2083 women (80%) with complete exposure and confounder data were included in the analyses. For both men and women, a smaller proportion of the PD cases were current smokers compared with the subcohort and the cases were older at baseline. Female cases were slightly less physically active and less often overweight (table 1).

The percentage of cases and subcohort members ever only low or ever high exposed during their occupational history differed between the occupational risk factors investigated. For men, the percentage of cases ever exposed (ever only low or ever high) varied between 10% (herbicides) and 52% (ELF-MF) (table 2). Women had shorter occupational histories than men (13 vs 36 years on average) and very few women were ever high exposed to any of the occupational exposures, with ever high exposure to pesticides being most prevalent. Owing to the overall low prevalence of (high) exposed women, we only present the results for men here. The results for women can be found in the online supplementary table S1. Correlation plots of the occupational exposures are presented in the online supplementary figure S1.

Few significant associations were observed between the different occupational exposures and PD mortality among men in the adjusted main analyses (table 2). Non-significant elevated HRs were found for being ever exposed to pesticides. For overall pesticide exposure and insecticide exposure, significantly increased HRs were observed, although only in the first tertile of cumulative exposure (HR 1.89, 95% CI 1.11 to 3.22 and HR 1.87, 95% CI 1.07 to 3.28, respectively). A slightly elevated HR of 1.37 (95% CI 0.78 to 2.39) was found for participants ever high exposed to DME. Ever high exposure to ELF-MF was significantly associated with PD mortality (HR 1.54, 95% CI 1.00 to 2.36), but there was no trend with increasing cumulative exposure (p=0.79). Decreased HRs were observed for the first tertile of aromatic solvent exposure (HR 0.62, 95% CI 0.40 to 0.97), and for risk of electric shocks (ever high, HR 0.79, 95% CI 0.59 to 1.06), of which the latter association was non-significant. Grouping all exposed participants into an ever exposed category resulted in similar HRs (see online supplementary table S2).

When analysing exposure to pesticides, insecticides, aromatic solvents, ELF-MF, electric shocks or DME, pairwise adjusted for the other occupational exposures, the HRs for exposure to pesticides, insecticides and ELF-MF only changed marginally (see online supplementary table S3). However, when exposure to pesticides or insecticides was included in the analysis of DME exposure, the HR for being ever high exposed to DME attenuated from 1.37 (95% CI 0.78 to 2.39) to 0.94 (95% CI 0.47 to 1.88) and to 0.94 (95% CI 0.46 to 1.91), respectively.

No significant trends were found for cumulative exposure to any of the occupational exposures investigated (table 2). In addition, no association between exposure duration and PD mortality was observed for any of the exposures (see online supplementary table S4). Sensitivity analysis restricted to participants retired at enrolment did not result in materially different HRs. No changes in HRs were observed when missing

Table 1 Characteristics of the study population

	Men				Women			
	Cases (n=402)		Person-years in subcohort (n=29 228)		Cases (n=207)		Person-years in subcohort (n=31 701)	
	n	Per cent	n	Per cent	n	Per cent	n	Per cent
Age at baseline (years)								
55–59	58	14.4	11 499	39.3	28	13.5	12 357	39.0
60–64	125	31.1	10 323	35.3	64	30.9	10 598	33.4
65–69	219	54.5	7406	25.3	115	55.6	8746	27.6
Smoking status								
Never-smoker	76	18.9	3941	13.5	152	73.4	18 454	58.2
Former smoker	220	54.7	15 192	52.0	37	17.9	6804	21.5
Current smoker	106	26.4	10 095	34.5	18	8.7	6444	20.3
Non-occupational physical activity								
Less than 30 min/day	78	19.4	5116	17.5	65	31.4	7507	23.7
>30–60 min/day	116	28.9	9301	31.8	74	35.7	10 068	31.8
>60–90 min/day	91	22.6	5569	19.1	30	14.5	7180	22.6
More than 90 min/day	117	29.1	9242	31.6	38	18.4	6946	21.9
Body mass index								
Underweight (<18.5 kg/m^2)	4	1.0	108	0.4	9	4.3	406	1.3
Normal weight (18.5–24.9 kg/m^2)	211	52.5	15 397	52.7	118	57.0	17 157	54.1
Overweight (25.0–29.9 kg/m^2)	173	43.0	12 595	43.1	70	33.8	11 403	36.0
Obese (>30.0 kg/m^2)	14	3.5	1127	3.9	10	4.8	2735	8.6

occupational histories were coded 'unexposed' instead of 'missing' or when the analysis was restricted to participants who ever had a paid job. Finally, using a lag time of 20 years did not change the results (data not shown).

DISCUSSION

This study investigated the association between different occupational exposures, previously suggested to be related to PD, and PD mortality in a population-based prospective cohort in the Netherlands. Elevated HRs for PD mortality were observed for exposure to pesticides and ELF-MF, which remained so even after adjusting for the other occupational exposures. However, we found no association with exposure duration and no trend in cumulative exposure for these two exposures. No associations between PD mortality and occupational exposure to solvents, metals, DME or risk of electric shocks were observed.

Limitations of our study include the case identification through the use of death certificates and the limited number of high-exposed cases, especially among women. PD is a chronic condition that is non-fatal in itself[32] and substantial under-reporting of PD on death certificates has been described, with no more than half of the patients with PD receiving a PD diagnosis as underlying cause of death.[33] This indicates that we will probably have under-reporting of PD deaths in our study. Under-reporting of PD deaths is likely non-differential with respect to the occupational history underlying the exposure assessment and will, therefore, not bias the results. Under-reporting will, however, reduce the power to detect associations. The ICD codes used to identify PD deaths in this study were 332.0 (ICD-9) and G20 (ICD-10). These codes are generally accepted for identifying PD, but do not distinguish between PD and parkinsonism. It has been estimated that roughly 25% of participants who had ever been classified under 332.0 (ICD-9) were not PD cases[34] but had parkinsonism, another movement disorder or something else. This indicates that among the participants classified as PD deaths in this study, there is likely to be a fraction of parkinsonism cases and other misclassified deaths. This potential outcome misclassification will most likely be independent of exposure status and we do not expect this to result in bias. Another issue with using mortality data is that we cannot exclude the possibility that participants already had PD (motor) symptoms at enrolment, potentially affecting their working career and occupational exposures in some years prior to enrolment. However, when we used a 20-year lag in the analysis, the results were unchanged, indicating that there is no evidence for such reversed causation in this study. The associations described in this paper are between the occupational exposures and PD mortality, and we cannot make any direct inferences on PD incidence and/or survival after diagnosis.

We observed an inverse association between smoking and PD mortality. The HR for being a current smoker was 0.61 (95% CI 0.48 to 0.78) and for being a former smoker 0.78 (95% CI 0.63 to 0.97). These numbers are in line with the lowered risk of PD associated with smoking described in other studies, where PD was confirmed by clinical evaluation and other study designs were applied.[10 35] This gives some confidence in the use of PD mortality data for disease ascertainment in our cohort study. In addition, the observed male-to-female ratio of 1.9 in our study is also in line with reports from other studies.[5] Despite the relatively large number of PD cases, which is higher than most other prospective cohort studies,[36–39] the percentage of cases ever high exposed to the occupational exposures investigated was generally less than 10%, which might have prevented the detection of significant associations. We stratified all analyses by sex, as exposure patterns and intensities are different between men and women, but the small number of (high) exposed female cases limited our ability to look at possible sex-specific associations.

Among the strengths of this study are the large sample size, the prospective study design, the complete occupational history and the exposure assessment based on JEMs, which are not

Table 2 PD mortality in men associated with occupational exposure to pesticides, solvents, DME, metals, ELF-MF or risk of electric shocks

Exposure	Cases (n=402)	Person-years in subcohort (n=29 228)	Adjusted HR* (95% CI)
Pesticides, all			
Ever exposed			
Background	338	25 696	1
Ever only low exposed	22	1204	1.35 (0.81 to 2.26)
Ever high exposed	42	2328	1.27 (0.86 to 1.88)
Cumulative exposure			
1st tertile, 1–27 unit-years	23	1115	**1.89 (1.11 to 3.22)**
2nd tertile, 28–87 unit-years	19	1273	1.01 (0.59 to 1.72)
3rd tertile, 88–224 unit-years	22	1144	1.19 (0.70 to 2.03)
Test for trend†			p=0.44
Herbicides			
Ever exposed			
Background	360	26 833	1
Ever only low exposed	23	1097	1.53 (0.90 to 2.59)
Ever high exposed	19	1299	0.95 (0.54 to 1.65)
Cumulative exposure			
1st tertile, 1–23 unit-years	13	754	1.57 (0.80 to 3.10)
2nd tertile, 24–47 unit-years	16	833	1.47 (0.80 to 2.70)
3rd tertile, 48–216 unit-years	13	809	0.81 (0.42 to 1.57)
Test for trend†			p=0.96
Insecticides			
Ever exposed			
Background	341	25 840	1
Ever only low exposed	19	1078	1.35 (0.78 to 2.34)
Ever high exposed	42	2310	1.27 (0.86 to 1.88)
Cumulative exposure			
1st tertile, 1–27 unit-years	21	1022	**1.87 (1.07 to 3.28)**
2nd tertile, 28–91 unit-years	18	1276	1.00 (0.58 to 1.72)
3rd tertile, 92–224 unit years	22	1090	1.23 (0.72 to 2.09)
Test for trend†			p=0.40
Fungicides			
Ever exposed			
Background	351	26 338	1
Ever only low exposed	19	1114	1.19 (0.69 to 2.08)
Ever high exposed	32	1777	1.25 (0.80 to 1.95)
Cumulative exposure			
1st tertile, 1–27 unit-years	15	855	1.56 (0.83 to 2.93)
2nd tertile, 28–52 unit-years	17	1014	1.29 (0.72 to 2.30)
3rd tertile, 53–220 unit-years	19	1021	1.01 (0.58 to 1.77)
Test for trend†			p=0.71
Solvents, all			
Ever exposed			
Background	258	18 596	1
Ever only low exposed	88	5884	1.11 (0.84 to 1.48)
Ever high exposed	56	4747	0.97 (0.70 to 1.36)
Cumulative exposure			
1st tertile, 1–23.5 unit-years	43	3418	0.96 (0.66 to 1.39)
2nd tertile, 24–47 unit-years	58	3677	1.26 (0.90 to 1.76)
3rd tertile, 48–204 unit-years	43	3537	0.95 (0.65 to 1.38)
Test for trend†			p=0.92
Aromatic solvents			
Ever exposed			
Background	294	19 951	1
Ever only low exposed	95	8269	0.84 (0.64 to 1.10)
Ever high exposed	13	1008	0.84 (0.45 to 1.57)
Cumulative exposure			
1st tertile, 1–14 unit-years	27	3079	**0.62 (0.40 to 0.97)**
2nd tertile, 15–35.5 unit-years	42	3169	1.11 (0.76 to 1.62)
3rd tertile, 36–204 unit-years	39	3029	0.82 (0.56 to 1.21)

Continued

Table 2 Continued

Exposure	Cases (n=402)	Person-years in subcohort (n=29 228)	Adjusted HR* (95% CI)
Test for trend†			p=0.65
Chlorinated solvents			
Ever exposed			
Background	316	22 276	1
Ever only low exposed	46	3300	1.09 (0.76 to 1.56)
Ever high exposed	40	3652	0.93 (0.63 to 1.35)
Cumulative exposure			
1st tertile, 1–21 unit-years	31	2322	1.00 (0.65 to 1.54)
2nd tertile, 22–51 unit-years	29	2397	1.05 (0.68 to 1.61)
3rd tertile, 52–204 unit years	26	2233	0.97 (0.60 to 1.55)
Test for trend†			p=0.97
Metals			
Ever exposed			
Background	329	22 984	1
Ever only low exposed	35	2555	1.10 (0.73 to 1.65)
Ever high exposed	38	3689	0.96 (0.66 to 1.42)
Cumulative exposure			
1st tertile, 1–24 unit-years	21	2123	0.83 (0.50 to 1.37)
2nd tertile, 25–67 unit-years	27	2115	1.12 (0.71 to 1.77)
3rd tertile, 68–204 unit-years	25	2006	1.14 (0.71 to 1.83)
Test for trend†			p=0.49
DME			
Ever exposed			
Background	284	20 313	1
Ever only low exposed	99	7870	0.94 (0.72 to 1.23)
Ever high exposed	19	1045	1.37 (0.78 to 2.39)
Cumulative exposure			
1st tertile, 0.5–11 unit-years	35	2963	0.96 (0.64 to 1.44)
2nd tertile, 12–32 unit-years	40	2857	1.15 (0.78 to 1.72)
3rd tertile, 33–188 unit-years	43	3096	0.90 (0.62 to 1.31)
Test for trend†			p=0.95
ELF-MF			
Ever exposed			
Background	191	13 999	1
Ever only low exposed	172	13 043	0.97 (0.76 to 1.24)
Ever high exposed	39	2185	**1.54 (1.00 to 2.36)**
Cumulative exposure			
1st tertile, 1–21 unit-years	68	5047	0.99 (0.72 to 1.37)
2nd tertile, 22–38.1 unit-years	73	4987	1.29 (0.93 to 1.79)
3rd tertile, 39–188 unit-years	70	5195	0.90 (0.65 to 1.24)
Test for trend†			p=0.79
Electric shocks			
Ever exposed			
Background	269	17 627	1
Ever only low exposed	58	4424	0.84 (0.60 to 1.17)
Ever high exposed	75	7177	0.79 (0.59 to 1.06)
Cumulative exposure			
1st tertile, 1–31 unit-years	39	3723	0.77 (0.52 to 1.13)
2nd tertile, 32–91 unit-years	44	3997	0.70 (0.48 to 1.02)
3rd tertile, 92–204 unit-years	50	3881	1.00 (0.70 to 1.42)
Test for trend†			p=0.91

Bold type indicates statistical significance (p<0.05).
*Adjusted for smoking status, non-occupational physical activity and BMI.
†Test for linear trend calculated from midpoints tertiles.
BMI, body mass index; DME, diesel motor exhaust; ELF-MF, extremely low frequency magnetic fields; PD, Parkinson's disease.

biased through differential recall. The detailed information on nutrition and lifestyle collected at baseline provided the opportunity to investigate a wide range of potential confounding factors, such as smoking and non-occupational physical activity. No information on race or ethnicity of the participants was collected in this cohort study. In 1986, there was a limited number of inhabitants of non-western ethnicity in the Netherlands (roughly 3% of the total population) and the questionnaire was

only administered in Dutch. As such, participation of non-western ethnicities in the study can be considered low. At baseline, the majority of participants had already retired (88% of cases and 78% of the subcohort) and therefore, the exposure estimates derived from the collected occupational histories covered lifetime occupational exposure for most participants. As information on occupations was not updated after 1986, we cannot exclude the possibility that more recent occupational exposures contributed to PD mortality for a small proportion of the cohort not retired at enrolment. However, a sensitivity analysis, restricted to the participants retired at baseline, did not result in different associations.

The epidemiological evidence that exposure to pesticides may increase the risk of PD is suggestive, but remains inconclusive. The elevated HRs observed in this study for ever only low or ever high pesticide exposure and PD mortality in men did not reach statistical significance, but the HRs are similar to the risk estimates in recent meta-analyses.[11 12] Van der Mark *et al* found a pooled summary risk ratio of 1.39 (95% CI 0.92 to 2.10) for the four prospective cohort studies included in their meta-analysis, which is in line with the HRs observed in our cohort study for exposure to pesticides. Duration of exposure to pesticides was not related to PD mortality and we did not observe a trend for cumulative exposure. A statistically significant increased HR of PD mortality emerged in the first tertile of cumulative exposure to pesticides and the first tertile of cumulative exposure to insecticides. This first tertile comprised a diverse group of participants, in terms of jobs held over time. These participants had on average 3.2 jobs of 11.3 years each, with a substantial fraction of non-agricultural jobs. In comparison, the third tertile consisted mainly of participants working in an (agricultural) job for a longer period of time (on average 1.5 jobs of 29.2 years). Although consistent with current knowledge, our results add only limited support to the evidence base of pesticide exposure and PD risk.

A significant increased HR was observed for PD mortality among men ever high exposed to ELF-MF. Literature on the association between ELF-MF exposure and PD primarily shows null findings,[20] which is strengthened by the absence of knowledge on possible biological mechanisms involved. Studies focusing on occupations with potentially high ELF-MF exposure did find weak associations with other neurodegenerative diseases, such as AD and ALS, but generally not with PD.[19 20] As no effect of cumulative exposure or exposure duration was observed in our study, the weight given to this finding is limited, but we cannot rule out that high exposures to ELF-MF may be related to PD. In this study we did not observe an association between the risk of electric shocks and PD mortality. Little knowledge exists regarding a potential association between electric shocks and PD, but this occupational factor was included because for ALS the suggested association with ELF-MF has been hypothesised to be related to electric shocks, rather than the magnetic fields.[20] When the analysis of ELF-MF exposure was adjusted for risk of electric shocks, the association between ever high exposure to ELF-MF and PD mortality became stronger (HR 1.81, 95% CI 1.15 to 2.85). This suggests that, if the observed association between high exposure to ELF-MF and PD risk is true, this is likely not driven by electric shocks.

DME was included as occupational risk factor in this study as it has been hypothesised that traffic-related air pollution might be associated with PD risk[17] and DME is an important contributor to traffic-related air pollution. We observed a small non-significant increased HR among participants ever high exposed to DME. This increased risk disappeared after adjustment for exposure to pesticides, indicating that coexposure to pesticides was likely driving this finding. In addition, no association between cumulative exposure to DME or exposure duration and PD mortality was observed. These findings are in line with a previous cohort study where no association between DME and PD was observed.[36]

We did not find consistent associations between occupational exposure to solvents and PD mortality. Some solvents have well-established neurotoxic effects and there are case reports of parkinsonism related to solvent exposure.[13] However, overall evidence from toxicological and epidemiological research on specific solvents or solvent classes as a cause of PD is limited. A recent meta-analysis indicated a positive association between solvent exposure and PD in case–control studies, but no such association was found in the two cohort studies included.[14] The described positive findings may, therefore, be caused by limitations associated with a case–control design, such as recall bias when relying on self-reported exposures. The results on solvent exposure and PD from two cohort studies[36 40] are in line with our findings. It should be noted that no complete occupational history was collected in either of these cohort studies and thereby our findings, based on a complete occupational history up to baseline, are an informative addition to the existing knowledge. Furthermore, we explored exposure to solvents in general and also investigated exposure to the subgroups of aromatic solvents and chlorinated solvents. For metals, neurotoxic effects in toxicological studies and case reports of parkinsonian symptoms or parkinsonism induced by exposure to metals, such as manganese and lead, have been described,[1] and lead levels in the human bone have been associated to PD.[15 16] The overall epidemiological evidence for a causal role in PD, however, is limited as most studies investigating the association between exposure to metals and PD were generally small, and prospective data is minimal.[1] We did not find an association between occupational exposure to metals and PD mortality in our cohort study. Exposure to metals was investigated as a broad category as we did not have information on exposure to individual metal compounds. Therefore, we cannot rule out that specific metals, such as lead or manganese, could be associated with PD.

In this large prospective population-based cohort study of Dutch men and women, with 17.3 years of follow-up, we found some suggestions for an association between PD mortality and occupational exposure to pesticides and ELF-MF. However, the weight given to these findings is limited by the absence of a monotonic trend with either duration of exposure or cumulative exposure. We found no evidence for associations between PD mortality and occupational exposure to solvents, metals, DME or risk of electric shocks. This study does not support the hypothesis that the investigated occupational exposures increase PD mortality, although we cannot exclude that small risks do exist.

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Occupational exposures and Parkinson's disease mortality in a prospective Dutch cohort

Maartje Brouwer, Tom Koeman, Piet A van den Brandt, Hans Kromhout, Leo J Schouten, Susan Peters, Anke Huss and Roel Vermeulen

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Notes