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Agricultural work and the risk of Parkinson's disease in Denmark, 1981—1993

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Objectives This study examined the possible association between agricultural and horticultural work and the subsequent morbidity of Parkinson's disease.

Methods Fixed cohorts of 2 273 872 men and women aged 20—59 years on 1 January 1981 and identified in the Central Population Register of Denmark were followed, and all first-time hospitalizations with Parkinson's disease as the principal diagnosis during the 13 years until 31 December 1993 were recorded. Standardized hospitalization ratios (SHR) were calculated using all gainfully employed persons as the standard and by multiplying the ratio by 100. Ninety-five percent confidence intervals (95% CI) were calculated on the assumption of a Poisson distribution.

Results A high risk of Parkinson's disease was found for the men and women in agriculture and horticulture (134 cases, SHR 132, 95% CI 111—156). Statistically significantly high risks were found for farmers (79 cases, SHR 130, 95% CI 103—163) and for all men in agriculture and horticulture (109 cases, SHR 134, 95% CI 109—162).

Conclusions A consistent pattern of high Parkinson's disease morbidity was found among occupational groups employed in agriculture and horticulture.

Key terms agriculture, epidemiology, farming, horticulture, human, pesticides, rural living.

Parkinson's disease is a neurological syndrome usually resulting from deficiency of the neurotransmitter dopamine as the consequence of degenerative, vascular, or inflammatory changes in the basal ganglia, characterized by rhythmic muscular tremors, rigidity of movement, droopy posture, and a mask-like face. Some studies have shown that farming as an occupation (1—4) and living in rural areas (2—3, 5) may result in a higher than normal risk of Parkinson's disease, possibly because of exposure to pesticides. Some support for this finding was also found in a recent Swedish study, although no statistically significant associations were found between the handling of pesticides and Parkinson's disease (6). The association between pesticide exposure and Parkinson's disease has been summarized in a recent review as follows: "Although results are not fully consistent and are often statistically imprecise, there are reports of elevated risks related to exposure to the nonspecific category

of 'pesticides' and more pointedly to insecticides and herbicides" [p 330] (7). Some epidemiologic studies have published information about the specific pesticides to which cases may have been exposed, for instance, rotenone (4—5) and paraquat (3, 8—9). Other studies refer to pesticide families, such as organochlorines (10—11), thiocarbamates (11), and organophosphorus compounds (12). According to a recent report pesticide exposure and a positive family history were risk factors for Parkinson's disease expressed by glutathione transferase (GST) polymorphism (12). GST is an enzyme involved in the metabolism of pesticides. Tanner & Goldman (13) warned that earlier results may have been due to recall bias, as they found no prospective studies concerning farming and Parkinson's disease.

Our present study had the advantages that it was prospective and that it included all cases in Denmark. Migration in and out of Denmark is well recorded, and there

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is virtually no loss of follow-up. Our aim was to estimate the risk of Parkinson's disease among occupational groups potentially exposed to pesticides because they are living in rural areas and occupied with farming and horticulture.

Subjects and methods

Fixed cohorts of 2 273 872 men and women aged 20–59 years on 1 January 1981 and identified in the Central Population Register of Denmark were followed, and all first-time hospitalizations due to Parkinson's disease as the principal diagnosis during the 13 years until 31 December 1993 were recorded. The Occupational Hospitalization Register, which links data from the annual register-based population census of Denmark to the National Inpatient Register, was used for this purpose.

The Central Population Register was used to identify men and women actually living in Denmark on 1 January 1981. We restricted the analysis to economically active people (20–59 years of age at the beginning of the study), because only 68% of the men and 33% of the women between 60 and 64 years of age were gainfully employed.

Occupations were coded by means of the Employment Classification Module at Denmark's Central Bureau of Statistics. Using various administrative registers, this module annually classifies all men and women in Denmark aged 16 years or more according to occupation. The module holds information on economic activity, occupational classification, and industrial sector. The occupational code is an extended classification of the International Standard Classification of Occupations, 1968 version, and it includes the self-employed. The industrial code is a national extension of the International Standard Classification of all Economic Activity, 1968 version. Altogether 90 430 men and 38 505 women in farming, horticulture, and related occupational groups were expected to be occupationally exposed to pesticides.

The National Inpatient Register holds data on all admissions to Danish hospitals and is updated each year. First-time hospitalizations with Parkinson's disease (International Classification of Diseases, 8th revision = 342) in Danish hospitals were included in this study, while readmissions in the follow-up period were excluded. We had no data to exclude prevalent cases at the beginning of the study.

Standardized hospitalization ratios (SHR) were calculated by dividing the observed number of hospitalizations in a given subcohort as defined by the occupational and industrial sector code by an expected number and multiplying the ratio by 100. The expected number was based on incidence ratios for men or women economically active on 1 January 1981 and on the age distribution of the cohort. People were no longer eligible from the date of death, and their data were censored in the

same way as when standardized mortality ratios are calculated. In the SHR calculations account was also taken of date of first emigration and date of first admission due to Parkinson's disease. From the date of such an event, these men and women were excluded from the denominator in the risk calculations. The period of risk was calculated for each person. Ninety-five percent confidence intervals (95% CI) (2-tailed) were calculated on the assumption of a Poisson distribution.

Results

We found a high risk of Parkinson's disease for the men and women in agriculture and horticulture. The results are shown in table 1.

In the 13-year follow-up period, 611 men and 338 women were admitted to the hospital due to Parkinson's disease. A statistically significant higher risk of hospitalization for Parkinson's disease was found for male self-employed farmers (79 cases, SHR 130, 95% CI 103–163). This finding was supported by the finding of a non-significant higher-than-normal risk in all other groups known to handle pesticides (ie, self-employed men in an agricultural machine pool and tractor stations (2 cases, SHR 254, 95% CI 31–918), self-employed men in horticulture and fruit growing (4 cases, SHR 160, 95% CI 44–410), self-employed male landscape gardeners (2 cases, SHR 448, 95% CI 54–1617). A similar pattern was found for female self-employed farmers (3 cases, SHR 149, 95% CI 31–435) and wives assisting farmers (24 cases, SHR 120, 95% CI 77–179). The number of cases among the 90 430 men and 38 505 women who may have been occupationally exposed to pesticides because they worked with agriculture and horticulture summed up to 105 men and 27 women, the SHR being 134 (95% CI 109–162) and 118 (95% CI 78–172), respectively.

In table 2 the remaining occupational groups with a statistically significant high or low risk for Parkinson's disease are shown. The majority of the cases were found among people who were already early-age pensioners at the beginning of the study. Many of these admissions may have been due to prevalent Parkinson's disease. The remaining high risks were based on small numbers.

Most of the outcomes may have been due to chance, but exposure to pesticides, or other neurotoxic substances, cannot be ruled out for these few cases. Some of the dealers in the group of paint dealers and pharmacists dealt in pesticides (SMR 752, 95% CI 244–1754). It is also noteworthy that self-employed women in laundry and dry-cleaning shops may have an increased risk (SMR 1555, 95% CI 321–4544), because solvents have been suspected to cause Parkinson's disease (9). Carpenters and joiners and female cleaners were recently found to have an increased risk in southeastern Sweden (6). We found that 3 carpenters-joiners were admitted with

Table 1. Age-standardized hospitalization ratio (SHR) for Parkinson's disease (International Classification of Diseases, 8th revision = 342) among agriculturally and horticulturally employed Danes, 1981–1993. (95% CI = 95% confidence interval)

Occupation ^a	Total population (N)	Cases (N)	Expected (N)	SHR	95% CI
<i>Men</i>					
Farmer (11001)	63 990	79	60.5	130	103–163
Self-employed, agricultural machinery station (11002)	1 414	2	0.8	254	31–918
Self-employed, agriculture, not elsewhere classified (11009)	452	-	0.4	0	0–946
Self-employed in horticulture, fruit growing (11200)	2 810	4	2.5	160	44–410
Self-employed landscape gardener (11210)	553	2	0.5	448	54–1617
Other agricultural occupations (11240)	471	1	0.2	422	11–2352
Skilled worker, agriculture and horticulture (43610)	3 507	4	2.9	136	37–348
Unskilled worker, agriculture and horticulture (46610)	17 233	13	10.7	121	65–207
All men in agriculture and horticulture	90 430	105	78.6	134	109–162
<i>Women</i>					
Self-employed, agriculture (11000)	3 155	3	2.0	149	31–435
Assisting wife, agriculture, horticulture, forestry (21000)	32 575	24	20.0	120	77–179
Skilled worker, agriculture and horticulture (45610)	450	-	0.0	0	0–922
Unskilled worker, agriculture and horticulture (46610)	2 325	-	0.9	0	0–434
All women in agriculture and horticulture	38 505	27	22.9	118	78–172
All men and women in agriculture and horticulture	128 935	134	101.5	132	111–156

^a Code of the Danish Employment Classification Module in parentheses.

Table 2. Age-standardized hospitalization ratio (SHR) for Parkinson's disease (International Classification of Diseases, 8th revision = 342) among other statistically significant occupations, 1981–1993.

Occupation ^a	Total population (N)	Cases (N)	Expected (N)	SHR	95% CI
<i>Men</i>					
Paint and wallpaper dealer, pharmacist (13110)	842	5	0.7	752	244–1754
Psychologist, welfare staff with local authority (42070)	2 520	5	1.1	440	143–1027
Lawyer (42120)	1 858	3	0.6	503	104–1469
Railway and transport staff (43970)	1 383	5	1.6	316	103–739
Bus driver (44972)	696	3	0.4	677	140–1979
Construction worker, with private contractors (46952)	13 334	1	6.7	15	0–84
Pensioner (54000)	41 286	112	39.1	286	238–344
<i>Women</i>					
Self-employed, laundry and dry-cleaning (13530)	299	3	0.2	1555	321–4544
Cleaner, sector unspecified (46991)	2 389	4	1.1	381	104–974
Pensioner (54000)	61 889	183	56.3	325	281–376
People, not economically active (55000)	210 258	154	124.5	124	106–145

^a Code of the Danish Employment Classification Module in parentheses.

Parkinson's disease. The expected number was 2.5 and the SHR 119 (95% CI 24–346). For female cleaners we found a standardized mortality ratio of 381 (95% CI 104–974) based on 4 cases.

Discussion

We found an increased risk of Parkinson's disease among male self-employed farmers and a consistent but nonsignificant pattern of high risks among other occupational groups known to be potentially exposed to pesticides, either because they apply pesticides themselves or they live in agricultural areas, where windborne pesticide exposure may occur or the drinking water may have a higher risk of being contaminated by pesticides.

The consistent pattern of high risk found in this study was unlikely to occur by chance, even if the results of each occupational group by itself had not been statistically significant. Other studies have shown that Parkinson's disease may be associated with farming and exposure to pesticides. Among these studies is a recent Swedish investigation which also reported, for the first time, an increased risk of Parkinson's disease among female cleaners (6). Our data offer some support for this result. The same study also reported a high risk for carpenters and joiners. Our results do not contradict this finding.

These studies were all case-referent in nature, and therefore recall bias was difficult to avoid. Recall bias will usually cause overestimations. However, Parkinson's disease patients may be unable to remember their

exposures and, if so, the risk may be underestimated. We therefore conducted the present study as a historical prospective cohort study. The drawback of the historical prospective cohort design is that no individual information about exposure is available, apart from the occupation and industry, which serves as a proxy measure for the exposure. Possible confounding exposures may include other neurotoxic substances in food, drugs, and air pollution, as well as other occupational exposures. It is a shortcoming of our design that we were unable to control adequately for these possible confounders. A possible secondary healthy worker effect may have been well controlled by our long follow-up time, while a primary healthy worker effect was more difficult to avoid. However, the clinical manifestation of Parkinson's disease usually occurs rather late in life, after people have chosen their occupation, and its occurrence was therefore unlikely to have influenced occupation, especially among the farmers.

The classification of occupations and industry was also rather crude. This crudeness may have diluted the results. We have no data on the length of exposure, except that we used the occupation with the highest income during 1 year, which may give a better proxy of the exposure than the occupation on a particular census day. The large number of people involved and the long follow-up time were necessary because the disease is rare, especially in the rather young age groups we considered. The high number of cases found among early-age pensioners may have been due to prevalent Parkinson's disease at the beginning of the study. This shortcoming has not biased the estimates because only economically active persons were included in the standard population. Future studies should, however, exclude prevalent cases and use even longer follow-up periods or introduce a latency time in the calculations.

The current study is the first cohort investigation showing that work in agriculture and horticulture may be associated with a high risk of Parkinson's disease. This risk is demonstrated in defiance of the general belief that the handling of pesticides in Denmark is, and has been, safe due to regulations and the training of workers. Recall bias was not a problem for our study design. Therefore, the results of this study support the hypothesis that

pesticide exposure may be an important risk factor for Parkinson's disease.

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