Published in final edited form as:
Occup Environ Med. 2011 April ; 68(4): 273–278. doi:10.1136/oem.2010.057448.

Outdoor work and risk for Parkinson's disease: a population-based case–control study

Line Kenborg[1], **Christina F Lassen**[1], **Beate Ritz**[2], **Eva S Schernhammer**[3,4], **Johnni Hansen**[1], **Nicole M Gatto**[5], and **Jørgen H Olsen**[1]

[1]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

[2]Department of Epidemiology and Environmental Sciences, School of Public Health, University of California, Los Angeles, California, USA

[3]Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA

[5]Department of Epidemiology, School of Public Health, University of California, Los Angeles, California, USA

Abstract

Objectives—Sunlight is the main contributor to vitamin D in humans. Since inadequate levels of vitamin D have been linked to increased risks for neurodegenerative diseases, we examined whether outdoor work is associated with a reduced risk for Parkinson's disease in a population-based case–control study of Danish men.

Methods—We identified 3819 men with a primary diagnosis of Parkinson's disease in the period 1995–2006 in the Danish National Hospital Register and selected 19 282 age- and sex-matched population controls at random from the Central Population Register. Information on work history was ascertained from the Danish Supplementary Pension Fund and the Central Population Register. Based on trade grouping codes and job titles, we evaluated the extent of outdoor work of study subjects as a proxy of exposure to sunlight.

Results—Relying on trade grouping codes, we estimated ORs for study subjects with moderate, frequent and maximal outdoor work compared with exclusive indoor work of 0.90 (95% CI 0.78 to 1.02), 0.86 (95% CI 0.75 to 0.99) and 0.72 (95% CI 0.63 to 0.82), respectively, for Parkinson's disease. Reduced risks were also found for Parkinson's disease among outdoor workers based on study subjects' job titles.

Conclusions—Our findings suggest that men working outdoors have a lower risk for Parkinson's disease. Further studies of measured vitamin D levels in outdoor workers are warranted to clarify a potential inverse association between vitamin D and the risk for Parkinson's disease.

Correspondence to Line Kenborg, Institute of Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, 2100, Copenhagen, Denmark; kenborg@cancer.dk.

Competing interests None.

Ethics approval The study protocol was approved by the Danish Data Protection Agency (no. 2002–41–2112) and the University of California at Los Angeles institutional review board for human subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

INTRODUCTION

Parkinson's disease is the most common neurodegenerative disease after Alzheimer's disease.[1] It is characterised by degeneration of the dopaminergic neurons in the substantia nigra, resulting in clinical symptoms such as resting tremor, rigidity and bradykinesia.[2] It has been suggested that Parkinson's disease is the result of a complex interplay of genetic susceptibility, ageing and environmental factors[3]; however, the nature of the environmental factors remains largely unclear.

An inadequate level of vitamin D has been linked, in some studies, to excess mortality[4] and more frequent occurrence of a variety of diseases, including neurodegenerative diseases.[5] Since the activity of normal brain cells, including neurons in substantia nigra, partly depends on absorption on vitamin D, Newmark and Newmark recently proposed that chronic inadequacy of vitamin D results in chronic, continuous loss of dopaminergic neurons in the substantia nigra, leading to Parkinson's disease.[6]

Sunlight is the most important source of vitamin D in humans.[7] Therefore, outdoor workers with year-round exposure to the sun might be expected to have a lower risk for Parkinson's disease. Up to now, no study has examined outdoor workers' risk for Parkinson's disease. We conducted a population-based case–control study to examine whether men working outdoors have a lower risk for Parkinson's disease than men working exclusively indoors.

MATERIALS AND METHODS

Study populations

All 4368 male inhabitants of Denmark with a primary diagnosis of Parkinson's disease (ICD-8 code 342 and ICD-10 code G-20) at the age of 35 years or above were identified in the Danish National Hospital Register between 1995 and 2006. This register contains information on hospital admissions for somatic diseases in Denmark since 1977; information on outpatient visits and emergency consultations has been included since 1995. The register includes the personal identification numbers of patients, dates of admission and discharge, a code for the primary diagnosis made at discharge from hospital, and codes for up to 19 supplementary diagnoses.[8] The diagnoses were coded according to a Danish version of the International Classification of Diseases, 8th revision (ICD-8) until the end of 1993 and according to the 10th revision thereafter (ICD-10). The personal identification number, which is unique to every Danish citizen, incorporates sex and date of birth and permits accurate linkage among registers. The date of first recorded hospital contact under any diagnosis of Parkinson's disease was considered to be the index date. However, only patients with a primary diagnosis of Parkinson's disease were included since this diagnosis is considered to be more reliable than a supplementary diagnosis. In a previous Danish study of 13 695 patients with Parkinson's disease (also including the patients from this study), 65% of the patients with a primary Parkinson's disease diagnosis were diagnosed at a neurological department, whereas the corresponding proportion of patients with a supplementary diagnosis of Parkinson's disease was 7%.[9]

For each male patient, five controls were randomly selected from the Danish Central Population Register from among all Danish men born in the same year and without Parkinson's disease at the date of the case's first hospital contact for Parkinson's disease (index date); controls were assigned the same index date as their respective case. Although we aimed to recruit five controls per case, 13 patients were matched with only three or four controls each, for a total of 21 826 controls.

A full hospital history was obtained for all patients and population controls since 1977. We excluded all patients and their corresponding controls if they were older than 85 years on the date of diagnosis of Parkinson's disease (259 cases and 1310 controls). Furthermore, we excluded patients and controls in whom cerebrovascular disease (ICD-8 430–438; ICD-10 I60–I69, G45 and G46; 268 cases and 1182 controls) or dementia (ICD-8 290.09–290.19 and 293.09; ICD-10 F00–F03, F05.1 and G30; 22 cases and 52 controls) had been diagnosed between 1977 and up to 3 years before the index date. This was done to avoid including misclassified cases of Parkinson's disease in our patient group. After these exclusions, 3819 patients and 19 282 population controls remained for analysis.

Outdoor work

The study was restricted to the male component of the Danish population because work histories for women born before World War II were generally too crude to be used for a job-exposure matrix (JEM).

We obtained information on history of employment from the Supplementary Pension Fund and the Central Population Register by using the personal identification numbers of patients and population controls. The pension scheme has been a compulsory supplement to the state pension in Denmark since 1 April 1964 for wage earners 18–66 years of age and since September 1978 for those aged 16–66 years. The pension supplement is financed by the wage earners themselves and by their employers (companies). Both contributions are paid quarterly to a national central fund, which retains all information on employers, pensioners and deceased individuals.[10]

For each study subject in the labour market, we established a full employment history from 1964 to the index date, with the identity of the companies and associated dates of start and end of employment. A trade grouping code for each company was allocated by use of an extended version of the International Standard Industrial Classification of All Economic Activities of 1968.[11] We supplemented the employment information and the trade grouping codes with updated job titles as reported by subjects to the Danish authorities and stored in the files of the Central Population Register.

We developed a JEM to assess occupational exposure to sunlight based on outdoor work. Independently, two of us (CFL and LK) estimated the amount of compulsory time spent outdoors during work using trade grouping codes and job titles while being blinded to case status. We created four categories: exclusive indoor work, moderate outdoor work (<50% outdoor work), frequent outdoor work (50–75% outdoor work) and maximal outdoor work (>75% outdoor work). Disagreements in the categorisation were discussed and consensus was obtained. In order to ensure that the reference category mainly included individuals likely to have never worked outdoors, study subjects were categorised according to the trade grouping code and job title that indicated their highest exposure to sunlight throughout their working life. Thus, if a man had ever worked full-time in an outdoor trade or held a job title indicating all-day exposure to sunlight, he was assigned to maximal outdoor work regardless of other jobs he had ever held. The numbers and types of trades and job titles included in the four exposure categories are summarised in table 1.

Statistical analysis

We used unconditional logistic regression to compare the work histories of Parkinson's disease patients with those of the matched controls. The associations between outdoor work and Parkinson's disease were expressed as ORs and 95% CIs. We adjusted for chronic obstructive pulmonary disease (COPD; ICD-8 490–492; ICD-10 J40–J44) diagnosed 5 years or more before the index date to indirectly control for smoking, place of birth (large city,

provincial town, rest of the country, born abroad), comorbidity (Charlson comorbidity index) and social class in multivariate logistic regression models. The comorbidity index (0, 1, ≥2) was established on the basis of cumulated diagnostic information from the National Hospital Register on the study subjects up to 5 years before the index date.[12] Social class was based on the available job title from criteria developed by the Danish National Centre for Social Research, as follows: academics or executive managers, middle managers or 3–4 years of further education, other white-collar workers, skilled blue-collar workers, unskilled workers and unknown or unclassified.[13] First, risk analyses were based on trade grouping codes and job titles as indicators of sun exposure, followed by analyses that combined the two exposure indicators. In the latter analysis, we started with the categorisation according to the trade grouping code; however, if a subject's job title indicated a higher level of outdoor work, the exposure category was adjusted upwards. Study subjects with less than 1-year payment into the Supplementary Pension Fund were excluded from all analyses using trade grouping codes. We also conducted a sub-analysis based on trade grouping codes after exclusion of study subjects with less than 10 years of documented employment. Physical activity has been linked with a lower risk for Parkinson's disease.[14, 15] Since a positive correlation may exist between occupational physical activity and outdoor work, physical activity is a potential confounder when estimating the effect of outdoor work on Parkinson's disease. Thus, we also used job titles to categorise study subjects according to their likely level of physical activity during work (none or very low, low, moderate, high) and carried out additional analyses adjusting for level of physical activity. We included a lag time of 10 years between exposure and date of diagnosis in all analyses based on information from the Supplementary Pension Fund. This was done because symptoms of Parkinson's disease might start months to years before the patients actually establish a hospital contact for Parkinson's disease. Calculations were performed with SAS v 9.1.

Study of lip and lung cancer

To assess the validity of our JEM, we applied the JEM for outdoor work to data from a corresponding study of lip cancer, carried out by Kenborg *et al.*[16] Solar ultraviolet radiation has long been considered to cause lip cancer, and several studies have shown a positive association between outdoor occupations and lip cancer.[17-19] Thus, if our JEM for outdoor work functioned properly, we expected to observe a rising gradient of lip cancer with increasing outdoor work. We identified 2342 male patients with lip cancer diagnosed in 1970–2003 from the Danish Cancer Registry, and 9361 age- and sex-matched population controls from the Central Population Register. All study subjects were linked to the Supplementary Pension Fund and the Central Population Register and assessed for sunlight exposures according to the same occupational information used in the present Parkinson's disease study.

We applied the same JEM assessing outdoor work in another, similarly designed case–control study of lung cancer (unpublished data). Smoking is an undisputed major risk factor for lung cancer.[20] Thus, if smoking habits differed between indoor and outdoor workers this should be mirrored by increasing risk levels of lung cancer for level of outdoor work compared with indoor work as defined by the JEM. From the 1970–2003 files of the Danish Cancer Registry, we identified 50 739 male patients with lung cancer (ICD-7 162; ICD-10 C33–C34 and C39), together with 50 739 age- and sex-matched controls from the Central Population Register. We estimated the risk of lung cancer in each of the JEM-defined study groups and compared the risk of lung cancer among study subjects with moderate, frequent and maximal outdoor work with that of study subjects with exclusive indoor work.

RESULTS

The average age of the 3819 men at first hospital contact for Parkinson's disease and their 19 282 age-matched controls was 71.2 years (range, 35–85 years) (table 2). Other characteristics of the patients and controls included in the study are described in table 2.

Based on trade grouping codes as indicator of exposure to sunlight, the adjusted ORs for a first hospital contact for a primary diagnosis of Parkinson's disease were 0.90 (95% CI 0.78 to 1.02), 0.86 (95% CI 0.75 to 0.99) and 0.72 (95% CI 0.63 to 0.82) for study subjects with moderate, frequent and maximal outdoor work, respectively, compared with exclusive indoor work (table 3).

Using the job titles as indicator, we also observed decreased risks for Parkinson's disease among study subjects with outdoor work. When we combined the two indicators, we found a negative trend with increasing extent of outdoor work with ORs of 0.89 (95% CI 0.76 to 1.05), 0.78 (95% CI 0.65 to 0.92) and 0.75 (95% CI 0.64 to 0.88) for moderate, frequent and maximal outdoor work, respectively. In the sub-analysis including only study subjects with at least 10 years of documented work history in the Supplementary Pension Fund, the estimates for Parkinson's disease were essentially unchanged (data not shown). Further adjustment for physical activity did not change the pattern of significantly decreased risk estimates for study subjects with frequent or maximal outdoor work (data not shown). When we applied the JEM to our case–control study of lip cancer, we observed a steeply increasing risk with increasing extent of outdoor work (table 4). In our case–control study of lung cancer, we were unable to detect an increased risk of lung cancer among study subjects with maximal outdoor work compared with study subjects with exclusive indoor work. An increased risk was otherwise expected if maximal outdoor work was associated with higher smoking rates. The risk of lung cancer among study subjects with moderate and frequent outdoor work was weakly increased by 23–24% (table 4).

DISCUSSION

In this register-based case–control study of 3819 men with a first diagnosis of Parkinson's disease and 19 282 population controls, we found that maximal outdoor work was associated with an up to 28% decrease in the risk for Parkinson's disease. When we used trade grouping codes and job titles as indicators of occupational exposure to sunlight, we observed an inverse association between outdoor work and risk for Parkinson's disease. These findings are in accordance with the hypothesis that outdoor workers have a lower risk for Parkinson's disease, possibly due to an overall higher exposure to sunlight and a decreased risk of vitamin D insufficiency.

The association between exposure to sunlight and Parkinson's disease has not been studied previously, although data from death certificates and descriptive studies in Canada and the USA have shown a northwest to southeast gradient in mortality from Parkinson's disease.[21-24] The results of these studies led to speculations whether increased exposure to sunlight in the southeast regions of North America may reduce risk for Parkinson's disease.[6] Few studies have examined vitamin D levels in outdoor workers.[25-27] In a study conducted in Dundee, Scotland (56° N), located at the same latitude as Denmark (55–57° N), Devgun *et al*[27] measured seasonal variations in serum vitamin D levels in outdoor workers, indoor workers and long-term hospital inpatients. They found that outdoor workers had significantly higher levels of 25-hydroxyvitamin D in all seasons. Sunshine provides approximately 90% of vitamin D requirements,[28] and the result of the Scottish study indicates that outdoor workers benefit from high exposure to sunlight during work.

Vitamin D insufficiency and deficiency appear to be more prevalent in patients with Parkinson's disease than in the general population.[29, 30] Sato *et al* found that 51 Japanese patients with advanced Parkinson's disease (Hoehn and Yahr stages 3–5) had a mean 25-hydroxyvitamin D level of 8.9 ng/ml, whereas the level in age-matched volunteers was 21.6 ng/ml.[29] A similar pattern was reported in yet another study in Japan by Sato *et al*, of 115 patients with Parkinson's disease aged 65 years or older and 68 healthy age-matched controls.[30] In a recent cross-sectional study in the USA, Evatt *et al* found that vitamin D insufficiency (defined as ≤30 ng/ml 25-hydroxyvitamin D) was significantly more frequent in patients with Parkinson's disease (55%) than in age-matched healthy controls (36%) or patients with Alzheimer's disease (41%).[31] However, it is unclear whether the low levels of vitamin D may be a part of the causal pathway leading to Parkinson's disease or a consequence of the disease. An alternative explanation for the reduced risk of Parkinson's disease among outdoor workers is that ultraviolet radiation seems to suppress the immune system through mechanisms independent of vitamin D.[32] This is in line with the hypothesis that neuroinflammation caused by, for example, infectious agents or toxicants, might be an important factor in the pathogenesis of Parkinson's disease.[33]

The strengths of our study are the large number of patients identified in a nationwide hospital register and the unbiased selection of controls through linkage to a population registry. Furthermore, information on employment and job titles was drawn from the nationwide Supplementary Pension Fund and the Central Population Register, independently of the person's status as a case or a control, so that observational or recall bias is unlikely. To minimise the inclusion of patients with secondary Parkinsonism, we excluded those in whom dementia and cerebrovascular disease had been diagnosed 3 years or more before the hospital contact for Parkinson's disease. Furthermore, we included only patients with a primary diagnosis of Parkinson's disease, as this was considered to be more reliable than a supplementary diagnosis.

Our study has also some limitations. We used the date of first hospital contact for Parkinson's disease as the date of diagnosis, since we had no information for most cases on the date of first symptoms of the disease or of first treatment with anti-parkinsonian drugs, which may occur years before the date of first hospitalisation. In a previous study of patients with a primary diagnosis of Parkinson's disease in the National Hospital Register, 91% of the patients had received anti-Parkinson drugs. The treatment with anti-Parkinson drugs was often started months to years before the patients were hospitalised with a primary diagnosis of Parkinson's disease.[34] We included a 10-year lag-time in the analysis to ensure that the occupational exposure occurred years before the diagnosis of Parkinson's disease. Ascertainment of information on exposure from registers may introduce some degree of non-differential misclassification of exposure. In the corresponding study of lip cancer, however, we found, as expected, a clearly increasing trend in the risk for lip cancer with increasing outdoor work, indicating that our JEM worked properly, that is reflected the amount of exposure to sunlight during work.

Although we adjusted for several potential confounders, we cannot exclude the possibility of residual confounding by unmeasured factors associated with Parkinson's disease or with outdoor work. As there appears to be a strong inverse association between cigarette smoking and Parkinson's disease,[35] we tried to circumvent the missing information on smoking by adjusting for COPD. Also, to indirectly assess any differences in smoking habits among outdoor and indoor workers, we applied our JEM to a supplementary case–control study of lung cancer. Risk levels for lung cancer were almost identical in the categories of maximal outdoor work and exclusive indoor work, indicating little variation in smoking habits in the two extreme exposure groups. Slightly increased risks were seen for study subjects with moderate and frequent outdoor work compared with exclusive indoor work. Adjusting for

COPD in our main analysis of outdoor work and risk of Parkinson's disease likely eliminated most of the seemingly limited confounding effect of smoking habits among study subjects. In addition, we had no have information on exposure to sunlight in leisure time. In contrast to outdoor workers, indoor workers seem to be more exposed to sunlight on days off work,[36] which may impose an unknown degree of misclassification of the exposure variable. However, such a misclassification is likely to be non-differential, indicating that the direction of any bias would be towards underestimation of a true deviating risk.

Overall, the findings of the study suggest the existence of a reverse association between outdoor work and Parkinson's disease, even after adjustment for COPD and physical activity.

Acknowledgments

We thank Andrea Meersohn, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark, for help with data management and Thomas L Jørgensen, Institute of Cancer Epidemiology, Danish Cancer Society, for help with the statistical analyses.

Funding This study was supported by a grant from the National Institutes of Health, USA (grant no. R01 ES013717). The funding source had no role in the design and conduct of the study or in the collection, management, analysis, and interpretation of the data or with preparation, review, or approval of the manuscript.

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What this paper adds

- It has been hypothesised that chronic inadequacy of vitamin D results in chronic, continuous loss of dopaminergic neurons in the substantia nigra leading to Parkinson's disease.
- Sunlight is the main contributor to maintain adequate vitamin D levels in humans.
- The findings of our population-based case–control study suggest that men working outdoors have a lower risk for Parkinson's disease compared with indoor workers.
- This reduced risk might be due to increased exposure to sunlight among outdoor workers.

Table 1

Numbers and types of trades and job titles included in each exposure category according to estimated degree of outdoor work

Exposure category	No. of trades	Types of trade
Indoor work	270	All types of manufacture, factories and wholesale; administration, healthcare and teaching
Moderate outdoor work	31	Electrical contracting, moving business, iron shipyards, day nurseries and kindergartens, stone cutting, rescue squads, agricultural consultants, sewer departments and ferry operations
Frequent outdoor work	12	Public building and planning, general contracting, sewer experts, bricklaying firms, harbours, botanical and zoological gardens, landscapers, and extraction of oil and natural gas, clay and gravel pits
Maximal outdoor work	12	Roofers, paving experts, scaffolding, agriculture, animal husbandry, horticulture, forestry, ocean and coastal fishery, fresh-water and pond fisheries, chimneysweeps, truck gardens, orchards and nurseries
Unclassified	17	Defence and civil defence, air force, navy, postal services, daily papers, railroads, airports, personal services, other services connected with transport, repairs and other services, and other business
Exposure category	**No. of job titles**	**Types of job**
Indoor work	217	Working in manufacture, factories, healthcare, administration and teaching
Moderate outdoor work	35	Nursery or kindergarten teachers, station personnel, filling-station attendants, estate agents, firemen, policemen, miners and electricians
Frequent outdoor work	18	Postmen, window cleaners, millers, shipbuilders, building painters, joiners, seamen and bricklayers
Maximal outdoor work	32	Farmers, chimneysweeps, frogmen, smallholders, farmhands, farm workers, gardeners, foresters, well diggers and pavers
Unclassified	28	Workers, householders, pensioners, unemployed, students, self-employed and conscripts

Table 2

Characteristics of 3819 patients with Parkinson's disease and their 19 282 population controls

Characteristics	Patients No. (%)	Controls No. (%)
Age at diagnosis (years)		
<50	120 (3.1)	594 (3.1)
50–59	387 (10.1)	1964 (10.2)
60–69	878 (23.0)	4455 (23.1)
70–79	1637 (42.9)	8275 (42.9)
>80	797 (20.9)	3994 (20.7)
Year of birth		
<1920	1011 (26.5)	5070 (26.3)
1920–1929	1466 (38.4)	7447 (38.6)
1930–1939	850 (22.3)	4308 (22.3)
>1940	492 (12.9)	2457 (12.7)
COPD (5-year lag interval)	74 (1.9)	484 (2.5)
Charlson comorbidity index (5-year lag interval)		
0	3119 (81.7)	15617 (81.0)
1	412 (10.8)	2210 (11.5)
≥2	288 (7.5)	1455 (7.6)
Place of birth		
Large city	1071 (28.0)	4762 (24.7)
Provincial town	956 (25.0)	5283 (27.4)
Rest of country	1624 (42.5)	8481 (44.0)
Born abroad	168 (4.4)	756 (3.9)
Social class		
Academic or executive manager	464 (12.2)	1899 (9.9)
Middle manager or 3–4 years of further education	357 (9.4)	1594 (8.3)
Other white-collar worker	651 (17.1)	3408 (17.7)
Skilled blue-collar worker	1075 (28.2)	5559 (28.8)
Unskilled worker	840 (22.0)	4661 (24.2)
Unknown or unclassified	432 (11.3)	2161 (11.2)

COPD, chronic obstructive pulmonary disease.

Table 3

Unadjusted and adjusted ORs for Parkinson's disease by estimated proportion of working hours spent outdoors

	No. of cases	No. of controls	$OR_{unadjusted}$	$OR_{adjusted}$* (95% CI)
Trade grouping codes				
Indoor work	1295	6102	1	1
Moderate outdoor work	329	1735	0.89	0.90 (0.78 to 1.02)
Frequent outdoor work	314	1741	0.85	0.86 (0.75 to 0.99)
Maximal outdoor work	332	2246	0.70	0.72 (0.63 to 0.82)
p For linear trend				<0.001
Unclassified, unknown or <1 year of registration in the Supplementary Pension Fund	1549	7458	0.98	0.99 (0.92 to 1.08)
Job titles				
Indoor work	2093	9879	1	1
Moderate outdoor work	223	1116	0.94	0.96 (0.82 to 1.11)
Frequent outdoor work	169	981	0.81	0.83 (0.70 to 0.99)
Maximal outdoor work	490	2804	0.83	0.85 (0.76 to 0.95)
p For linear trend				<0.001
Unclassified, unknown or <1 year of registration in the Supplementary Pension Fund	844	4502	0.91	0.97 (0.86 to 1.09)
Trade grouping codes and job titles combined				
Indoor work	1708	8303	1	1
Moderate outdoor work	192	1067	0.88	0.89 (0.76 to 1.05)
Frequent outdoor work	171	1107	0.75	0.78 (0.65 to 0.92)
Maximal outdoor work	199	1347	0.72	0.75 (0.64 to 0.88)
p For linear trend				<0.001
Unclassified, unknown or <1 year of registration in the Supplementary Pension Fund	1549	7458	1.01	1.03 (0.95 to 1.11)

*Adjusted for year of birth, chronic obstructive pulmonary disease, comorbidity, place of birth and social class.

Table 4

Unadjusted and adjusted ORs for lip and lung cancer by estimated proportion of working hours spent outdoors

	Lip cancer				Lung cancer			
	No. of cases	**No. of controls**	**$OR_{unadjusted}$**	**$OR_{adjusted}$* (95% CI)**	**No. of cases**	**No. of controls**	**$OR_{unadjusted}$**	**$OR_{adjusted}$* (95% CI)**
Trade grouping codes and job titles combined								
Indoor work	980	4833	1	1	26403	25110	1	1
Moderate outdoor work	169	608	1.37	1.36 (1.13 to 1.64)	3240	3755	1.22	1.24 (1.18 to 1.31)
Frequent outdoor work	282	623	2.23	2.12 (1.81 to 2.49)	3673	4127	1.18	1.23 (1.17 to 1.29)
Maximal outdoor work	387	844	2.27	2.10 (1.82 to 2.42)	4574	4282	0.99	1.04 (0.99 to 1.09)
p For linear trend				<0.001				0.042
Unclassified, unknown or <1 year of registration in the Supplementary Pension Fund	523	2453	1.04	1.03 (0.92 to 1.16)	12849	13465	1.10	1.11 (1.08 to 1.15)

*Adjusted for place of birth and social class.