Received: 26 January 2022 | Revised: 16 March 2022 | Accepted: 18 March 2022

DOI: 10.1111/ane.13615

ORIGINAL ARTICLE

Acta Neurologica Scandinavica WILEY

Sports and trauma as risk factors for Motor Neurone Disease: New Zealand case–control study

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Abstract

Objectives: To assess whether sports, physical trauma and emotional trauma are associated with motor neurone disease (MND) in a New Zealand case–control study (2013–2016).

Methods: In total, 321 MND cases and 605 population controls were interviewed collecting information on lifetime histories of playing sports, physical trauma (head injury with concussion, spine injury) and emotional trauma (14 categories). ORs were estimated using logistic regression adjusting for age, sex, ethnicity, socioeconomic status, education, smoking status, alcohol consumption and mutually adjusting for all other exposures.

Results: Head injury with concussion ≥3 years before diagnosis was associated with MND (OR 1.51, 95% CI: 1.09–2.09), with strongest associations for two (OR 4.01, 95% CI: 1.82–8.86), and three or more (OR 2.34, 95% CI: 1.00–5.45) head injuries. Spine injury was not associated with MND (OR 0.81, 95% CI: 0.48–1.36). Compared to never playing sports, engaging in sports throughout childhood and adulthood increased MND risk (OR 1.81, 95% CI: 1.01–3.25), as was more than 12 years playing football/soccer (OR 2.35, 95% CI: 1.19–4.65). Reporting emotionally traumatic events in more than three categories was associated with MND (OR 1.88, 95% CI: 1.17–3.03), with physical childhood abuse the only specific emotional trauma associated with MND (OR 1.82, 95% CI: 1.14–2.90), particularly for those reporting longer abuse duration ($OR_{(5–8\ years)}$ 2.26, 95% CI: 1.14–4.49; $OR_{(>8\ years)}$ 3.01, 95% CI: 1.18–7.70). For females, having witnessed another person being killed, seriously injured or assaulted also increased MND risk (OR 2.68, 95% CI: 1.06–6.76).

Conclusions: This study adds to the evidence that repeated head injury with concussion, playing sports in general, and playing football (soccer) in particular, are associated with an increased risk of MND. Emotional trauma, that is physical abuse in childhood, may also play a role.

KEYWORDS
ALS, emotional trauma, head injury, neurodegenerative disorders, neuroepidemiology

1 | INTRODUCTION

Motor neurone diseases (MND) are a group of relatively rare, progressive and terminal neurodegenerative conditions (with amyotrophic lateral sclerosis (ALS) being the most common) characterized by the degeneration of upper and lower motor neurons leading to motor and extra-motor symptoms.[1,2] The aetiology of MND is believed to involve complex interactions of environmental, lifestyle and genetic factors,[3] but few conclusive risk factors have been established.

There is growing interest in the role of contact sports (football (or soccer in the United States), American football and rugby) following MND diagnoses in several high-profile professional athletes.[4] Several studies have since assessed the association between professional sports and MND. An Italian cohort study, comparing professional football (soccer) players with the general population,[5] reported a standardized morbidity ratio (SMR) of 6.5 (95% CI 2.1–15.1) (5 ALS cases observed, 0.77 expected); a longer career in professional football (soccer) was associated with a greater risk and earlier onset. A recent update[6] reported a twofold risk of ALS for professional football (soccer) players (34 ALS cases observed, 17.8 expected) and a 20-year earlier disease onset. Similar findings were reported for a Scottish cohort of professional football (soccer) players[7] for which an MND hazard ratio of 4.33 (95% CI 2.05–9.15) was observed.

Professional athletes in sports other than football (soccer) have been less studied. In a US cohort of National (American) Football League players,[8] ALS mortality was increased (SMR 4.31, 95% CI 1.73–8.87) with a higher risk for players in speed positions compared to non-speed positions. A Swedish study among cross-country skiers[9] showed an increased risk for elite skiers (OR 4.31 95% CI 1.78–10.4) but not for recreational skiers. A clinic-based observational study[10] showed that triathletes were overrepresented in a population of patients with ALS (OR 16.15, 95% CI 5.82–36.38) and also had earlier disease onset.

Association with professional sports may be due to high strenuous physical exertion and/or more frequent traumatic brain injury, although evidence is mixed. Several case–control studies reported an increased MND risk among people who engage in strenuous physical activities,[11–13] but other case–control studies reported no[14] or inverse associations.[15] A prospective cohort study among postmenopausal women showed that strenuous physical activities were associated with an increased risk of MND,[16] in contrast, another cohort study in European Prospective Investigation into Cancer and Nutrition showed a slightly reduced risk of dying from ALS in those with high levels of total physical activity at enrolment.[17] A recent Mendelian randomization study suggested a positive association between physical exercise and ALS in those with a specific risk genotype.[18]

Several studies have shown an increased risk with traumatic brain injury,[19–22] while others found no association.[11,23] Meta-analyses[19,24–26] have indicated a 1.3-fold to 1.7-fold increased risk of MND in relation to a head injury. However, another meta-analysis found that the association was weaker and suggested that due to reverse causation, head-injury-associated risk of ALS has been somewhat overestimated.[27]

Emotional trauma has also been proposed as a risk factor for MND (and other neurodegenerative diseases), possibly due to increased oxidative stress,[28] but evidence is limited. A Japanese case–control study[13] showed that self-reported stress was associated with an increased risk of ALS (OR 1.8, 95% CI 1.3–2.7) while a UK study[29] reported a 1.5-fold increased MND risk for a former diagnosis of depression. However, a recent Australian study[30] found no difference in exposures to potentially stressful life events between ALS cases and controls.

Thus, while studies have provided intriguing leads about the role of physical activity, traumatic brain injury and emotional trauma, the evidence remains largely inconclusive. As part of a New Zealand MND case–control study, we assessed the association between sports, physical trauma (head injury, spine injury), emotional trauma and the risk of MND.

2 | METHODS

2.1 | Study population

Cases were recruited primarily through the Motor Neurone Disease Association of New Zealand (MNDANZ) over a period of 3 years (2013–2016). This was supplemented with searches for all hospital outpatients with a primary or secondary diagnosis of MND (ICD 10 code – G122) from the National Minimum Dataset (2013–2015). The inclusion criterion for cases was a diagnosis by a neurologist, with all forms of MND included. A total of 2400 controls (two per case) were randomly selected from the New Zealand Electoral Roll (2008), frequency matched by age (based on the age distribution of the Unite Kingdom MND incidence distribution, as New Zealand MND incidence age distribution was not available)[31] and sex. Controls with any neurodegenerative disease were excluded.

All participants gave written informed consent. Ethical approval was obtained by the Multi-region Ethics Committee in New Zealand (ref: MEC/12/01/005).

2.2 | Data collection

Depending on the preference of the participants, a face-to-face (59% in cases vs 16% in controls) or a telephone interview (23% vs 66%), or a postal questionnaire (18% vs 18%) was used to collect information on demographic and personal characteristics, family history, physical trauma/injury, emotional trauma (life events) physical activities (sports), smoking, alcohol and a lifetime occupational history as described previously.[32] 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).

2.3 | Exposure assessment

2.3.1 | Physical trauma

All participants were asked whether they had ever had an injury that required medical care. If they answered yes, information for each injury was collected including injury type (head injury with a concussion, fracture, contusion, sprain, strain, other); circumstances of the injury (work, sport, leisure other than sport, traffic accident, other); age at which the injury occurred; body location of the injury (head, arms, chest, abdomen, legs, spine); and the severity of the injury (mild, moderate, severe). The number of times the specific injury occurred was calculated for (1) head injury with concussion and (2) spine injury.

2.3.2 | Sports

Participants were asked to complete a lifetime sports history. For each sport listed, information on year of start and cessation, and hours per week was obtained. A question on strenuous physical exertion was

TABLE 1 Characteristics of participants in a population-based case–control study of sports, physical trauma, emotional trauma and Motor Neurone Disease, New Zealand, 2013–2016

	Cases (n = 321) No. %		Controls (n = 605) No. %		p-value
Gender					.0142
Male	203	63.24	332	54.88	
Female	118	36.76	273	45.12	
Age at interview					<.0001
20–59	103	32.09	140	23.14	
60–69	125	38.94	188	31.07	
≥70	93	28.97	277	45.79	
Ethnicity					.7284
European/Pakeha[a]	295	91.90	563	93.06	
Māori[b]	14	4.36	25	4.13	
Pacific & others	12	3.74	17	2.81	
Deprivation index quintile					.4665
1–2 (least deprived)	99	30.84	165	27.27	
3–4	79	24.61	143	23.64	
5–6	68	21.81	129	21.32	
7–8	43	13.40	108	17.85	
9–10	32	9.97	60	9.92	
Highest education					.1157
Secondary school (college)	145	45.17	290	47.93	
Technical or trade school diploma	105	32.71	155	25.62	
Undergraduate university degree	46	14.33	98	16.20	
Postgraduate university degree	25	7.79	62	10.25	
Alcohol consumption					.1925
Never or less than once a month	75	23.36	166	27.44	
1–2 times a week	116	36.14	188	31.07	
3–5 times a week	76	23.67	129	21.32	
Daily	54	16.82	122	20.17	
Smoking (prior to diagnosis)					.9142
Never	165	51.40	319	52.73	
Ex	20	6.23	35	5.78	
Current	136	42.37	251	41.49	

Note: p-values were calculated using a chi-square test for categorical variables.

[a]Pakeha (a Māori word)—this is used as a term specifically for New Zealand European people.

[b]Māori—indigenous people of New Zealand.

also included ('Have you ever engaged in a sport that required great physical effort, for instance running a marathon?').

2.3.3 | Emotional trauma (life events)

Participants were asked whether life events had occurred in any of the following 14 emotional trauma categories at any point in their life, including life-threatening illness; life-threatening accident; been physically forced in a robbery; threatened by a weapon (a knife or gun); experienced a close relation die of an accident, homicide or suicide; miscarriage (for women only); been physically forced to have sex; sexual harassment; been physically beaten/harmed by a family member or caregiver as a child; been physically beaten/harmed as an adult; been bullied by a family member; witnessed another person being killed or seriously injured; life in danger (living in military combat or a war zone); and extremely frightening or horrifying situation. For each of these events, follow-up questions included how often and at what age the event occurred. Those who answered yes to 'physically beaten/harmed as a child' were also asked to describe the force/nature (the name and source of the force) used against them.

2.4 | Statistical analyses

Statistical analyses were conducted using SAS version 9.4. Differences in general characteristics between cases and controls were tested using chi-squared tests, and unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), for ever-exposed to a particular event (sports, head injury, spine injury, emotional traumas), compared to never being exposed to that particular event.

Analyses were adjusted for age (5-year categories); sex; ethnicity (European; Māori, the indigenous population of New Zealand; 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 (smoker at the time of diagnosis for cases)); alcohol consumption before diagnosis (≤once a month,1–2 times/week, 3–5 times/week, daily); and socioeconomic status (SES) using the New Zealand Deprivation Index (NZDep2006, quintiles). All analyses were repeated separately for males and females. Additional analyses were conducted mutually adjusting for all other exposures (sports, head injury, spine injury, and emotional trauma). We checked for multicollinearity by comparing the standard errors for the main effect estimates between the full model, and a minimally adjusted model,[33] this showed no evidence of collinearity. Analyses were also repeated while controlling for the interview method.

We also assessed associations with the lifetime number of years played in a particular sport (for each sport separately). Duration was categorized based on quartiles in the controls, specific to each sport. A test for trend was performed by assigning scores to the categories of the categorical duration variables, which were subsequently fitted as continuous variables.

As it cannot be excluded that accidents and injuries may be an early manifestation of MND, even before diagnosis,[23] analyses were repeated excluding all injuries that occurred within 3 years before the index date (diagnosis date for cases, interview date for controls).

3 | RESULTS

3.1 | Population characteristics

A total of 321 cases and 605 controls were included in the analyses. Of the cases, 63% were male versus 55% in controls. The majority of cases (68%) were aged >60 years. While the 70+ age group was overrepresented in the controls, there was little difference between cases and controls in ethnicity, socioeconomic status (SES), education, tobacco smoking and alcohol consumption (Table 1).

3.2 | Head injury with concussion and spine injury

Among cases, 33% reported having ever had a head injury with a concussion, compared to 22% among controls (OR 1.49, 95% CI 1.09, 2.05; Table 2). This difference remained after excluding all brain injuries that occurred within 3 years prior to diagnosis (OR 1.51, 95% CI: 1.09, 2.09). Reporting only one head injury with a concussion was not associated with an increased risk (OR 1.16, 95% CI 0.80, 1.69), while statistically significant increased risks were observed for reporting two (OR 4.01, 95% CI 1.82, 8.86; based on 22 cases and 10 controls), and 3 or more (OR 2.34, 95% CI 1.00, 5.45; based on 14 cases and 11 controls) head injuries. Elevated risks were observed for self-reported mild, moderate and severe head injuries, but this reached statistical significance only for moderate injury (OR 1.77, 95% CI 1.14, 2.77).

When considering the age at which head injury occurred (childhood only, adulthood only, or both childhood and adulthood), the highest risk was observed for having had head injuries in both childhood and adulthood (OR 1.87, 95% CI 1.09, 3.21). While more males reported head injuries with concussion than females (28% of male and 16% of female controls), the observed pattern of an increased risk associated with multiple head injuries was similar for males and females. Head injuries in two or more different circumstances (work-related, sport-related, leisure-related, traffic accident, other accidents and multiple circumstances) were associated with an almost 2.5-fold increased risk (OR 2.46, 95% CI 1.11, 5.44; Table 3). When the number of head injuries in each circumstance was considered, elevated risks were observed for having had more than one sport-related head injury (OR 3.05, 95% CI 1.06, 8.77) and more than one leisure-related head injury (OR 6.89, 95% CI 1.18, 40.3). Having had one work-related head injury was also associated with an increased risk (OR 2.48, 95% CI 1.01, 6.09; Table 3).

Having ever had a spine injury (9% for cases and controls), repeated spine injury, the severity of the injury, and the age at the injury, were not associated with the risk of MND (Table S1).

TABLE 2 Risk of motor neurone disease with head injuries in a population-based case–control study, New Zealand, 2013–2016

Exposure	All cases/controls (321/605) No %	OR	95% CI	OR[1]	95% CI	Male cases/controls (203/332) No %
Head Injury with concussion						
Never	216/469 (67/78)	1	Reference	1	Reference	130/239 (64/72)
Ever	105/136 (33/22)	1.54	1.13, 2.11*	1.49	1.09, 2.05*	73/93 (36/28)
Head injury with concussion (>3 years before diagnosis)[a]						
Never	224/483 (70/80)	1	Reference	1	Reference	134/248 (66/75)
Ever	97/122 (30/20)	1.57	1.13, 2.16*	1.51	1.09, 2.09*	69/84 (34/25)
Frequency of head injury [a]						
Never	224/483 (70/80)	1	Reference	1	Reference	134/248 (66/75)
Once	61/101 (19/17)	1.21	0.84, 1.74	1.16	0.80, 1.69	43/67 (21/20)
Twice	22/10 (7/1)	4.17	1.90, 9.15*	4.01	1.82, 8.86*	14/9 (7/3)
≥3 times	14/11 (4/2)	2.48	1.07, 5.74*	2.34	1.00, 5.45*	12/8 (6/2)
Severity of the head injury[a]						
Never	224/483 (70/80)	1	Reference	1	Reference	134/248 (66/75)
Mild	21/29 (6/5)	1.52	0.83, 2.77	1.41	0.77, 2.59	15/20 (7/6)
Moderate	48/53 (15/9)	1.78	1.14, 2.76*	1.77	1.14, 2.77*	34/36 (17/11)
Severe	28/40 (9/6)	1.33	0.79, 2.25	1.25	0.73, 2.12	20/28 (10/8)
Age of head injury[a]						
Never had a head injury	224/483 (70/80)	1	Reference	1	Reference	134/248 (66/75)
Childhood[b] only	18/30 (5/5)	1.18	0.63, 2.19	1.17	0.62, 2.18	11/21 (6/6)
Adulthood[c] only	47/61 (15/10)	1.57	1.02, 2.41*	1.49	0.96, 2.29	35/43 (17/13)
Childhood and adulthood	32/31 (10/5)	1.93	1.13, 3.30*	1.87	1.09, 3.21*	23/20 (11/6)

Note: OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR[1]: adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, spine injury & emotional trauma.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Excluding head injuries that occurred within 3 years before diagnosis (for cases) and within 3 years before the interview (for controls).

[b] Head injury occurred at age ≤18 years.

[c] Head injury occurred at age >19 years.

* $p < .05$.

3.3 | Sports

None of the participants reported having been professional athletes. The majority of study participants participated in leisure sports throughout childhood and adulthood (73% of male and 64% of female controls), which was associated with an almost doubling of the MND risk (OR 1.81, 95% CI 1.01, 3.25, Table 4).

Analysis by type of sports did not reveal statistically significant associations for any specific sport, although elevated ORs were observed for several common sports including football (soccer) (OR 1.40, 95% CI 0.95, 2.06), running (OR 1.48, 95% CI 0.92, 2.38), golf (OR 1.38, 95% CI 0.88, 2.16) and rugby (OR 1.26, 95% CI 0.86, 1.83). Analysis by duration for these sports revealed a positive association with longer duration of playing football (soccer) (p for trend = .04), with playing football (soccer) for >12 years associated with a more than twofold MND risk (OR 2.35, 95% CI 1.19, 4.65; Table S2). For rugby, running and golf, a trend with duration was not observed. For rugby and golf, only the shortest duration category was associated with a statistically significant increased risk (Table S2).

3.4 | Emotional trauma

The majority of cases (76%) and controls (72%) reported a traumatic life event within at least one of the 14 categories (Table 5), but this was not associated with MND (OR 1.17, 95% CI 0.84, 1.63). Multiple traumatic life events in different categories were associated with elevated risks, with the highest risk observed for reporting traumatic life events in ≥4 categories (OR 1.88, 95% CI 1.17, 3.03); elevated ORs were observed in both males (OR 1.76, 95% CI 0.92, 2.34) and females (OR 2.30, 95% CI 1.06, 5.00).

Results for the individual emotional trauma categories, mutually adjusted for life events in the other emotional trauma categories, showed that having been beaten by a family member or a

OR	95% CI	OR[1]	95% CI	Female cases/ controls (118/273) No %	OR	95% CI	OR[1]	95% CI
1	Reference	1	Reference	86/230 (73/84)	1	Reference	1	Reference
1.37	0.93, 2.03	1.32	0.89, 1.97	32/43 (27/16)	1.95	1.12, 3.38*	1.87	1.07, 3.27*
1	Reference	1	Reference	90/235 (76/86)	1	Reference	1	Reference
1.45	0.97, 2.16	1.38	0.92, 2.08	28/38 (24/14)	1.82	1.02, 3.26*	1.76	0.98, 3.17
1	Reference	1	Reference	90/235 (76/86)	1	Reference	1	
1.16	0.74, 1.83	1.12	0.71, 1.79	18/34 (15/12)	1.27	0.65, 2.46	1.20	0.61, 2.36
2.50	1.01, 6.20*	2.34	0.94, 5.83	8/1 (7/1)	23.36	2.74, 199*	24.19	2.81, 208*
2.59	0.98, 6.83	2.39	0.90, 6.37	2/3 (2/1)	1.48	0.21, 10.3	1.45	0.20, 10.50
1	Reference	1	Reference	90/235 (76/86)	1	Reference	1	Reference
1.41	0.68, 2.95	1.31	0.62, 2.77	6/9 (5/3)	1.64	0.53, 5.06	1.47	0.47, 4.58
1.56	0.91, 2.70	1.55	0.89, 2.68	14/17 (12/6)	2.01	0.91, 4.43	2.03	0.91, 4.52
1.32	0.69, 2.51	1.21	0.63, 2.33	8/12 (7/5)	1.68	0.64, 4.44	1.61	0.60, 4.29
1	Reference	1	Reference	90/235 (76/86)	1	Reference	1	Reference
0.93	0.42, 2.06	0.94	0.42, 2.10	7/9 (6/3)	1.87	0.64, 5.44	1.76	0.60, 5.17
1.49	0.89, 2.51	1.39	0.82, 2.38	12/18 (10/7)	1.82	0.81, 4.08	1.75	0.77, 3.96
1.89	0.96, 3.71	1.81	0.92, 3.56	9/11 (8/4)	1.79	0.68, 4.73	1.78	0.67, 4.75

carer during childhood was associated with an increased risk for MND (OR 1.82, 95% CI 1.14, 2.90), with similar ORs for males (OR 2.10, 95% CI 1.16, 3.83) and females (OR 2.06, 95% CI 0.88, 4.82). For females who witnessed another person being killed or seriously injured, an increased risk was also observed (OR 2.68, 95% CI 1.06, 6.76; Table 5). For females, having been bullied by a close relation was also associated with an increased risk, but this did not reach statistical significance (OR1.81, 95% CI 0.87, 3.38; Table 5).

More detailed analyses on the association between self-reported childhood physical abuse and MND are presented in Table 6. Increased risks were observed independent of the age at which the physical abuse first occurred (before the age of 7 or after). Reporting multiple episodes of physical abuse was associated with an increased risk, being statistically significant for having experienced physical abuse as a child 2–4 times (OR 5.72, 95% CI 1.41, 23.24) and more than 10 times (OR 2.04, 95% CI 1.13, 3.66). The pattern of elevated ORs for the higher frequency categories was observed for both males and females but reached statistical significance only in males.

Analyses by duration of childhood physical abuse suggested that longer duration was associated with a higher risk, that is physical abuse lasting 5–8 years was associated with a twofold risk (OR 2.26, 95% CI 1.14, 4.49) and physical abuse lasting >8 years with a threefold risk (OR 3.01, 95% CI 1.18, 7.70).

Of those reporting childhood physical abuse, half reported that this resulted in physical injury. While similar ORs were observed for physical abuse with (OR 1.73) and without (OR 1.89) physical injury, statistical significance was reached only for physical abuse without physical injury (OR 1.89; 95% CI 1.06, 3.38).

When considering the type of force used (fist, belt, stick, smacking on the hands, combined fist/belt/stick, other non-specific types), the use of fist, belt and stick were all associated with a more than twofold MND risk, reaching statistical significance for the use of a

TABLE 3 Risk of motor neurone disease with head injuries in different circumstances in a population-based case–control study, New Zealand, 2013–2016

Exposure	All cases/ controls (321/605) No %	OR	95% CI	OR[1]	95% CI	Male cases/ controls (203/332) No %	OR	95% CI	OR[1]	95% CI	Female cases/ controls (118/273) No %	OR	95% CI	OR[1]	95% CI
Circumstances of head injury															
Never	224/483 (70/80)	1	Reference	1	Reference	134/248 (66/75)	1	Reference	1	Reference	90/235 (76/86)	1	Reference	1	Reference
Work-related	14/11 (4/2)	2.25	0.98, 5.14	2.22	0.96, 5.12	12/9 (6/3)	2.46	0.97, 6.23	2.39	0.93, 6.10	2/2 (2/1)	1.81	0.22, 15.0	2.07	0.25, 17.4
Sport-related	29/37 (9/6)	1.48	0.87, 2.52	1.39	0.81, 2.38	22/30 (11/9)	1.27	0.68, 2.36	1.18	0.63, 2.21	7/7 (6/3)	2.47	0.78, 7.88	2.34	0.73, 7.53
Leisure-related	14/21 (4/3)	1.48	0.72, 3.03	1.50	0.73, 3.07	7/12 (3/4)	1.10	0.40, 3.06	1.13	0.40, 3.19	7/9 (6/3)	1.91	0.65, 5.65	1.83	0.61, 5.51
Traffic accident-related	17/27 (5/4)	1.34	0.70, 2.57	1.30	0.67, 2.50	10/15 (5/5)	1.30	0.54, 3.12	1.28	0.53, 3.11	7/12 (6/4)	1.55	0.57, 4.21	1.47	0.54, 4.04
Other accidents	6/14 (2/2)	0.85	0.32, 2.31	0.85	0.31, 2.30	3/8 (1/2)	0.63	0.16, 2.48	0.61	0.15, 2.42	3/6 (3/2)	1.09	0.25, 4.84	1.09	0.24, 4.92
Multiple events[a]	17/12 (5/2)	2.65	1.21,5.83*	2.46	1.11, 5.44*	15/10 (7/3)	2.32	0.98, 5.50	2.15	0.90, 5.14	2/2 (2/1)	3.44	0.42, 28.1	3.30	0.39, 27.9
Frequency of head injury in different circumstances															
Never	224/483 (70/80)	1	Reference	1	Reference	134/248 (66/75)	1	Reference	1	Reference	90/235 (76/86)	1	Reference	1	Reference
Work-related															
Once only	13/9 (4/1)	2.55	1.05, 6.21*	2.48	1.01, 6.09*	11/8 (5/2)	2.50	0.94, 6.64	2.39	0.89, 6.43	2/1 (2/0)	3.92	0.30, 52.0	4.46	0.33, 59.6
>1	1/2 (0/0)	0.85	0.08, 9.60	0.95	0.08, 10.66	1/1 (0/0)	2.02	0.12, 34.2	2.14	0.13, 35.86	0/1 (0/0)	—	—	—	
Sport-related															
Once only	18/31 (6/5)	1.13	0.60, 2.11	1.06	0.56, 1.98	14/25 (7/8)	1.04	0.51, 2.14	0.98	0.47, 2.02	4/6 (3/2)	1.53	0.38, 6.11	1.33	0.33, 5.40
>1	11/6 (3/1)	3.24	1.14, 9.22*	3.05	1.06, 8.77*	8/5(4/2)	2.32	0.69, 7.82	2.07	0.61, 7.05	3/1 (3/0)	7.57	0.72, 79.2	8.52	0.80, 90.9
Leisure-related															
Once only	10/19 (3/3)	1.09	0.49, 2.43	1.08	0.48, 2.42	5/11 (2/3)	0.75	0.24, 2.39	0.77	0.24, 2.47	5/8 (4/3)	1.40	0.41, 4.80	1.29	0.37, 4.48
>1	4/2 (1/0)	6.28	1.08,36.6*	6.89	1.18, 40.3*	2/1 (1/0)	6.66	0.55, 80.4	7.32	0.59, 90.9	2/1 (2/0)	5.05	0.41, 62.7	5.27	0.42, 65.5
Traffic accident-related															
Once only	14/25 (4/4)	1.16	0.58, 2.33	1.13	0.56, 2.27	9/13 (4/4)	1.25	0.50, 3.16	1.22	0.48, 3.12	5/12 (4/4)	1.06	0.35, 3.21	1.01	0.33, 3.09
>1	3/2 (1/0)	3.73	0.59, 23.8	3.49	0.54, 22.4	1/2 (0/1)	1.65	0.14, 20.1	1.64	0.13, 20.2	2/0 (2/0)	—	—	—	—

TABLE 3 (Continued)

Exposure	All cases/ controls (321/605) No %	OR	95% CI	OR[1]	95% CI	Male cases/ controls (203/332) No %	OR	95% CI	OR[1]	95% CI	Female cases/ controls (118/273) No %	OR	95% CI	OR[1]	95% CI
Other circumstances															
Once only	5/14 (2/2)	0.70	0.24, 2.03	0.70	0.24, 2.03	3/8 (1/2)	0.62	0.16, 2.44	0.6	0.15, 2.39	2/6 (2/2)	0.76	0.14, 4.14	0.76	0.14, 4.23
>1	1/0 (0/0)	—	—	—	—	0/0 (0/0)	—	—	—	—	1/0 (1/0)	—	—	—	—
Multiple circumstances[a]															
>1	17/12 (5/2)	2.69	1.22, 5.92*	2.48	1.12, 5.50*	15/10 (7/3)	2.32	0.98, 5.52	2.15	0.90, 5.14	2/2 (2/1)	3.67	0.45, 29.8	3.43	0.41, 29.0

Note: OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR[1] adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, spine injury & emotional trauma.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Multiple events: participants who had more than one type of circumstance of head injury.

* $p < .05$.

stick (OR 2.57, 95% CI 1.10, 5.97), with a particularly high risk observed for females (OR 6.35, 95% CI 1.31, 30.82; Table 6).

4 | DISCUSSION

We found significantly increased risks of MND with having experienced multiple head injuries with concussion, participating in leisure sports in general and playing football (soccer) in particular, and having experienced multiple emotionally traumatic life events. In addition, this is the first study to show an association with having experienced physical abuse as a child.

This study has several limitations. All exposure information was self-reported, potentially resulting in recall bias. To minimize this, questions on physical activity focussed on sports played rather than more subjective self-reported physical activity levels. Questions on head trauma specified a head injury with a concussion, to reduce recall bias that may be associated with using open questions on any head trauma. The questions on emotional trauma included highly sensitive and personal questions. False-positive associations due to reporting bias may occur if cases were more likely to report sensitive events as they may put more value on the study and the importance of being open when answering these questions. However, we did not observe a pattern of more positive answers to sensitive questions in cases. For example, equal proportions of cases and controls reported to have experienced sexual assault, which was among the most sensitive questions.

We did not have access to MND subtype-specific diagnosis (this was not recorded in New Zealand at the time of study recruitment), and analyses could therefore not be restricted to the ALS case group to improve comparability with other studies, which predominantly reported on ALS. However, ALS is the most common form of MND accounting for 85% of the total cases, and our case definition is therefore unlikely to differ substantially from those used in other studies.

The participation rate among population controls (48%) was lower than among cases (92%). To evaluate the potential for participation bias, we compared the occupations recorded on the Electoral Roll between participating and non-participating controls,[32] which showed no significant difference suggesting that responders and non-responders are comparable (at least in terms of occupation and therefore likely socioeconomic position), making it less likely that the observed increased risks are explained by non-response bias.

There were differences in the interview method used between cases and controls, with cases more likely to opt for a face-to-face interview than controls. We therefore repeated all analyses controlling for the interview method. This did not alter our main findings, suggesting that interview methods did not bias the results.

Smoking and alcohol consumption have also been studied as risk factors for MND in several studies; however, results have been inconsistent.[34,35] In this study population, neither smoking nor alcohol consumption was associated with MND (data not shown). Nonetheless, smoking status and alcohol consumption have been adjusted for in all analyses, and this did not alter our findings.

TABLE 4 Risk of motor neurone disease with physical activities in a population-based case–control study, New Zealand, 2013–2016

Exposure	All cases/controls (321/605) *N* %	OR	95% CI	OR[1]	95% CI	Male cases/controls (203/332) *N* %	OR
Playing sports							
Never	17/58 (5/10)	1	Reference	1	Reference	11/28 (5/8)	1
Ever	304/547 (95/90)	1.84	1.04, 3.28	1.74	0.98, 3.11	192/304 (95/92)	1.71
Playing sports at different age							
Never	17/58 (5/10)	1	Reference	1	Reference	11/28 (5/8)	1
Childhood only	53/109 (17/18)	1.56	0.81, 2.99	1.49	0.77, 2.86	29/51 (14/15)	1.39
Adulthood only	11/20 (3/3)	1.91	0.75, 4.91	1.79	0.69, 4.63	5/9 (2/3)	1.78
Childhood and adulthood	240/418 (75/69)	1.92	1.07, 3.43*	1.81	1.01, 3.25*	158/244 (78/73)	1.79
Type of sports[a]							
Rugby	140/204 (41/34)	1.35	0.93, 1.95	1.26	0.86, 1.83	137/201 (67/61)	1.29
Football (Soccer)	66/82 (21/14)	1.43	0.97, 2.10	1.40	0.95, 2.06	57/73 (28/22)	1.35
Cricket	52/103 (16/17)	0.88	0.60, 1.30	0.83	0.56, 1.23	46/88 (23/27)	0.88
Basketball/Netball	80/176 (25/29)	0.96	0.66, 1.40	0.98	0.67, 1.43	15/22 (7/7)	1.02
Cycling	27/37 (8/6)	1.38	0.81, 2.36	1.32	0.77, 2.25	18/22 (9/7)	1.38
Running	38/49 (12/8)	1.45	0.91, 2.33	1.48	0.92, 2.38	28/31 (14/9)	1.52
Athletetics	31/46 (10/8)	1.12	0.68, 1.83	1.08	0.66, 1.78	19/28 (9/8)	0.93
Tennis	92/193 (29/32)	0.96	0.70, 1.32	0.94	0.69, 1.30	56/94 (28/28)	0.97
Swimming	41/73 (13/12)	1.09	0.71, 1.67	1.05	0.68, 1.62	21/29 (10/9)	1.03
Hockey	47/96 (15/16)	1.03	0.69, 1.54	1.03	0.68, 1.54	19/28 (9/8)	1.23
Volleyball	7/15 (2/2)	0.71	0.27, 1.84	0.62	0.24, 1.62	4/4 (2/1)	1.22
Badminton	24/50 (7/8)	1.03	0.61, 1.74	1.02	0.60, 1.74	11/17 (5/5)	1.23
Table tennis	11/22 (3/4)	1.16	0.54, 2.50	1.10	0.51, 2.36	6/14 (3/4)	0.88
Lawn Bowl	14/36 (4/6)	0.85	0.44, 1.63	0.83	0.43, 1.61	7/21 (3/6)	0.71
Boxing	6/8 (2/1)	1.53	0.50, 4.65	1.46	0.48, 4.45	6/7 (3/2)	1.93
Golf	39/59 (12/10)	1.36	0.87, 2.13	1.38	0.88, 2.16	29/40 (14/12)	1.33
Gymnastics	16/29 (5/5)	1.06	0.55, 2.04	0.99	0.51, 1.92	7/9 (3/3)	1.51
Horse riding	7/10 (2/2)	1.57	0.57, 4.31	1.42	0.51, 3.93	3/3 (1/1)	1.87
Walking	12/22 (4/4)	1.18	0.56, 2.48	1.17	0.55, 2.48	2/7 (1/2)	0.52
Tramping	13/20 (4/3)	1.37	0.65, 2.89	1.45	0.68, 3.07	7/12 (3/4)	1.17
Softball	22/39 (7/6)	0.99	0.56, 1.75	0.98	0.55, 1.73	11/15 (5/5)	1.04
Surfing	8/10 (2/2)	1.21	0.46, 3.20	1.12	0.42, 2.97	6/8 (3/2)	0.94
Yachting	4/16 (1/3)	0.40	0.13, 1.25	0.40	0.13, 1.25	3/15 (1/5)	0.27
Rowing	8/23 (2/4)	0.50	0.22, 1.17	0.49	0.21, 1.14	7/20 (3/6)	0.53
Diving	4/8 (1/1)	0.78	0.22, 2.70	0.78	0.22, 2.74	4/7 (2/2)	0.86
Skiing	10/18 (3/3)	1.00	0.44, 2.27	0.96	0.42, 2.21	8/10 (4/3)	0.97
Endurance sports activities[b]	61/71 (19/12)	1.57	1.06,2.33*	1.50	1.01, 2.22*	45/47 (22/14)	1.52
Types of Endurance sports activities							
Marathons[c]	46/58 (14/10)	1.36	0.88, 2.11	1.30	0.83, 2.01	35/39 (17/12)	1.31
Full Marathons only	29/30 (9/5)	1.66	0.95, 2.88	1.63	0.93, 2.84	23/22 (11/7)	1.49
Other running	9/8 (3/1)	2.06	0.77, 5.51	2.05	0.77, 5.49	6/4 (3/1)	2.16
Cycling[d]	6/12 (2/2)	0.96	0.35, 2.65	0.87	0.31, 2.40	3/9 (1/3)	0.64
Others	3/2 (1/0)	1.72	0.28, 0.72	1.71	0.27, 11.0	3/2 (1/1)	1.75

Note: OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption. OR[1]: adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, head injury, spine injury & emotional trauma.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Analyses of never/ever of different types of sports was based on cases +controls ≥10 participants.

[b] Sports with great physical effort ('Have you ever engaged in a sport that required great physical effort, for instance running a marathon?').

[c]Marathons included a full marathon, full ironman, triathlon, half marathon & half ironman.

[d]Cycling includes both mountain biking and road biking, but the majority was road biking.

*$p < .05$.

95% CI	OR[1]	95% CI	Female cases/controls (118/273) N %	OR	95% CI	OR[1]	95% CI
Reference	1	Reference	6/30 (5/11)	1	Reference	1	Reference
0.80, 3.68	1.63	0.76, 3.51	112/243 (95/89)	2.48	0.98, 6.28	2.38	0.93, 6.09
Reference	1	Reference	6/30 (5/11)	1	Reference	1	Reference
0.57, 3.35	1.33	0.55, 3.21	24/58 (20/21)	2.20	0.78, 6.20	2.15	0.76, 6.11
0.45, 7.00	1.64	0.41, 6.51	6/11 (5/4)	3.54	0.88, 14.2	3.42	0.84, 14.0
0.83, 3.87	1.70	0.79, 3.69	82/174 (69/64)	2.52	0.99, 6.44	2.40	0.93, 6.21
0.88, 1.90	1.23	0.83, 1.83	3/3 (3/1)	1.92	0.36, 10.2	1.67	0.30, 9.13
0.88, 2.07	1.33	0.87, 2.04	9/9 (8/3)	2.43	0.87, 6.79	2.25	0.79, 6.38
0.58, 1.36	0.85	0.55, 1.31	6/15 (5/5)	0.81	0.29, 2.26	0.72	0.25, 2.03
0.49, 2.11	1.03	0.49, 2.16	65/154 (55/56)	0.90	0.57, 1.44	0.93	0.58, 1.49
0.69, 2.74	1.33	0.67, 2.66	9/15 (8/5)	1.20	0.48, 3.00	1.10	0.44, 2.76
0.85, 2.71	1.57	0.87, 2.83	10/18 (8/7)	1.25	0.52, 3.01	1.14	0.46, 2.83
0.49, 1.76	0.87	0.46, 1.67	12/18 (10/7)	1.43	0.62, 3.29	1.56	0.67, 3.63
0.63, 1.47	0.92	0.60, 1.42	36/99 (31/36)	0.91	0.55, 1.51	0.95	0.57, 1.59
0.55, 1.92	1.00	0.53, 1.88	20/44 (17/16)	1.11	0.60, 2.05	1.06	0.57, 1.98
0.64, 2.36	1.24	0.65, 2.39	28/68 (24/25)	0.90	0.53, 1.52	0.88	0.51, 1.50
0.27, 5.40	1.11	0.25, 4.90	3/11 (3/4)	0.36	0.08, 1.64	0.30	0.07, 1.35
0.54, 2.82	1.19	0.52, 2.75	13/33 (11/12)	0.91	0.45, 1.87	0.94	0.45, 1.96
0.32, 2.43	0.87	0.31, 2.39	5/8 (4/3)	1.67	0.51, 5.40	1.44	0.44, 4.74
0.28, 1.79	0.69	0.28, 1.73	7/15 (6/5)	1.09	0.41, 2.89	1.16	0.43, 3.10
0.59, 6.29	1.89	0.58, 6.16	0/1 (0/0)	—	—	—	—
0.78, 2.29	1.33	0.77, 2.29	10/19 (8/7)	1.49	0.63, 3.50	1.61	0.68, 3.82
0.53, 4.34	1.53	0.52, 4.46	9/20 (8/7)	1.00	0.41, 2.45	0.87	0.35, 2.17
0.35, 10.2	1.80	0.33, 9.96	4/7 (3/3)	1.53	0.41, 5.69	1.30	0.34, 4.98
0.10, 2.79	0.45	0.08, 2.44	10/15 (8/5)	1.53	0.62, 3.75	1.74	0.70, 4.33
0.43, 3.20	1.22	0.44, 3.36	6/8 (5/3)	2.16	0.68, 6.84	2.20	0.69, 7.08
0.44, 2.45	1.04	0.44, 2.45	11/24 (9/9)	1.04	0.47, 2.29	0.98	0.44, 2.21
0.30, 2.91	0.91	0.29, 2.85	2/2 (2/1)	2.25	0.29, 17.6	1.54	0.20, 12.2
0.07, 1.00	0.27	0.07, 1.01	1/1 (1/0)	1.69	0.08, 37.6	2.05	0.09, 47.0
0.21, 1.30	0.52	0.21, 1.29	1/3 (1/1)	0.73	0.07, 7.48	0.66	0.06, 7.07
0.23, 3.13	0.89	0.24, 3.31	0/1 (0/0)	-	-	-	-
0.36, 2.62	0.96	0.35, 2.62	2/8 (2/3)	0.77	0.15, 4.00	0.64	0.12, 3.58
0.94, 2.46	1.46	0.90, 2.37	16/24 (14/9)	1.52	0.72, 3.17	1.43	0.67, 3.03
0.77, 2.22	1.25	0.73, 2.13	11/19 (9/7)	1.24	0.53, 2.91	1.19	0.50, 2.84
0.78, 2.87	1.47	0.76, 2.84	6/8 (5/3)	1.74	0.56, 5.49	1.70	0.53, 5.44
0.58, 8.08	2.15	0.58, 8.01	3/4 (3/1)	1.71	0.36, 8.18	1.70	0.35, 8.28
0.16, 2.49	0.57	0.14, 2.26	3/3 (3/1)	2.08	0.38, 11.50	1.86	0.33, 10.4
0.27, 11.4	1.80	0.27, 11.9	1/0 (1/0)	—	—	—	—

TABLE 5 Risk of motor neurone disease with emotional trauma in a population-based case–control study, New Zealand, 2013–2016

Exposure	All cases/ controls (321/605) *N* %	OR	95% CI	OR[1]	95% CI	Male cases/ controls (203/332) *N* %	OR	95% CI	OR[1]	95% CI	Female cases/ controls (118/273) *N* %	OR	95% CI	OR[1]	
Emotional trauma (life events)															
Never	77/169 (24/28)	1	Reference	1	Reference	56/102 (28/31)	1	Reference	1	Reference	21/67 (18/25)	1	Reference	1	Reference
Ever	244/436 (76/72)	1.23	0.89, 1.71	1.17	0.84, 1.63	147/230 (72/69)	1.14	0.76, 1.71	1.11	0.74, 1.69	97/206 (82/75)	1.41	0.79, 2.49	1.27	0.71, 2.28
Number of different categories of life events reported															
None	77/169 (24/28)	1	Reference	1	Reference	56/102 (28/31)	1	Reference	1	Reference	21/67 (18/25)	1	Reference	1	Reference
One	68/194 (21/32)	0.78	0.53, 1.17	0.77	0.52, 1.15	42/101 (21/31)	0.71	0.43, 1.18	0.71	0.42, 1.19	26/90 (22/33)	0.87	0.44, 1.72	0.82	0.41, 1.64
Two	76/114 (24/19)	1.55	1.02, 2.34*	1.51	1.00, 2.29*	51/54 (25/16)	1.8	1.06, 3.06*	1.84	1.08, 3.15*	25/60 (21/22)	1.22	0.60, 2.49	1.11	0.54, 2.29
Three	36/57 (11/9)	1.28	0.77, 2.15	1.23	0.73, 2.07	21/38 (10/11)	0.89	0.46, 1.72	0.84	0.43, 1.63	15/19 (13/7)	2.31	0.95, 5.62	2.37	0.96, 5.82
Four or more	64/71 (20/12)	2.06	1.30, 3.26*	1.88	1.17, 3.03*	33/34 (16/10)	1.81	0.97, 3.39	1.76	0.92, 3.34	31/37 (26/14)	2.79	1.32, 5.88*	2.30	1.06, 5.00*
Life event categories															
Life-threatening illness	113/183 (35/30)	1.34	1.00, 1.81*	1.26	0.92, 1.71	69/109 (34/33)	1.16	0.79, 1.71	1.12	0.74, 1.68	44/74 (37/27)	1.58	0.97, 2.56	1.37	0.81, 2.31
Life-threatening accident	62/99 (19/16)	1.10	0.76, 1.60	0.88	0.59, 1.30	47/66 (23/20)	1.09	0.70, 1.72	0.94	0.58, 1.53	15/33 (13/12)	1.34	0.67, 2.69	1.03	0.47, 2.27
Physically forced in a robbery	22/20 (7/3)	2.04	1.06, 3.91*	1.90	0.95, 3.80	16/17 (8/5)	1.67	0.79, 3.53	1.65	0.73, 3.73	6/3 (5/1)	5.22	1.18, 23.11*	4.44	0.87, 22.71
Loss of close relation to accident/ homicide/ suicide	81/113 (25/19)	1.46	1.04, 2.05*	1.39	0.98, 1.98	48/60 (24/18)	1.50	0.95, 2.35	1.32	0.81, 2.13	33/53 (28/19)	1.51	0.89, 2.55	1.64	0.92, 2.92
Miscarriage (women only)											44/75 (37/27)	1.65	1.01, 2.70*	1.58	0.92, 2.72
Physically forced to have sex	14/28 (4/5)	1.01	0.50, 2.02	0.77	0.36, 1.64	3/4 (1/1)	1.26	0.27, 5.97	1.53	0.27, 8.63	11/24 (9/9)	1.10	0.49, 2.49	0.58	0.22, 1.55
Sexual harassment	24/46 (7/8)	1.08	0.63, 1.85	0.80	0.45, 1.43	6/10 (3/3)	1.07	0.37, 3.14	0.86	0.26, 2.79	18/36 (15/13)	1.10	0.58, 2.12	0.74	0.35, 1.55
Been beaten in childhood	57/52 (18/9)	2.13	1.40, 3.25*	1.82	1.14, 2.90*	36/31 (18/9)	2.13	1.22, 3.71*	2.10	1.16, 3.83*	21/21 (18/8)	2.61	1.30, 5.24*	2.06	0.88, 4.82
Been beaten in adulthood	37/44 (12/7)	1.48	0.91, 2.41	1.04	0.61, 1.77	23/20 (11/6)	1.82	0.94, 3.53	1.43	0.71, 2.91	14/24 (12/9)	1.04	0.47, 2.26	0.53	0.20, 1.40
Bullied by a close relation	49/59 (15/10)	1.73	1.13, 2.65*	1.44	0.88, 2.34	20/23 (9/7)	1.31	0.68, 2.53	1.10	0.54, 2.25	29/36 (25/13)	2.09	1.16, 3.77*	1.81	0.87, 3.78
Threatened with a weapon	30/54 (9/9)	0.93	0.57, 1.53	0.64	0.37, 1.10	18/36 (9/11)	0.66	0.35, 1.25	0.42	0.21, 0.87	12/18 (10/7)	1.64	0.71, 3.79	1.15	0.43, 3.12

TABLE 5 (Continued)

Exposure	All cases/ controls (321/605) N %	OR	95% CI	OR[1]	95% CI	Male cases/ controls (203/332) N %	OR	95% CI	OR[1]	95% CI	Female cases/ controls (118/273) N %	OR	95% CI	OR[1]	
Witness of killing/ serious injury/ assault	60/69 (19/11)	1.64	1.11, 2.44*	1.40	0.91, 2.16	43/53 (21/16)	1.44	0.89, 2.31	1.32	0.79, 2.22	17/16 (14/6)	2.94	1.35, 6.42*	2.68	1.06, 6.76*
Seriously injured or life was in danger	22/37 (7/6)	1.15	0.65, 2.03	1.06	0.58, 1.95	16/23 (8/7)	1.21	0.60, 2.43	1.29	0.60, 2.77	6/14 (5/5)	0.90	0.31, 2.60	0.40	0.11, 1.43
Extremely frightening situation	48/61 (15/10)	1.47	0.97, 2.23	1.21	0.77, 1.92	28/36 (14/11)	1.17	0.67, 2.03	0.92	0.50, 1.69	20/25 (17/9)	1.90	0.97, 3.70	1.43	0.66, 3.13

Notes: OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.
OR[1] adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, head injury, spine injury, and mutually adjusted for other emotional traumas (for analyses on specific life event categories only).
Abbreviations: CI, confidence interval; OR, odds ratio.
* $p < .05$.

4.1 | Head injury

Having had multiple head injuries with concussion was associated with a twofold risk of MND. These findings are consistent with several meta-analyses[24–27] reporting increased MND risk for head injury, and particularly for repeated head injuries.[25] It has been argued that this may, at least in part, be due to reverse causation[23] as accidents and injuries may be an early manifestation of MND. Our findings did not change after excluding head injuries that occurred 3 years before the index date, suggesting that reverse causation is unlikely to explain our findings.

A recent meta-analysis[24] showed that severe head injury was associated with a higher risk of MND. We did not observe a clear association with injury severity, although misclassification due to the self-reported nature of the injury severity may have contributed to this. However, several reports have suggested that repetitive mild traumatic brain injuries alone could be sufficient to trigger the physiological changes required to increase the risk of MND.[36–38] Head trauma is known to disrupt and deteriorate the blood–brain barrier,[39] which may play a role in MND pathogenesis.[40,41] In ALS animal models, traumatic brain injury has been found to trigger TAR DNA-binding protein 43 (TDP-43) associated pathology, which is a neuropathological hallmark lesion in the brain of patients with ALS.[42] TDP-43 pathology has also been shown in the brains of athletes that experienced repetitive head injury.[37]

In this study population, head injury with a concussion most commonly occurred as part of leisure sports (9% of male and 3% of female controls reported at least one sport-related head injury) and having more than one sport-related head injury was associated with a threefold MND risk. This identifies leisure sports as an important setting of preventable head injury that may be contributing to MND risk.

4.2 | Sports

In this study participating in sports throughout childhood and adulthood was associated with an increased risk for MND, which is consistent with several previous studies.[11,12,34,43] The association between physical activities and the risk of MND is biologically plausible as vigorous exercise may induce oxidative stress and glutamate excitotoxicity, two well-established mechanisms for MND.[44]

MND risk differed by the type of sport played. For many individual sports, we did not observe an increase in MND risk, including cricket, basketball/netball, tennis, swimming, hockey, volleyball, badminton, lawn bowl, yachting, rowing, diving and skiing. Taking part in endurance sports (when considered collectively) was associated with an increased MND risk, but when considering specific endurance sports separately, none of the associations reached statistical significance. A number of common sports in New Zealand were associated with elevated ORs that did not reach statistical significance, including rugby, football (soccer), running and golf.

Only for playing football (soccer), we observed a statistically significant positive association with duration, with a twofold MND risk for those who played football (soccer) >12 years. This is of interest, as several studies[5,45,46] have reported an increased MND risk for professional football (soccer) players. This study adds to this body of

TABLE 6 Risk of motor neurone disease with childhood physical abuse in a population-based case–control study, New Zealand, 2013–2016

Exposure	All cases/controls (321/605) *N* %	OR	95% CI	OR[1]	95% CI	Male cases/controls (203/332)*N* %	OR
Age when been beaten							
Never	264/553 (82/91)	1	Reference	1	Reference	167/301 (82/91)	1
Age <7	30/28 (10/5)	2.04	1.17, 3.58*	1.83	0.99, 3.37	18/13 (9/4)	2.39
Age 7+	27/24 (8/4)	2.23	1.24, 4.03*	1.81	0.97, 3.39	18/18 (9/5)	1.93
Frequency							
Never	264/553 (82/91)	1	Reference	1	Reference	167/301 (82/91)	1
Once	2/8 (1/1)	0.51	0.10, 2.52	0.42	0.08, 2.08	1/4 (0/1)	0.42
2–4 times	8/3 (2/1)	6.84	1.74, 26.9*	5.72	1.41, 23.24*	6/1 (3/0)	14.73
5–10 times	11/11 (3/2)	1.68	0.70, 4.03	1.44	0.58, 3.58	8/9 (4/3)	1.58
>10 times	36/30 (11/5)	2.32	1.36, 3.95*	2.04	1.13, 3.66*	21/17 (10/5)	2.23
Duration							
Never	264/553 (82/91)	1	Reference	1	Reference	167/301 (82/91)	1
<6 months	7/9 (2/1)	1.42	0.50, 3.99	1.36	0.47, 3.89	6/5 (3/2)	1.79
6 month to 2 years	6/4 (2/1)	3.04	0.81, 11.45	2.71	0.70, 10.42	5/3 (2/1)	3.26
3–4 years	4/11 (1/2)	0.66	0.20, 2.15	0.44	0.13, 1.52	1/9 (0/3)	0.22
5–8 years	24/19 (7/3)	2.59	1.36, 4.94*	2.26	1.14, 4.49*	16/11 (8/3)	2.78
>8 years	16/9 (5/2)	3.30	1.40, 7.82*	3.01	1.18, 7.70*	8/3 (4/1)	4.64
Reported injury							
Never	264/553 (82/91)	1	Reference	1	Reference	167/301 (82/91)	1
Injured	25/25 (8/4)	2.07	1.12, 3.81*	1.73	0.88, 3.40	12/12 (6/4)	2.04
Not injured	32/27 (10/4)	2.18	1.26, 3.78*	1.89	1.06, 3.38*	24/19 (12/6)	2.18
Method							
Never	264/553 (82/91)	1	Reference	1	Reference	167/301 (82/91)	1
Fist	8/6 (2/1)	3.01	0.98, 9.31	3.09	0.95, 10.05	5/4 (2/1)	2.93
Belt	16/14 (5/2)	2.22	1.03, 4.77*	2.03	0.91, 4.53	9/9 (4/3)	1.58
Stick	16/11 (5/2)	3.08	1.37, 6.91*	2.57	1.10, 5.97*	9/8 (4/2)	2.35
Other	4/5 (1/1)	1.38	0.36, 5.35	1.09	0.25, 4.76	3/2 (1/1)	3.13
Smacking on the hands	3/9 (1/1)	0.59	0.15, 2.28	0.47	0.12, 1.91	3/5 (1/2)	1.02
Combine (fist, belt, stick)	10/7 (3/1)	2.55	0.92, 7.08	1.76	0.60, 5.13	7/3 (3/1)	4.02

Notes: OR adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption.

OR[1] adjusted age, gender (for analyses combining males and females), education, ethnicity, socioeconomic status (SES), smoking, alcohol consumption, sport, head injury, spine injury, and mutually adjusted for other emotional traumas.

Abbreviations: CI, confidence interval; OR, odds ratio.

* $p < .05$.

evidence and suggests that non-professional football (soccer) may also increase the risk of MND.

The association observed for football (soccer) may be mediated through strenuous physical activities and/or head injury.[5,26] As our analyses were adjusted for head injury with a concussion, diagnosed concussions are unlikely to explain the observed association. Therefore, with football (soccer) being the only sport in which players purposefully use the head to deflect the ball, and it emerging as the only specific sport associated with an increased risk in our study, a role for sub-concussive impacts to the head in football (soccer) players cannot be excluded,[5,47] and merits further study.

4.3 | Emotional trauma

In the current study, elevated risks were associated with having experienced more than two different types of traumatic life events, with an almost twofold risk associated with having experienced four or more types of traumatic life events. An Australian ALS case–control study,[30] which used a checklist for potentially stressful life events as part of an anonymous online questionnaire, found no difference in life events inventory scores between cases and controls, but results for specific traumatic life events were not presented. We are not aware of other studies that evaluated

95% CI	OR[1]	95% CI	Female cases/controls (118/273) *N* %	OR	95% CI	OR[1]	95% CI
Reference	1	Reference	97/252 (82/92)	1	Reference	1	Reference
1.10, 5.21*	2.41	1.06, 5.52*	12/15 (10/6)	2.17	0.93, 5.06	1.61	0.58, 4.46
0.93, 4.00	1.88	0.87, 4.08	9/6 (8/2)	3.65	1.18, 11.23*	3.13	0.87, 11.21
Reference	1	Reference	97/252 (82/92)	1	Reference	1	Reference
0.04, 3.92	0.42	0.04, 4.10	1/4 (1/1)	0.78	0.08, 7.62	0.47	0.04, 5.49
1.69, 128.65*	12.07	1.36, 107.25*	2/2 (2/1)	3.05	0.37, 25.18	3.02	0.33, 27.49
0.57, 4.40	1.44	0.50, 4.15	3/2 (3/1)	3.65	0.54, 24.90	4.14	0.51, 33.68
1.08, 4.62*	2.39	1.09, 5.26*	15/13 (13/5)	2.89	1.27, 6.60*	2.15	0.78, 5.93
Reference	1	Reference	97/252 (82/92)	1	Reference	1	Reference
0.53, 6.11	1.96	0.55, 6.95	1/4 (1/1)	0.79	0.08, 7.64	0.75	0.07, 7.93
0.70, 15.28	3.08	0.63, 15.01	1/1 (1/0)	2.67	0.13, 54.01	2.55	0.13, 48.43
0.03, 1.82	0.17	0.02, 1.46	3/2 (3/1)	3.57	0.52, 24.56	3.31	0.37, 29.64
1.20, 6.45*	2.82	1.16, 6.84*	8/8 (7/3)	2.92	1.03, 8.27*	2.08	0.60, 7.14
1.14, 18.99*	4.78	1.07, 21.3*	8/6 (7/2)	2.96	0.92, 9.49	2.30	0.59, 8.99
Reference	1	Reference	97/252 (82/92)	1	Reference	1	Reference
0.83, 5.04	2.01	0.77, 5.27	13/13 (11/5)	2.66	1.09, 6.51*	2.10	0.70, 6.30
1.13, 4.21*	2.16	1.07, 4.35*	18/8 (7/3)	2.53	0.88, 7.28	2.01	0.63, 6.46
Reference	1	Reference	97/252 (82/92)	1	Reference	1	Reference
0.70, 12.37	3.21	0.69, 14.99	3/2 (3/1)	4.79	0.71, 32.55	5.27	0.63, 44.10
0.59, 4.28	1.85	0.66, 5.20	7/5 (6/2)	3.61	1.04, 12.57*	2.90	0.69, 12.20
0.83, 6.63	2.22	0.75, 6.57	7/3 (6/1)	7.01	1.68, 29.19*	6.35	1.31, 30.82*
0.50, 19.59	2.50	0.32, 19.46	1/3 (1/1)	0.67	0.06, 7.12	0.80	0.07, 9.87
0.23, 4.61	0.85	0.18, 4.07	0/4 (0/1)				
0.94, 17.14	3.84	0.87, 17.02	3/4 (3/1)	1.42	0.28, 7.29	0.45	0.07, 3.00

the association between traumatic life events and MND. Our findings show some parallels with a Japanese study,[13] which found that self-reported stress and type A behaviour pattern (related to emotional distress and to more keenly perceived life stress) were associated with an increased ALS risk. Emotional trauma has also been proposed as a risk factor for other neurodegenerative diseases, including Alzheimer disease[48] and Parkinson disease,[49] and mechanistic studies have demonstrated that psychological stress is associated with increased oxidative stress,[28,50] which plays an important role in the pathology of neurodegenerative diseases including MND.[51]

It cannot be fully excluded that self-reports of traumatic events may systematically differ between cases and controls, either because of differences in recall, or because of possible differences in personality type and the perception of life stress between cases and controls, as suggested by the Japanese study.[13] Our relative risk estimates for specific categories of traumatic events, which identified childhood physical abuse as a risk factor for MND, are, however, less

likely to be affected by this, as these were adjusted for the report of all other categories of traumatic events.

It is possible that physical trauma, including head injury, may play a role in the observed associations for emotionally traumatic events and MND, as several of the emotional trauma categories relate to physical violence that may result in physical trauma. In particular, we observed a twofold MND risk for having experienced physical abuse as a child. This association was consistently observed for both males and females, and risks increased for higher frequency, as well as longer duration of child abuse. While this association was adjusted for self-reported head injuries with concussion, physical child abuse may result in undiagnosed and unreported physical trauma that could not be taken into account in this study. A role for emotional trauma cannot be excluded either, as similar ORs were observed for physical child abuse with and without physical injury. While the underlying contributing factors could not be identified, this new finding warrants further research.

5 | CONCLUSIONS

This study supports earlier findings that repeated head injury with concussion and playing leisure sports in general and football (soccer) in particular are associated with an increased risk of MND, and suggests, for the first time, a possible role for physical child abuse in the development of MND. The observed associations are complex and inter-connected because both sports and emotional trauma may also involve physical trauma including head injury. These findings merit further scrutiny in future studies, as they may provide important opportunities for MND prevention and add to our understanding of the aetiological mechanisms involved in MND.

ACKNOWLEDGEMENTS

We are grateful to the Motor Neurone Disease Association New Zealand, and their field staff for their generous support. We would also like to thank Michelle Gray, Di Marshal, Heather Duckett, Deirdre Thurston, Aly Timmings, for their help with conducting interviews.

The study was funded by a grant from the Health Research Council (HRC) of New Zealand (Part of 11/1041 HRC Programme Grant—Building Research in Occupational Health in New Zealand [BROHNZ]). Open access publishing facilitated by Massey University, as part of the Wiley - Massey University agreement via the Council of Australian University Librarians. [Correction added on 14 May 2022, after first online publication: CAUL funding statement has been added.]

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ane.13615.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Chen GX, Douwes J, van den Berg LH, Glass B, McLean D, 't Mannetje AM. Sports and trauma as risk factors for Motor Neurone Disease: New Zealand case–control study. *Acta Neurol Scand*. 2022;*145*:770–785. doi:10.1111/ane.13615