Occupation and Motor Neurone Disease: A New Zealand Case-Control Study

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ABSTRACT

Objectives To assess associations between occupation and motor neuron disease (MND).

Methods We conducted a population-based case-control study with cases (n=321) recruited through the New Zealand Motor Neurone Disease Association and hospital discharge data. Controls (n=605) were recruited from the Electoral Roll. Information on personal and demographic details, lifestyle factors and a full occupational history was collected using questionnaires and interviews. Associations with ever/never employed and employment duration were estimated using logistic regression stratified by sex and adjusted for age, ethnicity, socioeconomic status, education and smoking.

Results Elevated risks were observed for field crop and vegetable growers (OR 2.93, 95%CI 1.10-7.77); fruit growers (OR 2.03, 95%CI 1.09-3.78); gardeners and nursery growers (OR 1.96, 95%CI 1.01-3.82); crop and livestock producers (OR 3.61, 95%CI 1.44-9.02); fishery workers, hunters and trappers (OR 5.62, 95%CI 1.27-24.97); builders (OR 2.90, 95%CI 1.41-5.96); electricians (OR 3.61, 95%CI 1.34-9.74); caregivers (OR 2.65, 95%CI 1.04-6.79), forecourt attendants (OR 8.31, 95%CI 1.79-38.54); plant and machine operators and assemblers (OR 1.42, 95%CI 1.01-2.01); telecommunications technicians (OR4.2, 95%CI 1.20-14.64) and draughting technicians (OR 3.02, 95%CI 1.07-8.53). Industries with increased risks were agriculture (particularly horticulture and fruit growing), construction, non-residential care services, motor vehicle retailing, and sport and recreation. Positive associations between employment duration and MND were shown for the occupations, fruit growers, gardeners and nursery growers, and crop and livestock producers, and for the horticulture and fruit growing industry. **Conclusions** This study suggests possible associations between MND and occupations in agriculture.

Key Messages

What is already known about this subject?

A number of possible occupational/environmental exposures have been suspected of contributing to the risk of developing MND.

What are the new findings?

- We observed positive associations between the risk of MND and a range of occupations within agriculture in both men and women.
- Positive duration-response associations were also seen in horticultural occupations.
- Positive associations were also found for building trades workers, forecourt attendants, electricians, telecommunication technicians and forecourt attends.

How might this impact on policy or clinical practice in the foreseeable future?

- These results have confirmed previous findings and generated a range of hypotheses for specific occupational risk factors for MND.
- If specific causal exposures can be identified, they may provide important opportunities for the prevention of MND.

INTRODUCTION

Motor Neurone diseases (MND) are progressive and terminal neurodegenerative conditions affecting the motor neurone system, with death usually occurring within 2-5 years after the first symptoms of weakness.[1 2] Amyotrophic lateral sclerosis (ALS) accounts for 70% of cases;[1] other forms include progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and primary lateral sclerosis (PLS).[1]

There is some evidence of increasing incidence and mortality rates of MND among high-income countries including New Zealand in the last two decades,[2 3]with MND mortality in New Zealand (2.8/100,000) reportedly higher than the estimated mean global mortality (1.7/100,000)[4]. The reasons for the increased incidence remain unclear, but are likely due to environmental and lifestyle factors, since genetic factors vary little over time and familial MND is relatively uncommon (5-10%).[1 2]

Several studies have reported increased relative risks for certain occupations and occupational exposures,[5 6] suggesting a role for agrichemicals,[7 8] extremely low-frequency electromagnetic fields (ELF-EMFs),[9] electric shocks,[10] some heavy metals,[2] welding fumes,[11] and solvents,[12] although the evidence is equivocal.

We report the findings of the first New Zealand population-based case-control study on modifiable risk factors of MND, with a focus on occupational risk factors.

METHODS

Study population

A national Motor Neurone Disease Registry was not available at the time of study commencement (a national registry has since been established).[13] Incident and prevalent cases (n=295) were invited between 2013-2016 through the Motor Neurone Disease Association of New Zealand (MNDANZ). This was supplemented by records contained in the New Zealand National Minimum Dataset (NMDS), a national collection of public and private hospital discharge information including coded clinical data for inpatients and day patients.[14] Incident cases were defined based on a primary or secondary diagnosis of MND (ICD10 code G122) for the period 2013-2015, and surviving cases (n=103) in the NMDS but not registered with MNDANZ were invited. Two of these were misclassified and excluded, leaving 396 eligible cases. The inclusion criterion for cases was a diagnosis by a neurologist, with all forms of MND included.

Controls were randomly selected from the New Zealand Electoral Roll (2008) with two controls for each case, frequency matched by age (5-year categories, based on the age-distribution of the UK MND incidence distribution),[15] and sex. Controls with a neurodegenerative disease were excluded.

Of the 396 eligible cases, 390 responded to invitation letters. Of these 44 were not eligible (27 deceased and 17 in intensive care), 25 (6%) refused to participate, leaving 321 participants equating to a 92% response rate.

Of the 2,400 potential controls, 333 (14%) could not be contacted, 230 (10%) were returned to sender, and 587 (24%) were not eligible. Of the remaining 1,250 controls, 645 declined. Thus, 605 participated in the study, equating to a 48% response rate.

All study participants gave written informed consent and ethical approval was

granted by the New Zealand Multi-region Ethics Committee (ref: MEC/12/01/005).

Data collection

Identical data collection methods were used for cases and controls. These included a face-to-face (59% of cases and 16% of controls), or telephone interview by research nurses (23% of cases and 66% of controls) or a postal questionnaire (18% in cases and 18% in controls). Three cases used a proxy (family member) for the face-to-face interview and six used proxy assistance for reading and writing.

We used a European questionnaire[16] with modifications to adapt it to New Zealand (with particular emphasis on agriculture) to collect information on demographic and personal data, lifestyle factors and lifetime occupational history.

Classification of occupational histories

Participants listed all jobs ever held for 6 months or more, and for each job provided information on job title, employer's name, industry, the year and month in which the job began and ended, and a detailed description of tasks performed and work processes undertaken.

Each job was classified according to the New Zealand Standard Classification of Occupations (NZSCO99),[17] industries were coded according to the Australian and New Zealand Standard Industrial Classification (ANZSIC96).[18] The occupational coding was based on the full job description, rather than on job title alone. Response outside scope was used for responses, such as "housewife", "pensioner" or "student", which are not covered by NZSCO99. The industry code was based on information provided on the activity of the employer. All coding was done blind to case-control status.

Statistical analyses

Analyses were conducted using SAS v9.3. Differences in general characteristics between cases and controls were tested using Chi-squared tests. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), for ever compared to never employed/self-employed in a particular occupation or industry.

Analyses were stratified by sex because men and women have different occupational profiles. Therefore, the specific occupational risk factors contributing to MND may differ between men and women. Analyses were adjusted for age (5-year categories), ethnicity (European/Pakeha, Maori, Pacific & others), highest education level (primary school or secondary school, technical or trade school diploma, undergraduate university degree, postgraduate university degree), smoking (never, ex-smokers, current) and for socioeconomic deprivation status using the New Zealand Deprivation Index (NZDep2006).[19] NZDep is census-based with a relative deprivation score assigned to geographical meshblocks based on place of residence recorded on the Electoral Roll (with 1 representing the least and 10 representing the most deprived areas).

In order to establish the role of duration of employment, categorical variables were constructed for each job/industry using cut-points of <2, 2-10, and >10 years. These cut-points, which we have previously used in studies on occupational risk factors and cancer,[20-22] ensured that sufficient numbers of cases and controls were available in each category. These categorical variables were included in the logistic regression using never employed in the occupation/industry as the reference. A test for trend was performed by fitting it as a continuous variable in the model.

Lag-time analyses to take into account potential disease latency were conducted,

in which employment 5, 10, 15 and 20 years prior to the interview date was disregarded. Analyses were repeated while adjusting for the mode of interview.

To reduce the number of associations presented, tables only include results for broad occupation and industry categories (1-digit codes), irrespective of statistical significance, as well as results for specific occupations and industries (2-5 digits) if the association was statistically significant ($p<0.05$), and based on at least 10 subjects (cases plus controls). Results for all 2,755 occupations and 3,149 industries are available in supplementary tables.

RESULTS

Population characteristics

Population characteristics are described in Table 1. MND was more common in males (64%) than females (36%), and most cases occurred over 60 years of age. While the 70+ age group was overrepresented in the controls, there was little difference between cases and controls in terms of smoking, ethnicity, and education. However, there was a difference in socioeconomic deprivation status for males, with cases being less deprived compared to controls. There was no difference in the number of occupations held by cases and controls (mean=6.8 for cases and controls). The median and interquartile range (IQR) of age was 64 and 13 for cases and 68 and 15 for controls. There were 225 incident and 96 prevalent cases and the time between diagnosis and interview was 6-18 months (median=238 days, IQR=269 days).

Broad occupation and industry categories

Tables 2 and 3 present the findings for MND risk associated with occupations and industries overall and by duration of employment.

Ever-employment in the following broad occupation categories (1-digit, Table 2) showed an increased risk: Service and Sales Workers; Agriculture and Fishery Workers; Plant and Machine Operators and Assemblers; and Elementary Occupations. A reduced risk was observed for Clerks.

Increased risks for ever-employed in the broad industry categories (1-digit, Table 3) were observed for: Agriculture, Forestry and Fishing; Mining; and Construction.

193 Table 1. Characteristics of this study population

Characteristics	Male Cases (N=204)	%	Male Controls (N=332)	%	*p*-Value	Female Cases (N=117)	%	Female Controls (N=273)	%	*p*-Value
Age at interview					0.0002					0.0386
20-49	20	9.80	16	4.82		10	8.55	24	8.79	
50-59	48	23.53	52	15.67		26	22.22	48	17.58	
60-69	79	38.73	112	33.73		45	38.46	76	27.84	
≥70	57	27.94	152	45.78		36	30.77	125	45.79	
Smoking					0.6712					0.4196
Never	103	50.49	155	46.69		62	52.99	164	60.07	
Current	16	7.84	26	7.83		4	3.42	9	3.30	
Ex	85	41.67	151	45.48		51	43.59	100	36.63	
Ethnicity					0.8861					0.1102
European/Pakeha[1]	189	92.65	304	91.56		106	90.60	259	94.87	
Māori[2]	8	3.92	14	4.22		6	5.13	11	4.03	
Pacific & others	7	3.43	14	4.22		5	4.27	3	1.10	
Deprivation Index Quintile					0.0235					0.1386
1-2 (least deprived)	76	37.25	83	25.00		23	19.66	82	30.04	
3-4	51	25.00	83	25.00		28	23.93	60	21.98	
5-6	32	15.69	71	21.39		36	30.77	58	21.24	
7-8	27	13.24	64	19.28		16	13.68	44	16.12	
9-10 (most deprived)	18	8.82	31	9.33		14	11.96	29	10.62	
Highest Education					0.2947					0.2481
Primary school	1	0.49	7	2.11		0	0	6	2.20	
Secondary school (college)	91	44.61	154	46.39		53	45.30	123	45.05	
Technical or trade school diploma	70	34.31	94	28.31		35	29.92	61	22.34	
Undergraduate university degree	28	13.73	45	13.55		18	15.38	53	19.41	
Postgraduate university degree	14	6.86	32	9.64		11	9.40	30	11.00	

194 Chi-square tested the differences in age, ethnicity, education, smoking status and socioeconomic deprivation status by gender.
195 *p*-Values were calculated using chi-square test for categorical variables.
196 1. Pakeha (Maori word) - This is used as a term specifically for New Zealand European people.
197 2. Maori – aboriginal people of New Zealand.
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205 Table 2. Odds Ratios (OR) and 95% CIs for Occupation by Duration Categories

Occupation	Never/Ever Cases/Controls (n)	Never/Ever OR (95% CI)	Exposure <2 years Cases/Controls (n)	Exposure <2 years OR (95% CI)	Exposure between 2-10 years Cases/Controls (n)	Exposure between 2-10 years OR (95% CI)	Exposure >10 years Cases/Controls (n)	Exposure >10 years OR (95% CI)	Trend *p*-Value
1-Legislators, Administrators and Managers	84/169	0.83[0.60-1.14]	4/21	0.30[0.10-0.90]*	33/43	1.28[0.78-2.10]	42/98	0.71[0.47-1.07]	0.232
2-Professionals	109/254	0.75[0.54-1.05]	11/19	1.00[0.45-2.19]	25/62	0.69[0.41-1.18]	63/155	0.69[0.47-1.03]	0.050
3-Technicians and Associate Professionals	103/197	0.97[0.72-1.32]	16/26	1.15[0.59-2.24]	27/63	0.78[0.48-1.29]	45/77	1.05[0.70-1.59]	0.877
31141-Telecommunications Technician	8/4	4.20[1.20-14.64]*	0/0	-	2/0	-	2/1	3.15[0.26-38.79]	0.102
3118-Draughting Technicians	9/7	3.02[1.07-8.53]*	2/1	6.17[0.53-72.08]	4/0	-	1/3	0.80[0.08-7.83]	0.122
3342- Education Associate Professionals	2/20	0.23[0.05-1.00]*	1/2	0.92[0.08-10.58]	0/9	-	0/1	-	0.119
4-Clerks	90/238	0.62[0.45-0.86]*	12/36	0.54[0.27-1.08]	31/81	0.61[0.38-0.97]*	29/85	0.61[0.38-0.99]*	0.008
5-Service and Sales Workers	130/205	1.40[1.04-1.90]*	25/41	1.23[0.71-2.12]	46/63	1.65[1.06-2.55]*	42/64	1.49[0.95-2.33]	0.015
51-Personal and Protective Services Workers	89/131	1.46[1.04-2.04]*	23/26	1.84[1.00-3.40]	29/44	1.41[0.84-2.37]	26/38	1.47[0.84-2.55]	0.048
52113-Forecourt Attendant	11/2	8.31[1.79-38.54]*	4/0	-	3/1	4.37[0.44-43.34]	3/0	-	0.030
6-Agriculture and Fishery Workers	106/144	1.66[1.21-2.29]*	17/24	1.50[0.76-2.96]	26/27	1.96[1.09-3.54]*	48/59	1.91[1.23-2.95]*	0.001
61-Market Oriented Agricultural and Fishery Workers	106/144	1.66[1.21-2.29]*	17/24	1.50[0.76-2.96]	26/27	1.96[1.09-3.54]*	48/59	1.91[1.23-2.95]*	0.001
611-Market Farmers and Crop Growers	47/46	2.15[1.37-3.38]*	10/12	1.52[0.62-3.75]	13/15	1.69[0.77-3.72]	17/12	3.50[1.59-7.70]*	0.001
6111-Field Crop and Vegetable Growers	11/8	2.93[1.10-7.77]*	5/3	3.67[0.82-16.38]	3/3	2.38[0.40-14.2]	2/1	3.46[0.30-40.30]	0.063
61112-Market Gardener and Related Worker	8/4	3.98[1.14-13.88]*	4/2	4.15[0.71-24.33]	2/1	4.20[0.35-49.75]	1/0	-	0.042
6112-Fruit Growers	23/24	2.03[1.09-3.78]*	3/7	0.77[0.18-3.22]	4/4	2.01[0.47-8.61]	10/7	3.51[1.26-9.78]*	0.014
61121-Fruit Grower, Worker	20/21	2.07[1.07-4.02]*	2/7	0.49[0.09-2.58]	2/2	2.33[0.30-17.94]	10/6	4.21[1.43-12.35]*	0.012
6113-Gardeners and Nursery Growers	20/19	1.96[1.01-3.82]*	4/5	1.14[0.29-4.42]	7/9	1.32[0.47-3.69]	7/4	4.56[1.28-16.28]*	0.030
61133-Grounds or Green Keeper	12/7	3.01[1.14-7.96]*	4/3	1.92[0.41-8.97]	5/1	8.21[0.91-73.71]	2/2	2.54[0.34-18.88]	0.034
6125-Crop and Livestock Producers	14/10	3.61[1.44-9.02]*	0/4	-	3/1	8.14[0.43-155.80]	6/1	12.50[1.45-107.86]*	0.009
614-Fishery Workers, Hunters and Trappers	7/3	5.62[1.27-24.97]*	2/0	-	3/0	-	2/3	1.79[0.26-12.20]	0.077
7-Trades Workers	93/128	1.28[0.89-1.83]	9/12	1.37[0.55-3.39]	18/28	1.05[0.55-2.02]	45/61	1.21[0.77-1.92]	0.411
71-Building Trades Workers	57/49	2.02[1.30-3.14]*	8/6	2.33[0.78-6.98]	10/10	1.78[0.71-4.47]	28/28	1.61[0.90-2.87]	0.045
711-Building Frame and Related Trades Workers	33/27	1.93[1.10-3.39]*	3/1	4.77[0.46-49.63]	4/5	1.57[0.40-6.15]	20/18	1.66[0.83-3.31]	0.097
7112-Carpenters and Joiners	32/25	1.97[1.11-3.48]*	3/1	4.73[0.45-49.22]	4/5	1.56[0.40-6.13]	19/17	1.59[0.79-3.20]	0.126
71122-Builder (Including Contractor)	23/13	2.90[1.41-5.96]*	1/1	2.49[0.15-42.04]	3/2	2.82[0.44-18.06]	12/10	1.82[0.75-4.38]	0.105
71311-Electrician	14/6	3.61[1.34-9.74]*	4/1	6.64[0.70-62.49]	2/1	2.31[0.20-26.64]	3/3	1.70[0.33-8.79]	0.197
8-Plant and Machine Operators and Assemblers	92/120	1.42[1.01-2.01]*	17/21	1.37[0.69-2.73]	32/39	1.43[0.85-2.41]	28/41	1.32[0.76-2.27]	0.133
9-Elementary Occupations (incl Residuals)	80/111	1.44[1.01-2.04]*	12/24	0.85[0.41-1.78]	32/38	1.62[0.96-2.74]	14/32	0.84[0.43-1.65]	0.561
9151-Labourers	48/55	1.61[1.03-2.52]*	11/8	2.18[0.84-5.70]	16/24	1.10[0.55-2.20]	8/12	1.31[0.50-3.39]	0.397

206 OR adjusted for age, sex, ethnicity, highest education level, socioeconomic deprivation status and smoking. The table includes results for all broad occupation categories (all 1-digit),and for specific occupations (2-5 digits) if the
207 association for ever vs. never employed was statistically significant (p<0.05). Based on at least 10 subjects (cases + controls). *p<0.05
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Table 3. Odds Ratios (OR) and 95% CIs for Industry by Duration Categories

Industry	Never/ever Cases/Controls(n)	Never/Ever OR (95% CI)	Exposure <2 years Cases/Controls(n)	Exposure <2 years OR1 (95% CI)	Exposure between 2-10 years Cases/Controls(n)	Exposure between 2-10 years OR2 (95% CI)	Exposure > 10 years Cases/Controls(n)	Exposure > 10 years OR3 (95% CI)	Trend *p*-Value
A-Agriculture, Forestry and Fishing	101/149	1.42[1.03-1.96]*	12/29	0.84[0.40-1.74]	21/33	1.19[0.66-2.16]	49/58	1.82[1.18-2.82]*	0.011
A01-Agriculture	92/123	1.68[1.20-2.35]*	12/24	1.00[0.47-2.11]	19/24	1.69[0.88-3.25]	44/46	2.19[1.37-3.49]*	0.001
A011-Horticulture and Fruit Growing	36/40	1.93[1.18-3.18]*	7/11	1.15[0.42-3.17]	6/11	1.19[0.42-3.38]	15/10	3.74[1.60-8.75]*	0.004
A0119-Fruit Growing nec	20/13	3.67[1.71-7.89]*	3/5	1.20[0.26-5.61]	2/1	6.07[0.50-72.96]	8/4	5.29[1.44-19.4]*	0.005
B-Mining	16/12	2.26[1.03-4.97]*	6/4	2.51[0.68-9.32]	7/5	2.51[0.77-8.24]	1/3	0.38[0.04-3.83]	0.325
B14-Other Mining	7/4	3.81[1.07-13.59]*	2/3	1.51[0.24-9.45]	2/1	5.86[0.51-67.64]	2/0	-	0.047
C-Manufacturing	131/237	0.99[0.74-1.32]	25/44	0.93[0.54-1.60]	40/62	1.20[0.76-1.89]	47/97	0.81[0.53-1.22]	0.567
C212-Dairy Product Manufacturing	11/5	4.98[1.64-15.06]*	3/2	3.34[0.54-20.80]	3/2	3.77[0.57-25.05]	3/1	6.53[0.62-68.43]	0.021
C2129-Dairy Product Manufacturing nec	8/4	4.10[1.16-14.45]*	2/2	2.21[0.29-16.51]	3/1	7.13[0.66-76.42]	2/1	3.33[0.27-41.17]	0.063
C24-Printing, Publishing and Recorded Media	6/35	0.31[0.13-0.75]*	2/9	0.42[0.09-2.01]	3/12	0.53[0.14-1.98]	1/11	0.12[0.02-0.98]*	0.014
C242-Publishing	2/20	0.20[0.05-0.88]*	0/3	-	2/9	0.43[0.09-2.09]	0/5	-	0.056
E-Construction	83/100	1.50[1.04-2.14]*	15/20	1.37[0.67-2.78]	22/30	1.34[0.73-2.44]	37/42	1.52[0.92-2.52]	0.065
E41-General Construction	53/50	1.81[1.16-2.82]*	12/9	2.18[0.88-5.37]	10/18	1.08[0.47-2.46]	26/19	2.24[1.18-4.24]*	0.014
E412-Non-Building Construction	16/11	2.36[1.05-5.29]*	4/2	3.04[0.53-17.37]	5/4	2.04[0.51-8.12]	7/4	3.08[0.87-10.86]	0.029
E4121-Road and Bridge Construction	12/6	3.00[1.09-8.30]*	2/1	2.19[0.19-25.43]	5/2	4.13[0.76-22.49]	5/3	2.59[0.60-11.20]	0.046
F-Wholesale Trade	32/79	0.66[0.42-1.03]	8/11	1.18[0.46-3.02]	12/30	0.67[0.33-1.36]	6/23	0.42[0.16-1.07]	0.047
F471-Food, Drink and Tobacco Wholesaling	4/20	0.35[0.12-1.06]*	2/3	0.96[0.15-6.13]	2/11	0.33[0.07-1.53]	0/2	-	0.105
G-Retail Trade	110/194	1.09[0.81-1.48]	21/44	0.85[0.48-1.49]	45/63	1.40[0.90-2.16]	29/49	1.29[0.77-2.16]	0.145
G5259-Retailing nec	12/6	3.70[1.33-10.24]*	3/2	2.69[0.42-17.13]	7/3	4.07[1.01-16.35]*	1/0	-	0.011
G53-Motor Vehicle Retailing and Services	47/48	1.78[1.14-2.78]*	9/12	1.38[0.56-3.39]	23/18	2.22[1.16-4.25]*	10/10	2.08[0.80-5.37]	0.006
G531-Motor Vehicle Retailing	18/9	3.73[1.62-8.60]*	5/1	10.00[1.13-88.68]*	8/5	3.04[0.95-9.79]	3/3	1.69[0.32-8.89]	0.027
G5311-Car Retailing	13/9	2.47[1.02-6.00]*	4/1	7.81[0.84-72.67]	6/6	1.68[0.52-5.46]	1/2	0.70[0.06-8.30]	0.315
G5321-Automotive Fuel Retailing	19/9	4.10[1.72-9.78]*	4/3	1.89[0.40-8.95]	8/2	10.83[1.82-64.46]*	5/2	6.10[0.91-40.74]	0.002
I-Transport and Storage	58/88	1.20[0.82-1.76]	8/14	1.11[0.44-2.78]	31/36	1.45[0.86-2.45]	11/31	0.61[0.29-1.26]	0.924
I62-Rail Transport	17/12	2.34[1.09-5.06]*	3/4	1.49[0.32-6.94]	4/2	2.81[0.50-15.94]	5/3	2.49[0.57-10.85]	0.088
I620-Rail Transport	12/6	3.19[1.16-8.79]*	0/3	-	4/0	-	3/1	4.11[0.41-40.84]	0.065
L-Property and Business Services	84/174	0.86[0.62-1.18]	16/39	0.80[0.43-1.49]	30/45	1.21[0.73-2.00]	31/69	0.75[0.47-1.20]	0.430
M-Government Administration and Defence	81/148	1.06[0.77-1.46]	18/28	1.21[0.65-2.27]	23/44	1.05[0.61-1.80]	25/47	1.10[0.65-1.86]	0.655
N-Education	61/160	0.75[0.52-1.10]	7/18	0.61[0.24-1.51]	18/41	0.85[0.46-1.55]	27/80	0.70[0.42-1.16]	0.144
O-Health and Community Services	63/139	0.96[0.66-1.39]	12/19	1.32[0.61-2.85]	29/52	1.15[0.69-1.93]	19/57	0.78[0.44-1.39]	0.736
O8729-Non-Residential Care Services nec	7/6	3.49[1.09-11.22]*	2/1	4.99[0.37-66.65]	2/2	4.24[0.55-32.72]	2/2	2.79[0.37-21.12]	0.077

OR adjusted for age, sex, ethnicity, highest education level, socioeconomic deprivation status and smoking. The table includes results for all broad industry categories (all 1-digit), , and for specific industries (2-5 digits) if the association for ever vs. never employed was statistically significant ($p<0.05$). Based on at least 10 subjects (cases+controls). *$p<0.05$

nec: not elsewhere classified

Specific occupations within the broad occupation and industry categories

Market-oriented agricultural and fishery workers

Elevated risks were found for Field Crop and Vegetable Growers (OR 2.93, 95%CI 1.10-7.77); Fruit Growers (OR 2.03, 95%CI 1.09-3.78); Gardeners and Nursery Growers (OR 1.96, 95%CI 1.01-3.82); Crop and Livestock Producers (OR 3.61, 95%CI 1.44-9.02, Table 2), with similar risks for both males and females (Supplementary Table T1). Positive associations between employment duration and MND were observed for most of these groups (Table 2). An increased risk was also found for Fishery Workers, Hunters and Trappers even based on small numbers (OR 5.62, 95%CI 1.27-24.97, Table 2). However, no increased risk was observed for Livestock Producers, which is the largest 4-digit group within agricultural workers (OR 1.10, 95%CI 0.72-1.69, Supplementary Table S1).

Similar results were observed in analyses by industry category, with increased risks in Agriculture (OR 1.68, 95%CI 1.20-2.35; Table 3), in particular Horticulture and Fruit Growing (OR 1.93, 95% CI 1.18-3.18, Table 3), with similar risks for both males and females (Supplementary Table T2). For Grain, Sheep and Beef Cattle Farming and Dairy Cattle Farming there was no statistically significant increased risk (Supplementary Table S2). With more than 10 years of employment, a particularly high risk was observed for Horticulture and Fruit Growing. (OR 3.74, 95%CI 1.60-8.75; Table 3).

Building trades workers

Employment as Building Trades Worker was associated with elevated risk (OR= 2.02, 95%CI 1.30-3.14; Table 2), particularly in Builders, and Electricians (OR 2.90, 95%CI 1.41-5.96 and OR= 3.61, 95%CI 1.34-9.74, respectively). These were only found in males as there were very few females in these occupations. Risks did not increase with duration of employment.

Analysis by industry also showed an increased risk for Construction (OR= 1.50, 95%CI 1.04-2.14; Table 3), particularly in General Construction, Non-Building Construction and Road and Bridge Construction (OR= 1.81, 95% CI 1.16-2.82, OR= 2.36, 95% CI 1.05-5.29, OR= 3.00, 95% CI 1.09-8.30, respectively), but notably not in Painting and Decorating Services (OR= 0.89, 95%CI 0.34-2.29; Supplementary Table S2).

Service and sales workers

An increased risk was observed among Service and Sales Workers (OR 1.40, 95%CI 1.04-1.90; Table 2). Within this occupational group, women who had ever worked as Caregiver had an increased risk (OR 2.65, 95%CI 1.04-6.79; Supplementary Table T1), and a similar result was observed for women who had worked in Non-Residential Care Services industry (OR 3.76, 95%CI 1.07-13.26; Table 5). However, increased risks were not observed for other healthcare related occupations or industries.

A particularly high risk was found for working as a Forecourt Attendant (OR 8.31, 95%CI 1.79-38.54; Table 2), and similar results were also found for employment in both Car Retailing and Automotive Fuel Retailing industry (OR 2.47, 95%CI 1.02-6.00 and OR 4.10, 95%CI 1.72-9.78, respectively; Table 3). None of the other retail trade sectors was associated with an increased risk (Supplementary Table S2).

Other occupations and industries

Occupations in white-collar categories were generally associated with a lower risk, with an inverse association for Clerks (OR= 0.62, 95%CI 0.45-0.86; Table 2). While male Finance and Administration Managers showed a decreased risk; in contrast, women in this job showed a increased risk (ORmale 0.44, 95%CI 0.20-0.98 and ORfemale 4.98, 95%CI 1.38-17.99; Supplementary Table T1). However, within white-collar occupations, an elevated risk overall was found for men who worked as Physical Science and Engineering Technicians (OR 1.98, 95%CI 1.05-3.77; Table 4). Within this occupation group, Telecommunications Technicians and Draughting

279 Technicians both had increased risks (OR 4.20, 95%CI 1.20-14.64 and OR 3.02, 95%CI 1.07-8.53,
280 respectively; Table 2).

281 An elevated risk was observed for Plant and Machine Operators and Assemblers (OR 1.42,
282 95%CI 1.01-2.01; Table 2), this risk did not increase with duration.

283 Analyses by industry also showed that men having worked in the Sport and Recreation
284 industry was associated with an increased risk (OR 3.01, 95%CI 1.18-7.70; Supplementary Table
285 T2), but not for women. A similar excess was observed in Mining especially Other Mining (OR 3.81,
286 95%CI 1.07-13.59, Table 3).

287 Neither latency analyses (Supplementary Table S3) nor adjustment for mode of interview
288 (Supplementary Table S4) made any appreciable difference.

DISCUSSION

This study found that certain occupations in agriculture and construction were associated with an increased risk of MND, which are consistent with prior studies,[8] thus further supporting that occupation may be an important aetiological factor for MND. This study also identified other occupations associated with increased risk including building trades workers, electricians (electrical occupations), telecommunications technicians, draughting technicians, forecourt attendants, caregivers, and plant and machine operators and assemblers.

Agricultural workers

A major finding was the strong association between agricultural employment and MND, with several horticultural occupations within this group showing increased risks. Similar results were observed for analysis by industry. When the duration of employment was considered, the risk increased monotonically for market farmers and crop growers, fruit grower and gardeners/nursery growers. The presence of an increased risk for multiple non-overlapping occupational groups, the presence of positive duration-response associations, and the presence of increased risks for both men and women in these occupations, strongly suggests these are not chance findings.

We found no difference in urban/rural residency between cases and controls (Supplementary Table S5), suggesting it is unlikely that risk factors associated with urban/rural residency could be responsible for the observed increased MND risks for agricultural workers. To test whether these associations could be explained by differences in urban/rural residency between participating and non-participating controls, the geographical meshblock for place of residence for all potential controls were linked to New Zealand geographic concordance files to obtain their urban/rural

classification,[23] which was then compared between participants and non-participants (Supplementary Table S5). This showed that participating controls were slightly more likely to live rurally (18%) compared to non-participating controls (14%), suggesting that participation bias could not explain the observed increased MND risks for agricultural workers.

Our findings are consistent with prior studies that observed increased MND risk among farmers and agricultural workers,[24-26] and workers exposure to herbicides/pesticides.[27 28] Also, several meta-analyses[6 8 29] have shown that previous exposure to agricultural chemicals, especially to pesticides, is associated with MND. Pesticide exposure is also a plausible explanation for the risk patterns observed in this study, given that risks were mainly elevated for agricultural occupations and industries in fruit and crop growing, while agricultural occupations and industries primarily in livestock production did not show an increased risk.

Construction workers

Building trades workers

A strong association was observed with construction workers, particularly building trades workers and general labourers. The analysis by industry category confirmed this and results are also consistent with earlier studies in construction workers,[12 30] heavy labour and blue-collar occupations.[31] Associated exposures to dusts, heavy metals,[2] and repetitive and strenuous work have also previously been shown to be a risk factor. As blue-collar workers have been related to lower socioeconomic deprivation status and higher smoking rates[32], these confounders were considered in our study. Although male cases were on average more deprived compared to controls, and there were no differences in education and smoking status between cases and controls in our study, we

also adjusted for socioeconomic deprivation status, education and smoking status. Therefore, the general pattern of increased MND risk for blue-collar occupations is unlikely due to confounding.

Electrical occupations

This study showed an elevated risk for electricians and telecommunications technicians, which is consistent with previous studies showing associations with electrical occupations.[33 34] Exposure to ELF-MFs or electric shocks have been suggested as an explanation for these findings.[6 9 35]

Other occupations

A increased risk was observed among forecourt attendants and in the automotive fuel retailing industry, but not for any of the other retailing industry sectors (except for motor vehicle retailing). Possible exposures that may explain these associations include gasoline emissions, associated solvents including benzene, and tetraethyl-lead (TEL), a petrol-fuel additive mixed with gasoline from the 1920s, which was banned in the 1970s in most western countries, but not in New Zealand until 1996.[36] A Spanish study[37] found that MND mortality was associated with higher air lead levels, and a recent Australian study[38] showed a one percent increase in life-time petrol lead exposure increased the MND death rate by approximately one-third of a percent. This lends further support to the supposition that lead exposure may be a risk factor for MND.

Other significant associations were observed in plant and machine operators and assemblers. This is a heterogeneous occupational group including stationary machine operators as well as vehicle drivers, but none of the specific occupations within this group showed an increased risk. The increased risk may, therefore, be associated with

non-specific exposures such as cutting, cooling, or lubricating oils,[12] diesel exhaust emissions[39] and ELF-MFs.[9]

We also observed an elevated risk for women caregivers but not for other healthcare related occupations, although two mortality studies[25 40] showed that female nurses and medical services workers had an increased risk for MND.

Strengths and limitations

Using the MNDANZ national register, the NMDS and the New Zealand Electoral Roll to identify cases and controls was an important strength of this study. In particular, the MNDANZ national register and NMDS provided a reliable source for all MND patients in New Zealand, and the Electoral Roll records virtually all New Zealand citizens and permanent residents in the age of particular relevance to this study (i.e. >40 years).[41] These sources are representative of the general population that generated the cases. Misclassification of disease status was also minimised as cases were diagnosed by a neurologist, and diagnosis details and neurologists' contact details were provided by all cases. The use of both prevalent and incident cases was necessary to achieve an adequate sample size, but as the time between diagnosis and interview (6-18 months) was short and within the normal survival time for all cases, this was considered unlikely to introduce a bias. Additional analyse excluding prevalent cases did not alter our main findings, apart from wider confidence intervals due to lower numbers. We also did an additional analysis by repeating all analyses controlling for sports and alcohol consumption in the model, which made very little difference and did not alter our findings. Another important strength of the study was that full occupational histories were collected from all cases and controls without the use of proxies to answer the questionnaire, a particular advantage compared to studies based on mortality and cause

389 of death data. The study is also relatively large in comparison with many other case-
390 control studies focusing on occupation,[31 42] and particularly compared to small clinic-
391 based samples.[43 44]

392 The limitations include the reliance on self-reporting, which could introduce
393 recall bias. To minimise this, the life-time work -history questionnaire was provided to
394 every participant a few weeks before the interview to allow sufficient time to recall their
395 work history, and the interviewers were trained to probe for the full occupational history
396 without any gaps. There was no difference in the number of occupations held by cases
397 and controls (mean=6.8) and there was therefore no indication of recall bias in the
398 occupational histories (i.e. cases searching their memories more thoroughly than
399 controls), although this cannot be fully excluded.

400 Another limitation was the lower response rate in controls (48%) compared to
401 cases (92%). We tested whether participation was associated with occupation by
402 comparing the occupation, as recorded on the Electoral Roll, between participating and
403 non-participating controls. The frequency of digit 1and 2 job codes showed no
404 difference within the controls for the occupations for which we found an increased risk,
405 e.g. 61-Market-Oriented Agricultural and Fishery workers, 4.29% non-participating
406 controls vs 4.63% participating controls (Supplementary Table S6). It is therefore less
407 likely that the increased risks observed in this study are explained by non-response bias.

408 There were nine cases with proxy, all of whom were proxy-assisted for the
409 interview only. Given that this represents only 2.8% of the total case population, we
410 consider that any bias resulting from this would be negligible.

411 There were also differences in the interview method used between cases and
412 controls. For cases, it was often difficult to engage in a long telephone interview or to
413 complete the full postal questionnaire. As a result, 62% of cases preferred a face-to-face

414 interview, with only 18% interviewed over the phone and 20% completing a postal
415 questionnaire. In controls, 65% preferred a telephone interview, 17% chose a face-to-
416 face interview and 18% completed a postal questionnaire. To minimise potential bias,
417 the completeness of questionnaires was checked, and follow-up interviews by telephone
418 were made for all cases and controls where there was missing or incomplete data. We
419 also did an additional analysis by repeating all analyses controlling for the interview
420 method in the model, which made very little difference and did not alter our findings.
421 Genetic data was not available as genetic testing is not routinely offered to
422 patients in New Zealand, unless there is a clear family history, and then often only at the
423 request of the patient patient.[13] However, familial MND only accounts for 5-10% of all
424 MND cases, and genetic differences are therefore unlikely to explain our findings.
425 The other limitation was that the age distribution between cases and controls
426 was different between men and women. This is likely due to age matching controls
427 using the age distribution of MND incidence in the UK, which may be different from
428 that in New Zealand (equivalent New Zealand data was not available at the time of
429 participant recruitment).

CONCLUSIONS

The findings of this study indicate increased MND risks associated with certain occupations and industries in New Zealand. These possible associations were consistent for agricultural occupations. Agriculture also represented the largest occupational group for which an increased risk was observed (i.e. 33% of cases and 24% of controls had worked in agriculture), illustrating that occupational risk factors for MND have high prevalence in the New Zealand population. If specific causal exposures can be identified, this may provide important opportunities for the prevention of MND. We also observed increased MND risk for other large occupational groups such as building trades workers, plant and machine operators and assemblers, and unspecified labourers, but also for smaller more specific occupational groups including care workers, forecourt attendants, telecommunications technicians, draughting technicians, and electricians. These results have suggested specific occupational risk factors for MND (e.g. agricultural chemicals, organic solvents, metals, ELF-MFs, and electric shocks) that merit further scrutiny in future analyses.

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DECLARATION OF COMPETING FINANCIAL INTERESTS

The authors declare they have no actual or potential competing financial interests.

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