Original research

Occupational exposures to pesticides and other chemicals: a New Zealand motor neuron disease case–control study

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ABSTRACT

Objectives To assess associations between occupational exposures to pesticides and other chemicals and motor neuron disease (MND).

Methods A population-based case–control study that included 319 MND cases (64% male/36% female) recruited through the New Zealand MND Association complemented with hospital discharge data, and 604 controls identified from the Electoral Roll. For each job held, a questionnaire collected information on 11 exposure categories (dust, fibres, tobacco smoke, fumes, gas, fumigants, oils/solvents, acids/alkalis, pesticides, other chemicals and animals/animal products). ORs were estimated using logistic regression adjusting for age, sex, ethnicity, socioeconomic status, education, smoking, alcohol consumption, physical activities, head/spine injury and other occupational exposures.

Results Two exposure categories were associated with increased MND risks: pesticides (OR 1.70, 95% CI 1.17 to 2.48) and fumigants (OR 3.98, 95% CI 1.81 to 8.76), with risks increasing with longer exposure duration (p<0.01). Associations were also observed for: methyl bromide (OR 5.28, 95% CI 1.63 to 17.15), organochlorine insecticides (OR 3.28, 95% CI 1.18 to 9.07), organophosphate insecticides (OR 3.11, 95% CI 1.40 to 6.94), pyrethroid insecticides (OR 6.38, 95% CI 1.13 to 35.96), inorganic (copper) fungicides (OR 4.66, 95% CI 1.53 to 14.19), petrol/diesel fuel (OR 2.24, 95% CI 1.27 to 3.93) and unspecified solvents (OR 1.91, 95% CI 1.22 to 2.99). In women, exposure to textile fibres (OR 2.49, 95% CI 1.13 to 5.50), disinfectants (OR 9.66, 95% CI 1.29 to 72.44) and cleaning products (OR 3.53, 95% CI 1.64 to 7.59) were also associated with MND; this was not observed in men (OR 0.80, 95% CI 0.44 to 1.48; OR 0.72, 95% CI 0.29 to 1.84; OR 0.57, 95% CI 0.21 to 1.56, respectively).

Conclusions This study adds to the evidence that pesticides, especially insecticides, fungicides, and fumigants, are risk factors for MND.

Key messages

What is already known about this subject?

- Several occupational exposures such as pesticides, solvents and metals have been hypothesised to be associated with motor neuron disease (MND).

What are the new findings?

- In this population-based case–control study with complete lifetime job histories, occupational exposure to pesticides (especially insecticides, fungicides) and fumigants were associated with an increased risk of MND in both men and women.
- Occupational exposure to petrol/diesel fuel and unspecified solvents were also associated with an increased MND risk.

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

- These results confirm previous findings and support policies to reduce exposures to specific chemicals in the workplace, for example, by using effective exhaust ventilation, or, where that is not feasible, by using appropriate personal protective equipment.
- Where feasible, hazardous pesticides should be substituted with less harmful alternatives, and methods of pesticide application need to be improved to reduce exposure and resultant risk of MND.

INTRODUCTION

Motor neuron disease (MND) comprises a group of progressive and fatal neurodegenerative conditions with largely unknown aetiology,[1] although age (with a peak onset between 70 and 75 years),[2] male sex and a family history of MND are well-known risk factors.[2–4] Amyotrophic lateral sclerosis (ALS) is the most common form of MND, accounting for 85% of cases[3 5 6]; other forms include progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis (PLS).[2] Despite the growing evidence about the genetics of MND, more than 90% of patients occur sporadically without a clear family history and/or obvious inherited genetic mutations,[7] suggesting an important role for environmental factors, including occupational exposures.[3]

Pesticide exposure has been shown to be associated with an approximately 1.5-fold to 2.0-fold risk of ALS, as shown in three meta-analyses[7–9] and two systematic reviews.[10 11] However, most studies investigated the association of ALS with pesticides exposure as a group, and have not been able to identify the specific pesticide classes involved (ie, insecticides, herbicides, fungicides).

The few that considered specific pesticides showed inconclusive results,[12 13] although a role for organochlorine[7] and organophosphate[14] insecticides has been suggested.

Solvents have also been associated with ALS,[13] with a recent meta-analysis reporting a 40% increased MND risk for solvents exposure as a group,[9] however, results have not always been consistent.[12 15] Some studies reported associations for specific solvents, but results have been mixed.[12 16 17]

Other exposures that have been studied in relation to MND include heavy metals,[13 15] with several studies showing positive associations with blood or bone lead levels[18 19] and systemic reviews reporting an 80% increase in MND risk associated with a history of lead exposure.[11 20]

Although these studies provide support for a role of environmental and occupational chemicals, particularly those known to have neurotoxic properties (ie, insecticides, solvents, lead), the evidence is currently insufficient to inform effective MND prevention strategies, highlighting the need for more and larger studies, underpinned by detailed exposure assessment.

We have previously reported associations between MND and employment in specific occupations, such as agricultural and construction workers, electricians, forecourt attendants, and plant and machine operators and assemblers,[21] and occupational exposure to electric shocks and extremely low-frequency magnetic fields (ELF-MF).[22] Using data from the same population-based case–control study, we have now assessed associations with specific occupational exposures, based on detailed questionnaire information and full occupational histories.

METHODS

Study population

A New Zealand population-based case–control study was conducted to assess associations between occupational exposures and MND using self-reported lifetime occupational histories with specific information on occupational exposures.[21] Cases were recruited primarily through the New Zealand MND Association register from 2013 to 2016. This was supplemented with searches for patients with a primary or secondary diagnosis of MND (ICD10–G122) in the National Minimum Dataset (2013–2015), which holds records of all hospital outpatients in New Zealand. The inclusion criterion for cases was a diagnosis for any form of MND by a neurologist. A total of 396 (275 incident and 121 prevalent) cases with a primary diagnosis of MND were recruited. Controls were randomly selected from the 2008 New Zealand Electoral Roll, frequency matched on the age and sex distribution of the UK's MND incidence data, as the MND incidence by age and sex was not available for New Zealand at the time of recruitment.[23] We aimed to include two controls for each case and assumed an approximate 50% response rate. In total 2400 potential controls were therefore selected from the Electoral Roll. Controls with any neurodegenerative disease were excluded.

Questionnaire

Data on demographics, lifestyle factors, injuries, smoking and drinking, and lifetime occupational history were collected by using a questionnaire,[21] which was administered depending on participants' own preference; a face-to-face interview (59% in cases vs 16% in controls); a telephone interview (23% vs 66%); or a postal questionnaire (18% vs 18%). All controls completed the questionnaire themselves, while nine cases used a proxy (three required proxy assistance with a face-to-face interview and six used proxy assistance for reading and writing only).

Exposures

Participants were asked to complete a full work history (all jobs ever held for ≥6 months) and for each job, information on job title, employer, industry, start and end date, and tasks and work processes was obtained. Participants were asked whether the following 11 exposure categories were present (yes/no) in each job: dust (eg, coal, metal, wood, grain); fibres (textile fibres, asbestos or insulation material); environmental tobacco smoke (from other workers); other smoke or fume (eg, combustion products, engine emission, metal fume); gas (eg, combustion gases, refrigerant); fumigants (eg, methyl bromide, chloropicrin); oils and solvents (eg, lubricants, cutting oils, degreasers, thinners); acids or alkalis; pesticides (fungicides, insecticides, herbicides or timber preservatives); other chemical products (eg, dyes, inks, adhesives, etc); and animals or animal products (eg, living animals, meat, faeces). Exposure duration for all 11 exposure categories was determined based on the duration of the job(s) in which the exposure occurred.

For each exposure, participants were asked the name and source of the substance, and how often they were exposed. Based on this free-text information, new variables for occupational exposure subcategories (yes/no) were constructed, blind to the case–control status of the participant, through automated keywords searches (including alternative spelling and trade names). For each newly created exposure subcategory, the original job descriptions were checked to ensure that the new category captured only participants considered to be truly exposed.

Statistical analyses

Analyses were conducted using SAS V.9.4. Differences in general characteristics between cases and controls were tested using χ^2 tests, and unconditional logistic regression was used to estimate ORs and 95% CIs, for ever-exposed to a particular occupational exposure, compared with never being exposed to that particular exposure.

Analyses were adjusted for age (5 year categories); sex; ethnicity (European, Māori (the indigenous population of New Zealand) and other); highest achieved education level (primary and secondary school, technical or trade school diploma, undergraduate university degree, postgraduate university degree); smoking status (never, ex, current smoker; before diagnosis for cases; and at the time of the interview for controls); alcohol consumption frequency (average alcohol consumption of the lifetime: ≤once a month, 1–2 times/week, 3–5 times/week, daily; up to diagnosis for cases and up to the interview for controls); sports (never vs ever having played sports as an adult (>18 years)); head injury (ever/never); spine injury (ever/never); and socioeconomic status (SES) using the New Zealand Deprivation Index (NZDep2006, quintiles).[24] Additional analyses were conducted mutually adjusting for all other exposure categories. We checked for multicollinearity by comparing the SEs for the main effect estimates between the full model, and a minimally adjusted model,[25] there was no evidence of collinearity affecting the study findings. All analyses were repeated separately for males and females. Analyses were also repeated controlling for the questionnaire method, exposure to ELF-MF and electric shocks.

We also assessed associations with exposure duration (for each category) defined as the number of years worked in each exposed job, summed over the entire job history. Exposure duration was categorised based on the quartiles of duration in the controls, specific to each exposure. A test for trend was performed by

Table 1 Characteristics of participants in a population-based case–control study of occupational exposures and the risk of motor neuron disease, New Zealand, 2013–2016

Characteristics	Male cases (n=203) No. %		Male control (n=331) No. %		P value*	Female cases (116) no. %		Female controls (273) no. %		P value*
Age at interview					0.001					0.047
20–49	20	9.9	16	4.8		10	8.6	24	8.8	
50–59	47	23.1	51	15.4		26	22.4	48	17.6	
60–69	79	38.9	112	33.8		44	37.9	76	27.8	
≥70	57	28.1	152	46.0		36	31.1	125	45.8	
Ethnicity					0.946					0.122
European/Pakeha†	188	92.6	304	91.8		106	91.4	259	94.9	
Māori‡	8	3.9	14	4.2		5	4.3	11	4.0	
Pacific and others	7	3.5	13	4.0		5	4.3	3	1.1	
Deprivation index quintile					0.024					0.167
1–2 (least deprived)	76	37.4	83	25.1		23	19.8	82	30.1	
3–4	50	24.6	83	25.1		28	24.1	60	22.0	
5–6	32	15.8	71	21.4		35	30.2	58	21.2	
7–8	27	13.3	64	19.3		16	13.8	44	16.1	
9–10 (most deprived)	18	8.9	30	9.1		14	12.1	29	10.6	
Highest education					0.409					0.395
Primary and secondary school	92	45.3	160	48.3		52	44.8	129	47.3	
Technical or trade school diploma	70	34.5	94	28.4		35	30.2	61	22.3	
Undergraduate university degree	27	13.3	45	13.6		18	15.5	53	19.4	
Postgraduate university degree	14	6.9	32	9.7		11	9.5	30	11.0	
Smoking (prior diagnosis)					0.697					0.471
Never	102	50.2	155	46.8		62	53.5	164	60.1	
Smoker at the time of diagnosis	16	7.9	25	7.6		4	3.5	9	3.3	
Ex-smoker	85	41.9	151	45.6		50	43.0	100	36.6	
Total jobs (mean (range))	6.8	(1–22)	6.6	(1–20)	0.533	7.0	(1–23)	7.1	(1–22)	0.686

χ^2 tested the differences in age, ethnicity, education, smoking status, socioeconomic status and the number of jobs by gender.
*P values were calculated using a χ^2 test for categorical variables.
†Pakeha (a Māori word)—this is used as a term specifically for New Zealand European people.
‡Māori—indigenous people of New Zealand.

assigning scores to the categories of the categorical duration variables and fitting them as continuous variables.

RESULTS

Population characteristics

A total of 321 (92% participation) cases and 605 controls (48% participation) took part in the study. Two cases and one control with missing occupational history were excluded, leaving 319 cases and 604 controls for analyses. The time between diagnosis and interview was 6–18 months (median=238 days, IQR=269 days) for cases.

Table 1 summarises the characteristics of the cases (203 (64%) male/116 (36%) female) and controls (331 (55%) male/273 (45%) female). There was little difference between the groups in smoking status, ethnicity and education. However, the 70+ age group was over-represented in the controls, and male cases were less deprived compared with male controls. There was no difference in the number of jobs held by cases and controls (mean=7 for both).

Exposure categories

Two of the 11 occupational exposure categories were associated with an increased risk of MND after adjustment for all other exposure categories: fumigants (OR 3.98, 95% CI 1.81 to 8.76) and pesticides (OR 1.70, 95% CI 1.17 to 2.48; table 2). Of those reporting exposures to pesticides, half reported having applied the pesticides themselves, while the other half reported being exposed indirectly (online supplemental table 1). An increased risk was observed for those who applied pesticides themselves (OR 2.72, 95% CI 1.66 to 4.44), an occupational activity more common among males than females (13.3% vs 2.6% in controls). This association was stronger in males (OR 2.88, 95% CI 1.61 to 5.16 vs OR 2.01, 95% CI 0.56 to 7.24 in females; online supplemental table 1). Of interest, no association was found for those exposed indirectly (online supplemental table 1).

Analyses stratified by sex (table 2) showed stronger or similar findings for males (fumigants: OR 9.69, 95% CI 3.00 to 31.35; pesticides OR 1.72, 95% CI 1.08 to 2.75), while for females, an elevated OR of similar magnitude was only found for pesticides, but this did not reach statistical significance (OR 1.82, 95% CI 0.84 to 3.93). For females, exposure to fibres (OR 2.24, 95% CI 1.09 to 4.61) and other chemical products (OR 1.82, 95% CI 1.03 to 3.24) was also associated with an increased risk, which was not observed in males.

A positive association with duration of exposure was observed for: fibres (for females, p test for trend=0.038); fumigants (for males, p test for trend=0.001); oils and solvents (for males, p test for trend=0.004); pesticides (for males, p test for trend=0.001); and other chemical products (for females, p test for trend=0.004; table 3). For the other exposure categories, a trend with exposure duration was not observed (online supplemental table 2).

Table 2 Risk of motor neuron disease with self-reported occupational exposures in a population-based case–control study, New Zealand, 2013–2016

Self-reported exposures	All Cases/controls (319/604) no.	%	OR (95% CI)	OR† (95% CI)	Male Cases/controls (203/331) no.	%	OR (95% CI)	OR† (95% CI)	Female Cases/controls (116/273) no.	%	OR (95% CI)	OR† (95% CI)
Dust	170/287	53.3/47.5	1.00 (0.74 to 1.36)	0.72 (0.51 to 1.03)	133/204	65.5/61.6	1.00 (0.67 to 1.50)	0.68 (0.42 to 1.10)	37/83	31.9/30.4	0.79 (0.47 to 1.33)	0.56 (0.30 to 1.03)
Fibres	91/126	28.5/20.9	1.33 (0.95 to 1.86)	1.26 (0.87 to 1.84)	65/100	32/30.2	1.01 (0.67 to 1.52)	0.92 (0.57 to 1.47)	26/26	22.4/9.5	2.54 (1.33 to 4.86)*	2.24 (1.09 to 4.61)*
Environmental tobacco smoke	166/289	52.0/47.9	1.06 (0.79 to 1.43)	1.00 (0.73 to 1.36)	113/183	55.7/55.3	0.93 (0.63 to 1.36)	0.86 (0.57 to 1.31)	53/106	45.7/38.8	1.23 (0.76 to 2.01)	1.26 (0.74 to 2.15)
Other smoke or fume	135/193	42.3/32	1.28 (0.92 to 1.76)	1.05 (0.72 to 1.53)	116/158	57.1/47.7	1.39 (0.95 to 2.06)	1.10 (0.69 to 1.76)	19/35	16.4/12.8	0.93 (0.48 to 1.83)	0.72 (0.33 to 1.58)
Gas	51/62	16.0/10.3	1.33 (0.88 to 2.03)	1.06 (0.66 to 1.69)	42/45	20.7/13.6	1.51 (0.92 to 2.46)	1.27 (0.73 to 2.23)	9/17	7.8/6.2	0.81 (0.33 to 2.02)	0.58 (0.20 to 1.64)
Fumigants	26/10	8.2/1.7	4.95 (2.29 to 10.70)*	3.98 (1.81 to 8.76)*	22/4	10.8/1.2	12.32 (3.89 to 39.03)*	9.69 (3.00 to 31.35)*	4/6	3.5/2.2	1.43 (0.36 to 5.61)	1.12 (0.27 to 4.60)
Oils and solvents	133/195	41.7/32.3	1.26 (0.91 to 1.73)	1.09 (0.74 to 1.59)	115/157	56.7/47.4	1.36 (0.92 to 1.99)	1.30 (0.82 to 2.07)	18/38	15.5/13.9	1.09 (0.57 to 2.10)	0.78 (0.36 to 1.72)
Acids or alkalis	48/72	15.1/11.9	1.02 (0.67 to 1.57)	0.79 (0.50 to 1.26)	41/59	20.2/17.8	1.00 (0.62 to 1.63)	0.80 (0.47 to 1.34)	7/13	6/4.8	1.10 (0.40 to 3.03)	1.00 (0.32 to 3.08)
Pesticides	109/122	34.2/20.2	1.92 (1.38 to 2.67)*	1.70 (1.17 to 2.48)*	87/96	42.9/29	1.95 (1.31 to 2.91)*	1.72 (1.08 to 2.75)*	22/26	19/9.5	2.07 (1.07 to 4.01)*	1.82 (0.84 to 3.93)
Other chemical products	137/193	43/32	1.43 (1.07 to 1.92)*	1.29 (0.94 to 1.78)	90/119	44.3/36	1.28 (0.88 to 1.87)	1.15 (0.76 to 1.74)	47/74	40.5/27.1	1.74 (1.06 to 2.83)*	1.82 (1.03 to 3.24)*
Animals or animal products	105/142	32.9/23.5	1.53 (1.11 to 2.10)*	1.22 (0.85 to 1.77)	73/97	36/29.3	1.45 (0.97 to 2.17)	1.11 (0.70 to 1.78)	32/45	27.6/16.5	1.73 (0.99 to 3.02)	1.51 (0.76 to 2.98)

OR adjusted for age and sex (or age only in case of sex-stratified analyses), education, ethnicity, socioeconomic status (SES), smoking status, sports, alcohol, head injury, spine injury.
*P<0.05.
†OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, SES, smoking status, sports, alcohol, head injury, spine injury and for the respective other self-reported exposures.

Table 3 Motor neuron disease risk by duration of exposure in a population-based case–control study, New Zealand, 2013–2016

	All Cases/controls		Male Cases/controls		Female Cases/controls	
	(319/604)	OR (95% CI)	(203/331)	OR (95% CI)	(116/273)	OR (95% CI)
Fibres						
Never exposed	228/478	1	138/231	1	90/247	1
Exposed <5 years	28/37	1.34 (0.76 to 2.35)	15/24	0.85 (0.39 to 1.84)	13/13	1.83 (0.71 to 4.72)
Exposed 5–10 years	20/29	1.31 (0.67 to 2.54)	13/24	0.86 (0.38 to 1.95)	7/5	3.44 (0.93 to 12.76)
Exposed 11–29 years	16/29	0.73 (0.35 to 1.49)	14/23	0.60 (0.26 to 1.39)	2/6	0.68 (0.11 to 4.16)
Exposed >29 years	27/31	1.70 (0.92 to 3.15)	23/29	1.37 (0.68 to 2.75)	4/2	6.48 (0.93 to 45.29)
P (trend)		0.255		0.908		0.038
Fumigants						
Never exposed	293/594	1	181/327	1	112/267	
Exposed <4 years	4/4	2.04 (0.48 to 8.73)	2/1	5.16 (0.31 to 84.93)	2/3	1.36 (0.19 to 9.78)
Exposed 4–6 years	5/2	3.97 (0.72 to 21.92)	3/1	8.06 (0.72 to 90.11)	2/1	3.17 (0.24 to 42.26)
Exposed 7–10 years	5/1	9.32 (0.96 to 90.20)	5/0		0/1	
Exposed >10 years	12/3	4.77 (1.28 to 17.84)*	12/2	7.54 (1.57 to 36.19)*	0/1	
P (trend)		0.001		0.001		0.691
Oils and solvents						
Never exposed	186/409	1	88/174	1	98/235	1
Exposed <5 years	22/50	0.73 (0.40 to 1.34)	15/37	0.63 (0.29 to 1.38)	7/13	0.88 (0.29 to 2.66)
Exposed 5–14 years	26/51	0.86 (0.48 to 1.54)	24/41	0.99 (0.51 to 1.96)	2/10	0.34 (0.06 to 1.87)
Exposed 15–31 years	37/47	1.28 (0.72 to 2.27)	29/37	1.46 (0.74 to 2.90)	8/10	1.36 (0.39 to 4.74)
Exposed >31 years	48/47	1.79 (1.04 to 3.10)*	47/42	2.60 (1.39 to 4.85)*	1/5	0.41 (0.03 to 4.99)
P (trend)		0.056		0.004		0.633
Pesticides						
Never exposed	210/482	1	116/235	1	94/247	1
Exposed <5 years	19/32	1.13 (0.59 to 2.15)	12/28	0.76 (0.34 to 1.72)	7/4	4.34 (1.03 to 18.32)*
Exposed 5–15 years	26/33	1.60 (0.87 to 2.93)	19/25	1.37 (0.64 to 2.92)	7/8	2.29 (0.69 to 7.62)
Exposed 16–30 years	27/27	1.89 (1.00 to 3.54)*	21/19	2.09 (0.96 to 4.54)	6/8	1.08 (0.30 to 3.94)
Exposed >30 years	37/30	2.39 (1.32 to 4.31)*	35/24	3.04 (1.54 to 5.97)*	2/6	0.52 (0.09 to 3.17)
P (trend)		0.001		0.001		0.659
Other chemical products						
Never exposed	182/411	1	113/212	1	69/199	1
Exposed <5 years	32/46	1.36 (0.81 to 2.29)	20/21	1.33 (0.63 to 2.79)	12/25	1.66 (0.71 to 3.90)
Exposed 5–11 years	34/49	1.12 (0.66 to 1.88)	26/24	1.28 (0.65 to 2.53)	8/25	0.58 (0.21 to 1.63)
Exposed 12–26 years	33/49	1.27 (0.75 to 2.16)	17/32	0.90 (0.44 to 1.83)	16/17	3.11 (1.24 to 7.80)*
Exposed >26 years	38/49	1.41 (0.85 to 2.35)	27/42	1.13 (0.61 to 2.10)	11/7	6.27 (1.88 to 20.95)*
P (trend)		0.142		0.743		0.004

OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury and for the respective other self-reported exposures.
*P<0.05.

Exposure sub-categories

For exposure categories that showed significant associations with MND, we conducted further analyses on specific exposures within each category (table 4). Among the most frequently reported fibre types, insulation fibre was associated with an increased risk (OR 3.63, 95% CI 1.59 to 8.26), while asbestos was not associated with MND (OR 0.95, 95% CI 0.59 to 1.52). Exposure to textile fibres was associated with an increased risk in women (OR 2.49, 95% CI 1.13 to 5.50) but not in men.

Elevated ORs were found for each fumigant subcategory, but this reached statistical significance only for methyl bromide (OR 5.28, 95% CI 1.63 to 17.15). This association was found only in males, as very few females were exposed to methyl bromide.

Among specific exposures within the oils and solvents category, a positive association was observed for non-specified solvents, but only in males (OR 2.72, 95% CI 1.61 to 4.58). A positive association was also observed for exposure to petrol and diesel fuel (OR 2.24, 95% CI 1.27 to 3.93). Most of those reporting exposures to petrol and diesel fuel were exposed before 1996, the year lead was phased out from petrol in New Zealand. The OR was slightly higher for this group (OR 2.20, 95% CI 1.27 to 3.79; online supplemental table 3) compared with that reported for the overall group (table 3) and compared with those exposed to only unleaded fuel oil (after 1996) (OR 1.64, 95% CI 0.37 to 7.18; online supplemental table 3), with the latter risk estimate based on small numbers.

Among the different pesticide groups, statistically significant increased risks were found for insecticides (OR 3.06, 95% CI 1.90 to 4.94) and fungicides (OR 2.40, 95% CI 1.30 to 4.42), for both males and females (table 4). Several specific insecticide subcategories were also associated with increased risk: organochlorines (OR 3.28, 95% CI 1.18 to 9.07), organophosphates (OR 3.11, 95% CI 1.40 to 6.94) and pyrethroids (OR 6.38, 95% CI 1.13 to 35.96). Among fungicides, inorganic (copper)

Table 4 Risk of motor neuron disease with self-reported occupational exposure subcategories in a population-based case–control study, New Zealand, 2013–2016

	All Cases/controls		Male Cases/controls		Female Cases/controls	
	(319/604)	OR (95% CI)	(203/331)	OR (95% CI)	(116/273)	OR (95% CI)
Fibres						
Asbestos	42/71	0.95 (0.59 to 1.52)	40/66	0.98 (0.59 to 1.65)	2/5	0.72 (0.12 to 4.37)
Insulation fibre†	22/10	3.63 (1.59 to 8.26)*	20/9	3.82 (1.56 to 9.34)*	2/1	4.33 (0.29 to 63.74)
Textile fibre	51/60	1.36 (0.87 to 2.14)	28/40	0.80 (0.44 to 1.48)	23/20	2.49 (1.13 to 5.50)*
Fibreglass	17/16	1.57 (0.72 to 3.43)	16/14	1.81 (0.76 to 4.32)	1/2	2.17 (0.15 to 31.41)
Fumigants						
Methyl bromide	15/4	5.28 (1.63 to 17.15)*	13/4	5.29 (1.52 to 18.39)*	2/0	
Formaldehyde	6/3	3.73 (0.85 to 16.40)	4/0		2/3	1.59 (0.22 to 11.39)
Chloropicrin	3/1	5.71 (0.53 to 61.29)	3/1	9.22 (0.83 to 101.82)	0/0	
Non-specified fumigants	3/3	1.27 (0.23 to 7.01)	3/0		0/3	
Oils and solvents						
Oils	76/112	1.08 (0.72 to 1.61)	68/93	1.19 (0.75 to 1.89)	8/19	0.87 (0.32 to 2.36)
Cutting fluid	13/20	0.98 (0.44 to 2.21)	12/20	0.99 (0.42 to 2.31)	1/0	
Fuel oil	44/34	2.13 (1.27 to 3.59)*	40/28	2.56 (1.42 to 4.63)*	4/6	1.26 (0.28 to 5.61)
Petrol and diesel	39/28	2.24 (1.27 to 3.93)*	35/24	2.45 (1.30 to 4.60)*	4/4	2.04 (0.37 to 11.25)
Kerosene	6/9	1.11 (0.37 to 3.31)	6/7	1.71 (0.52 to 5.64)	0/2	
Engine oil/lubricants	40/75	0.65 (0.40 to 1.05)	34/67	0.56 (0.32 to 0.97)*	6/8	1.09 (0.31 to 3.90)
Non-specified oils	3/13	0.53 (0.14 to 1.99)	2/6	0.54 (0.10 to 3.00)	1/7	0.41 (0.04 to 3.78)
Solvents	95/116	1.31 (0.88 to 1.94)	82/95	1.54 (0.96 to 2.46)	13/21	1.07 (0.42 to 2.71)
Chlorinated solvents	29/29	1.37 (0.76 to 2.46)	22/23	1.22 (0.61 to 2.46)	7/6	2.53 (0.69 to 9.23)
Other organic solvents	29/56	0.65 (0.37 to 1.13)	26/52	0.68 (0.37 to 1.25)	3/4	1.54 (0.25 to 9.59)
Non-specified solvents	69/65	1.91 (1.22 to 2.99)*	62/51	2.72 (1.61 to 4.58)*	7/14	0.72 (0.28 to 2.28)
Pesticides						
Herbicides	64/76	1.34 (0.85 to 2.10)	55/61	1.40 (0.82 to 2.40)	9/15	1.06 (0.37 to 3.08)
245T	21/31	1.11 (0.58 to 2.11)	19/28	1.13 (0.55 to 2.32)	2/3	1.92 (0.27 to 13.83)
24D	12/21	0.85 (0.38 to 1.88)	12/20	0.85 (0.36 to 2.01)	0/1	
MCPA	4/6	0.85 (0.22 to 3.25)	4/6	0.91 (0.23 to 3.56)	0/0	
MCPB	2/2	0.82 (0.11 to 6.24)	2/2	0.98 (0.12 to 7.71)	0/0	
Glyphosate	16/17	1.16 (0.54 to 2.47)	13/12	1.17 (0.47 to 2.93)	3/5	0.81 (0.16 to 4.11)
Non-specified herbicides	26/20	2.22 (1.15 to 4.30)*	22/14	2.57 (1.17 to 5.69)*	4/6	1.21 (0.25 to 5.83)
Insecticides	60/38	3.06 (1.90 to 4.94)*	43/29	2.86 (1.57 to 5.18)*	17/9	4.24 (1.66 to 10.78)*
Organochlorines	12/8	3.28 (1.18 to 9.07)*	10/8	2.27 (0.73 to 7.07)	2/0	
Organophosphates	22/11	3.11 (1.40 to 6.94)*	20/6	5.97 (2.16 to 16.53)*	2/5	0.72 (0.12 to 4.43)
Pyrethroids	5/2	6.38 (1.13 to 35.96)*	3/2	2.99 (0.42 to 21.53)	2/0	
Carbamates	0/2		0/1		0/1	
Non-specified insecticides	25/16	2.42 (1.22 to 4.78)*	14/13	1.49 (0.62 to 3.57)	11/3	7.86 (1.85 to 33.35)*
Fungicides	36/22	2.40 (1.30 to 4.42)*	28/17	2.24 (1.07 to 4.69)*	8/5	3.77 (1.08 to 13.13)*
Aromatic hydrocarbons	3/0		3/0		0/0	
Phthalimides	5/3	2.87 (0.60 to 13.76)	4/2	3.62 (0.53 to 24.91)	1/1	2.25 (0.11 to 46.04)
Inorganic (copper)	14/5	4.66 (1.53 to 14.19)*	10/3	5.13 (1.18 to 22.21)*	4/2	4.51 (0.70 to 29.24)
Non-specified fungicides	15/14	1.19 (0.52 to 2.72)	12/12	0.99 (0.37 to 2.62)	3/2	3.66 (0.48 to 27.48)
Sheep/cattle dip‡	20/17	1.90 (0.91 to 3.94)	18/13	2.27 (0.97 to 5.30)	2/4	0.59 (0.09 to 3.95)
Timber treatments	31/25	1.73 (0.94 to 3.18)	28/22	1.71 (0.87 to 3.36)	3/3	1.82 (0.28 to 11.61)
Non-specified pesticides	18/14	1.98 (0.90 to 4.35)	11/9	1.54 (0.54 to 4.34)	7/5	2.47 (0.63 to 9.62)
Other chemical products						
Dyes	27/26	1.55 (0.84 to 2.88)	14/15	1.16 (0.48 to 2.76)	13/11	2.44 (0.93 to 6.40)
Inks	13/18	1.27 (0.58 to 2.81)	7/10	1.11 (0.36 to 3.42)	6/8	1.90 (0.57 to 6.38)
Adhesives	47/71	0.84 (0.53 to 1.34)	40/54	1.08 (0.61 to 1.89)	7/17	0.88 (0.30 to 2.56)
Disinfectants	16/18	1.14 (0.53 to 2.44)	11/16	0.72 (0.29 to 1.84)	5/2	9.66 (1.29 to 72.44)*
Cleaning products	33/35	1.98 (1.13 to 3.44)*	9/15	0.57 (0.21 to 1.56)	24/20	3.53 (1.64 to 7.59)*
Non-specified other chemical products	36/63	0.97 (0.61 to 1.55)	30/38	1.35 (0.76 to 2.39)	6/25	0.47 (0.17 to 1.30)

OR adjusted for age, sex (for analyses combining males and females), education, ethnicity, socioeconomic status, smoking status, sports, alcohol, head injury, spine injury and for the respective other self-reported exposures.
*P<0.05.
†Insulation fibre, mostly fibreglass.
‡Sheep/cattle dip: pesticides, mainly insecticides and fungicides, used to protect cattle and sheep from external parasites.

fungicides showed a statistically significant elevated risk (OR 4.66, 95% CI 1.53 to 14.19). Among herbicides, a statistically significant association was found only for non-specified herbicides (OR 2.22, 95% CI 1.15 to 4.30).

Specific exposures most commonly reported under 'other chemical products' were dyes, inks, adhesives, disinfectants and cleaning products, with increased risks observed for disinfectants (OR 9.66, 95% CI 1.29 to 72.44) and cleaning products (OR 3.53, 95% CI 1.64 to 7.59), but this was found only in females.

Additional adjustment for the interview method (face-to-face/telephone/postal) in these models made little difference and did not alter our findings (data not shown). We previously reported on associations with exposure to ELF-MF and electric shocks assessed through job-exposure matrices for this study population,[22] additional adjustment for these occupational exposures did not alter the findings of the analyses presented here (data not shown).

DISCUSSION

This study found that several common occupational exposures were associated with an increased risk of MND, including pesticides, fumigants, petrol/diesel fuel, unspecified solvents, textile fibres, and cleaning products.

Exposure to pesticides was associated with a 70% increase in MND risk (OR 1.70; 95% CI 1.17 to 2.48), with very similar relative risk estimates for males and females, and with a lifetime exposure prevalence of 20% among controls (29% males 9.5% females). Estimating a population attributable fraction (PAF=100×(Px×(OR−1))/(1+(Px×(OR−1))); Px is the exposure prevalence among the controls) based on these numbers suggests that 12.4% of MND cases in our study population may be attributable to pesticide exposure (17.3% for males and 7.2% for females). The associations were strongest for those with the longest exposure duration and for those who had applied pesticides themselves and were therefore more likely to have been exposed to higher levels compared with those who were exposed indirectly for whom we found no association. These findings are consistent with three meta-analyses and two recent systematic reviews that reported positive associations between pesticide exposure and ALS.[7–11] It is also consistent with previous studies showing no associations in people who were indirectly exposed to pesticides.[26 27]

In this study, exposure to insecticides was associated with a three times greater MND risk, with associations observed for several insecticide classes (organochlorines, organophosphates and pyrethroids). Other studies focusing on specific pesticide classes have also reported associations for organochlorines,[8 28] including pentachlorobenzene, cis-chlordane,[28] aldrin, dieldrin, DDT and toxaphene.[8] The role of organochlorines in MND is biologically plausible, given their known neurotoxicity,[29] but these have largely been discontinued in New Zealand. Consistent with previous studies[30] we observed increased MND risks for organophosphates, a class of insecticides of continued high use. This is biologically plausible as polymorphisms in paraoxonase 1, an enzyme that detoxifies organophosphates,[31] have been associated with the development of ALS,[32] and high exposure to organophosphates can result in OP-induced delayed neuropathy, a condition akin to ALS.[14] Organophosphates also induce oxidative stress,[33] which plays an important role in the pathogenesis of MND.[34] We observed an elevated MND risk from exposure to pyrethroids insecticides, which is consistent with an earlier case report that presented a patient who developed MND after 3 years of chronic exposure to pyrethroids.[35] An increased risk for exposure to fungicides, in particular inorganic fungicides, was also found, which is similar to two previous case–control studies that reported an elevated, but not statistically significant risk for occupational fungicides exposure.[13 36]

For fumigants, which are predominantly used as insecticides, we also observed an elevated risk in both men and women, with the greatest risk observed for those with the longest exposure duration. All fumigant subcategories were positively associated with MND, but only the association with methyl bromide was statistically significant. A meta-analysis reported positive associations with fumigants (OR 1.8) and methyl bromide (OR 1.2), but the findings did not reach statistical significance.[8] An earlier New Zealand report suggested a role for methyl bromide in a cluster of MND cases in port workers,[37] however, a subsequent investigation noted that the evidence was inconclusive.[38] In our study, exposure to methyl bromide predominantly occurred in horticulture where it has been used to sterilise the soil. While this application of methyl bromide is now discontinued in New Zealand, methyl bromide continues to be used for the fumigation of export logs. Chronic exposure to methyl bromide can damage both the central and peripheral nervous systems,[39] but a specific mechanistic pathway for methyl bromide has not been established.

We observed elevated risks for exposure to petrol/diesel fuel (OR 2.24), which was different from an earlier study that found no association,[12] although another study found an association between diesel motor exhaust and ALS.[40] Lead, a petrol additive until 1996 in New Zealand and a known neurotoxin that can cross the blood–brain barrier and accumulate in neuronal and glial cells,[11] may explain the association with petrol/diesel fuel oil. In particular, several studies have reported positive associations with lead exposure,[13 19 36] including a recent meta-analysis.[20] For the majority of participants, petrol/diesel fuel oil exposure occurred before 1996 when lead was phased out from petrol in New Zealand, hence, we were not able to elucidate whether associations observed in our study were attributable to lead, or other petrol components, for example, benzene.

Solvents have been associated with an increased MND risk,[16] but most studies did not specify the type of solvent. Case–control studies have reported positive associations for alcohols or ketones, cleaning solvents or degreasers,[13] n-hexane,[12] thinners and paint removers.[36] A recent Danish study, using job exposure matrices (JEM) to estimate cumulative solvent exposure, found associations with methylene chloride and benzene in men.[16] However, a Dutch prospective cohort study, using a JEM to assess occupational exposures to total solvents, chlorinated and aromatic solvents found no significant association with ALS mortality.[15] In our study, the overall category of solvents was not associated with MND, although an increased risk for men exposed to non-specified solvents was found (the majority of participants reporting solvent exposure could not recall which specific solvent was used). Organic solvents are known neurotoxins and long-term exposure may cause encephalopathy, cognitive deficits, disrupt motor function[41] and increase oxidative stress,[42] which play a role in MND.[34] In addition, exposure to solvents has been associated with other neurodegenerative conditions including Alzheimer's disease, Parkinson's disease and multiple sclerosis,[41] with which MND shares some underlying biological mechanisms.[43]

We found that several exposures were associated with MND only among women including exposure to textile fibres, despite analyses being based on similar numbers of exposed males and females. Textile and clothing workers have previously been shown to have an increased risk of MND,[44] although another

study observed an inverse association between textile work and ALS.[17] The observed increased risk for textile fibres could be the result of exposure to other compounds commonly associated with textiles, such as dyes, solvents, antimicrobial agents, or organophosphorus and organobromine flame retardants.[45]

An increased MND risk was observed for disinfectants and cleaning products, again only among women. In a Danish cohort, an inverse association was found for women employed in the cleaning industry.[46] An association between disinfectants and MND has not been reported previously. The use of disinfectants may also be a marker of exposure to infectious agents, which may play a role in the development of ALS.[47]

This study has several limitations. Exposure was assessed through self-reports, which can be subject to exposure misclassification and recall bias. On average, cases and controls reported the same number of jobs, suggesting no differential recall in lifetime occupational histories between cases and controls. For each job, exposures were initially assessed using tick-boxes for 11 categories, after which participants were asked (for each ticked category) to provide more information on product names, sources, and tasks related to the exposure(s). Self-reported exposures were subsequently compared with job titles and task descriptions to ensure that they were relevant for that job, thus reducing exposure misclassification. This was done blind to the case/control status of participants, thus limiting differential exposure misclassification. However, it cannot be excluded that cases recall their exposures differently from controls, particularly for exposures widely known to adversely impact health. Nevertheless, for our main findings, including the observed increased risks associated with insecticides, fungicides and petrol/diesel fuel oil, we have previously found corresponding elevated risks for occupational groups where these exposures are most common (eg, agricultural occupations, forecourt attendant),[21] for which, as noted above, recall bias is less likely. Furthermore, we found positive and statistically significant duration-response associations for these exposures, with exposure duration based on job duration, which is unlikely to be subject to differential recall. Therefore, we consider recall bias to be an unlikely explanation for the observed associations. However, self-reports have clear limitations, particularly when attempting to assess exposures to highly specific agents, as illustrated by the high proportion of participants reporting exposure to non-specified solvents (table 4).

We had no detailed information on personal protective equipment (PPE)-use but consider that this would have minimal impact on the study results, given that effective PPE such as full protective clothing and respirators have only more recently become available. Moreover, the lack of information on exposure level is a limitation.

While participation was high among cases (92%), lower participation was achieved for controls (42%), which may contribute to participation bias. We had access to basic information (age, sex, deprivation, address, occupation) from the Electoral Roll for all non-participating controls and compared this with participating controls; this showed no large differences[21] and suggests that participation bias is unlikely to explain our findings. For example, participating controls were slightly more likely to live rurally (18%) compared with non-participating controls (14%), suggesting that participation bias is unlikely to explain the observed increased MND risks for pesticide exposures.

Another limitation is that cases more often opted for a face-to-face interview. To evaluate potential bias, we repeated all analyses controlling for the interview method which made very little difference and did not alter our findings (data not shown). We also conducted analyses stratified by interview method, which resulted in wider confidence intervals, but largely identified the same exposures as being associated with an elevated risk (online supplemental table 4). This suggests that our main findings are unlikely to be affected by differential information bias due to using different interview methods. Moreover, as both incident and prevalent cases were included, we also conducted stratified analyses to assess whether associations differed by case type (online supplemental table 5). Findings were very similar for the incident and prevalent cases, suggesting that case status did not affect the results.

The age and sex distribution differed between cases and controls. This is due to controls being matched based on the age/sex distribution of MND incidence in the UK, as equivalent New Zealand data were not available at the time of participant recruitment. However, all associations were adjusted for age and sex, and the main findings are therefore unlikely to be explained by differences in age/sex distribution between case and controls.

Finally, we had no information on specific MND subtypes (this was not recorded in New Zealand at the time of study recruitment). Analyses could therefore not be restricted to ALS to improve comparability with other studies, the majority of which reported on ALS. However, as ALS is the most common form of MND accounting for 80%–90% of the total cases,[6] our case definition is therefore unlikely to differ substantially from those used in other studies.

Our study has several strengths. First, the MND diagnosis was confirmed by neurologists. Second, the study size is relatively large in comparison with many other case–control studies with access to lifetime occupational exposure histories. Third, cases and controls mostly answered the questionnaire without the use of proxies, which is a particular advantage compared with studies based on MND mortality. Fourth, 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. These sources are therefore representative of the general population that generated the cases. Finally, we were able to adjust analyses for potential confounders by collecting extensive information on education, SES, smoking, alcohol consumption and injury, as well as other (self-reported) occupational exposures, ELF-MF, and electric shocks.

CONCLUSIONS

In conclusion, this study shows that several common occupational exposures are associated with MND, including pesticides to which a relatively large proportion of the population continues to be exposed to. Measures to reduce these exposures may contribute to a reduction in MND incidence.

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