Family Medicine and Community Health

Associations between concussion and risk of diagnosis of psychological and neurological disorders: a retrospective population-based cohort study

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ABSTRACT

Objective To investigate associations between concussion and the risk of follow-up diagnoses of attention-deficit hyperactivity disorder (ADHD), mood and anxiety disorders (MADs), dementia and Parkinson's disease.

Design A retrospective population-based cohort study.

Setting Administrative health data for the Province of Manitoba between 1990–1991 and 2014–2015.

Participants A total of 47 483 individuals were diagnosed with a concussion using International Classification of Diseases (ICD) codes (ICD-9-CM: 850; ICD-10-CA: S06.0). All concussed subjects were matched with healthy controls at a 3:1 ratio based on age, sex and geographical location. Associations between concussion and conditions of interest diagnosed later in life were assessed using a stratified Cox proportional hazards regression model, with adjustments for socioeconomic status and pre-existing medical conditions.

Results 28 021 men (mean age ±SD, 25±18 years) and 19 462 women (30±21 years) were included in the concussion group, while 81 871 men (25±18 years) and 57 159 women (30±21 years) were included in the matched control group. Concussion was associated with adjusted hazard ratios of 1.39 (95% CI 1.32 to 1.46, p<0.001) for ADHD, 1.72 (95% CI 1.69 to 1.76; p<0.001) for MADs, 1.72 (95% CI 1.61 to 1.84; p<0.001) for dementia and 1.57 (95% CI 1.41 to 1.75; p<0.001) for Parkinson's disease.

Conclusion Concussion was associated with an increased risk of diagnosis for all four conditions of interest later in life.

Key points

Question

- Our research sought to investigate the relationships between concussion-specific injuries and psychological and neurological disorders using 25 years of population-based administrative health data, in a large sample of more than 47 000 cases of concussion.

Findings

- Concussion was associated with an increased risk of diagnosis of attention-deficit hyperactivity disorder, mood and anxiety disorders, dementia and Parkinson's disease later in life.

Meaning

- Our findings suggest that concussion may be a risk factor for the development of comorbid conditions in the years following initial injury in the cohort examined in this study.

INTRODUCTION

Concussions are a potentially debilitating injury and have shown a steady increase in incidence over recent years—namely, in adolescents.[1] Concussion-related pathophysiological impairments are believed to include dysregulation of the autonomic nervous system,[2] cerebral blood flow[3 4] and cerebral metabolism,[5] and are thought to be the impetus for development of symptoms following concussion.[6] Despite clinical recovery from concussion typically occurring within the first week of injury,[7] long-term pathological disturbances may persist beyond this point[4]; the prolonged implications of which remain unknown. Previous research has identified associations between head injuries and an increased risk of attention-deficit hyperactivity disorder (ADHD),[8] depression,[9–11] anxiety,[12] Alzheimer's disease/dementia[13] and Parkinson's disease (PD),[14] however many of these studies are limited by a number of factors; most notably a reliance on self-reported medical history[9–11] and the inclusion of all forms of traumatic brain injuries.[12–14] Other common limitations include a failure to account for either pre-existing health conditions,[9–11] the time between incident concussion and subsequent diagnosis of conditions of interest,[9–11] or the occurrence of repeat mild traumatic brain injuries/concussions.[11–14] Given the diagnosis of concussion can be difficult and is often missed or not reported, a more robust understanding of

concussion and associated risks has the potential to aid primary care and family medicine physicians in understanding and managing the long-term needs of their patients.

Therefore, the primary objective of our study was to elucidate the associations between concussion and subsequent diagnoses of ADHD, mood and anxiety disorders (MADs), dementia and PD. Secondary research objectives focused on investigating the effects of sex, multiple concussions, diagnosis of other conditions of interest in time to follow-up and time under study on the associations between concussion and the conditions of interest.

METHODS

Study design and setting

We conducted a retrospective population-based cohort study using province-wide medical health data that was collected on a fiscal basis (1 April to 31 March) from 1990–1991 to 2014–2015 (inclusive). The study was conducted

Table 1 Demographic data of control and concussion groups by sex

	Control		Concussion	
Demographic data	**Men**	**Women**	**Men**	**Women**
Age, mean (SD), years	25 (18)	30 (21)	25 (18)	30 (21)
SEFI-2, mean (SD)	−0.04 (1.02)	−0.05 (1.00)	−0.05 (1.02)	−0.04 (1.00)
CCI, mean (SD)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.3 (0.7)
Number of individuals included by fiscal year, n (%)	**Men (81 871)**	**Women (57 159)**	**Men (28 021)**	**Women (19 462)**
1990–1991	3111 (3.8)	2076 (3.6)	1043 (3.7)	697 (3.6)
1991–1992	3297 (4.0)	2100 (3.7)	1108 (4.0)	704 (3.6)
1992–1993	2952 (3.6)	1824 (3.2)	997 (3.6)	615 (3.2)
1993–1994	2869 (3.5)	1855 (3.2)	972 (3.5)	626 (3.2)
1994–1995	2837 (3.5)	1917 (3.4)	966 (3.4)	648 (3.3)
1995–1996	2867 (3.5)	1815 (3.2)	976 (3.5)	618 (3.2)
1996–1997	2599 (3.2)	1613 (2.8)	889 (3.2)	548 (2.8)
1997–1998	2556 (3.1)	1595 (2.8)	872 (3.1)	541 (2.8)
1998–1999	2909 (3.6)	1757 (3.1)	997 (3.6)	601 (3.1)
1999–2000	3151 (3.8)	1877 (3.3)	1082 (3.9)	642 (3.3)
2000–2001	3628 (4.4)	2098 (3.7)	1253 (4.5)	717 (3.7)
2001–2002	3161 (3.9)	1994 (3.5)	1089 (3.9)	685 (3.5)
2002–2003	3464 (4.2)	2035 (3.6)	1190 (4.2)	695 (3.6)
2003–2004	3288 (4.0)	2153 (3.8)	1140 (4.1)	733 (3.8)
2004–2005	3405 (4.2)	2073 (3.6)	1174 (4.2)	712 (3.7)
2005–2006	3253 (4.0)	2247 (3.9)	1121 (4.0)	768 (3.9)
2006–2007	3167 (3.9)	2265 (4.0)	1089 (3.9)	777 (4.0)
2007–2008	3060 (3.7)	2222 (3.9)	1058 (3.8)	762 (3.9)
2008–2009	2801 (3.4)	2306 (4.0)	969 (3.5)	785 (4.0)
2009–2010	2806 (3.4)	2258 (4.0)	963 (3.4)	771 (4.0)
2010–2011	3382 (4.1)	2467 (4.3)	1159 (4.1)	840 (4.3)
2011–2012	4431 (5.4)	3115 (5.4)	1518 (5.4)	1060 (5.4)
2012–2013	4097 (5.0)	3291 (5.8)	1409 (5.0)	1123 (5.8)
2013–2014	4335 (5.3)	3852 (6.7)	1478 (5.3)	1316 (6.8)
2014–2015	4445 (5.4)	4354 (7.6)	1509 (5.4)	1478 (7.6)
Number of secondary condition diagnoses, n (%)	**Men**	**Women**	**Men**	**Women**
Attention-deficit hyperactivity disorders	3453 (4.2)	927 (1.6)	1674 (6.0)	594 (3.1)
Mood and anxiety disorders	13 524 (16.5)	16 277 (28.5)	7823 (27.9)	8856 (45.5)
Dementia	1159 (1.4)	1592 (2.8)	779 (2.8)	943 (4.8)
Parkinson's disease	423 (0.5)	560 (1.0)	276 (1.0)	327 (1.7)

CCI, Charlson Comorbidity Index; SEFI-2, Socioeconomic Factor Index - version 2.

Table 2 Hazard ratios for risk of attention-deficit hyperactivity disorder diagnosis

Age at diagnosis	Mean±SD		
Control	17.2±11.7		
Concussion	17.8±11.9		
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.40 (1.33 to 1.47)	<0.001	1.39 (1.32 to 1.46)	<0.001
Model 2a		**Model 2b**	
1.29 (1.14 to 1.45)	<0.001	1.28 (1.14 to 1.45)	<0.001
Model 3a		**Model 3b**	
1.39 (1.32 to 1.46)	<.001*	1.38 (1.31 to 1.45)	<.001*
1.20 (0.98 to 1.48)	0.08†	1.20 (0.97 to 1.47)	0.09†
0.92 (0.51 to 1.67)	0.78‡	0.94 (0.52 to 1.70)	0.83‡
Model 4a		**Model 4b**	
1.28 (1.21 to 1.35)	<0.001	1.27 (1.21 to 1.34)	<0.001
Model 5a		**Model 5b**	
1.01 (1.00 to 1.02)	0.23	1.01 (1.00 to 1.02)	0.30

Model 1a, Cox proportional HR adjusted for age, sex and geographical location via stratified analysis. Model 1b, model 1a plus adjustment for socioeconomic status and comorbidities. Model 2a, sex-interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 2b, model 2a plus adjustment for socioeconomic status and comorbidities. Model 3a, multiple concussion HR adjusted for age, sex and geographical location via stratified analysis. Model 3b, model 3a plus adjustment for socioeconomic status and comorbidities, Model 4a, control for occurrence of other outcomes of interest between index date and date of outcome of interest in question adjusted for age, sex and geographical location via stratified analysis. Model 4b, model 4a plus adjustment for socioeconomic status and comorbidities. Model 5a, time under study interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 5b, model 5a plus adjustment for socioeconomic status and comorbidities.
For both models 3a and 3b: *HR of 1 concussion vs 0 concussions; †HR of 2 concussions vs 1 concussion; ‡HR of 3+ concussions vs 2 concussions.

within the Manitoba Centre for Health Policy (MCHP), a research unit at the University of Manitoba in Winnipeg, Manitoba, Canada, which houses data pertaining to residents of Manitoba (excluding federally funded individuals) in various healthcare, education, social, justice and registry databases.[15] Date of incident concussion served as an individual's study start time, and a 3:1 matched control group was used for comparison. Both control and concussion groups comprised 59% men and had an average age of 25±18 years for men and 30±21 years for women once included in the study.

Data source

De-identified population-based administrative health data were accessed from the following databases housed within the Manitoba Population Research Data Repository at MCHP: Manitoba Health Insurance Registry, Medical Services, Hospital Abstracts and Drug Program Information Network. Nearly every Manitoba resident has a unique personal health identification number (PHIN) that can be used to create a longitudinal record of a person's medical history. The following individual-level information was linked via scrambled PHIN and then extracted:

- Individuals diagnosed with a concussion
- Subsequent diagnosis of ADHD, MADs, dementia and/or PD

Subjects

Residents were included in the study if they received an International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) code 850[16] or International Classification of Diseases, 10th Revision, Canada (ICD-10-CA) code S06.0[17] from 1990–1991 to 2014–2015 (inclusive). A 1-year washout period was used prior to the start of the study (1989–1990) for individuals with an incident concussion in 1990–1991, and successive concussion diagnoses separated by <2 months were considered a single event. Individuals in the concussion group were excluded if they had a diagnosis of dementia or PD prior to incident concussion during the study time period.

Cases of ADHD, MADs, dementia and PD were identified using either ICD-9-CM or ICD-10-CA codes, and/or medication prescription data, as previously established by MCHP (online supplementary methods appendix 1).[18–21]

A matched group of individuals was assembled for comparisons using a 3:1 ratio to help minimise the effects of bias and attrition[22] and was based on age (birth year), sex and geographical location (first three digits of postal code). Controls were selected for each case from all people in the registry who were alive on the date of concussion of the matched case. This date, whether for a case or control is referred to as the index date. Individuals were eligible for this matched group if they were free

Table 3 Hazard ratios for risk of mood and anxiety disorder diagnosis

Age of diagnosis	Mean±SD		
Control	36.5±19.1		
Concussion	36.0±18.2		
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.75 (1.71 to 1.78)	<0.001	1.72 (1.69 to 1.76)	<0.001
Model 2a		**Model 2b**	
1.07 (1.03 to 1.12)	<0.001	1.07 (1.03 to 1.11)	0.001
Model 3a		**Model 3b**	
1.74 (1.71 to 1.78)	<.001*	1.72 (1.69 to 1.75)	<.001*
1.04 (0.96 to 1.13)	0.35†	1.04 (0.96 to 1.13)	0.31†
1.16 (0.95 to 1.42)	0.14‡	1.17 (0.96 to 1.43)	0.12‡
Model 4a		**Model 4b**	
1.73 (1.70 to 1.77)	<0.001	1.71 (1.68 to 1.75)	<0.001
Model 5a		**Model 5b**	
0.96 (0.95 to 0.96)	<0.001	0.96 (0.95 to 0.96)	<0.001

Model 1a, Cox proportional HR adjusted for age, sex and geographical location via stratified analysis. Model 1b, model 1a plus adjustment for socioeconomic status and comorbidities. Model 2a, sex-interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 2b, model 2a plus adjustment for socioeconomic status and comorbidities. Model 3a, multiple concussion HR adjusted for age, sex and geographical location via stratified analysis. Model 3b, model 3a plus adjustment for socioeconomic status and comorbidities, Model 4a, control for occurrence of other outcomes of interest between index date and date of outcome of interest in question adjusted for age, sex and geographical location via stratified analysis. Model 4b, model 4a plus adjustment for socioeconomic status and comorbidities. Model 5a, time under study interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 5b, model 5a plus adjustment for socioeconomic status and comorbidities.
For both models 3a and 3b: *cHR of 1 concussion vs 0 concussions; †HR of 2 concussions vs 1 concussion; ‡HR of 3+ concussions vs 2 concussions.

of diagnosis of concussion during the study time period, while also free of diagnosis of dementia and PD prior to the index date.

Outcomes

The time from the index date to the date of subsequent coding for ADHD, MADs, dementia and/or PD, or date of the end of insurance coverage in the registry, was identified to calculate a time to follow-up (time under study) for each outcome of interest. The primary statistic of interest was the hazard ratio between those with a concussion and their matched controls for all conditions of interest.

Statistical analyses

Cox proportional hazards regression models were constructed to model the time to outcome of interest from the index date. Subjects were censored if they died, were lost to follow-up, moved out of province or reached the study end date without receiving a diagnosis for any of the conditions of interest.

Two potential confounding variables were controlled for, including:

- Socioeconomic Factor Index, version 2 (SEFI2): a measure of socioeconomic status that was defined at index date, whereby a lower score is indicative of more favourable socioeconomic conditions.[23] Census variables that make-up the SEFI2 scores include[23]:
  - Unemployment rate at age >15
  - Average household income at age >15
  - Proportion of single parent households
  - Proportion of population age >15 without high-school graduation.
- Charlson Comorbidity Index (CCI): a score that categorises an individual's pre-existing medical conditions using ICD codes was defined at the index date, with a score of zero representing an absence of comorbidities.[24 25]

Five hazard ratio models were included in analyses for each condition of interest. The first model was a crude Cox proportional hazards regression analysis with a binary indicator for concussion, calculated independently from potential modifying variables (model 1). The second model included a sex-interaction variable (men as reference group) to examine the effect of sex in those who had a concussion, as sex-based analyses were limited to subjects diagnosed with a concussion due to sex being part of the matching process (model 2). The third model included a time-varying covariate to assess the effect of multiple concussions (model 3). The fourth model aimed at controlling for the occurrence of the other conditions of interest within the time to follow-up of the condition in question by creating a time-varying covariate (model 4). The fifth model included time under study and

Table 4 Hazard ratios for risk of dementia diagnosis

Age of diagnosis			
	Mean±SD		
Control	73.8±19.3		
Concussion	71.0±19.6		
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.75 (1.63 to 1.87)	<0.001	1.72 (1.61 to 1.84)	<0.001
Model 2a		**Model 2b**	
0.95 (0.83 to 1.09)	0.49	0.93 (0.82 to 1.07)	0.33
Model 3a		**Model 3b**	
1.70 (1.59 to 1.82)	<.001*	1.67 (1.56 to 1.79)	<.001*
1.63 (1.26 to 2.11)	<0.001†	1.62 (1.25 to 2.10)	<0.001†
1.19 (0.62 to 2.28)	0.60‡	1.20 (0.63 to 2.30)	0.60‡
Model 4a		**Model 4b**	
1.55 (1.45 to 1.67)	<0.001	1.54 (1.43 to 1.65)	<0.001
Model 5a		**Model 5b**	
0.97 (0.97 to 0.98)	<0.001	0.97 (0.97 to 0.98)	<0.001

HR, hazard ratio. 95% CI, 95% confidence interval. N/S, not significant. Model 1a, Cox proportional HR adjusted for age, sex and geographical location via stratified analysis. Model 1b, model 1a plus adjustment for socioeconomic status and comorbidities. Model 2a, sex-interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 2b, model 2a plus adjustment for socioeconomic status and comorbidities. Model 3a, multiple concussion HR adjusted for age, sex and geographical location via stratified analysis. Model 3b, model 3a plus adjustment for socioeconomic status and comorbidities, Model 4a, control for occurrence of other outcomes of interest between index date and date of outcome of interest in question adjusted for age, sex and geographical location via stratified analysis. Model 4b, model 4a plus adjustment for socioeconomic status and comorbidities. Model 5a, time under study interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 5b, model 5a plus adjustment for socioeconomic status and comorbidities.
For both models 3a and 3b: *HR of 1 concussion vs 0 concussions; †HR of 2 concussions vs 1 concussion; ‡HR of 3+ concussions vs 2 concussions.

concussion status as an interaction variable to assess the proportionality assumption (model 5). All five models used a stratified analysis based on a grouping variable created by combining subjects' age at the index date, sex and first three digits of their area code, allowing for comparisons between a greater number of subjects with the same age, sex and postal code (model a). Further subanalyses of all five models added control for SEFI2 and CCI in addition to model a (model b).

Finally, two sensitivity analyses were performed. The first was to assess the effect of age at the time of incident concussion on risk of diagnosis for each condition of interest, as various conditions are more prevalent in different age groups.[26 27] The second was to assess the association between concussion and risk of diagnosis of conditions of interest for incident concussions occurring before 1998, and during and after 1998. It remains possible that a number of concussions could have been either missed or misdiagnosed prior to the establishment of rudimentary guidelines in 1998.[28] Additionally, the severity of injury as it pertains to concussion could have had a greater impact prior to these guidelines, as there was a greater focus on loss of consciousness and/or post-traumatic amnesia.[29] As such, associations between concussion and the conditions of interest may be altered depending on the year of diagnosis of incident concussion. Cox proportional hazard ratios were calculated using SAS software version 9.4 (SAS Institute Inc., USA). A significance level of p<0.05 was used for all statistical tests.

RESULTS

Baseline characteristics and number of diagnoses are shown in table 1.

A breakdown of matching, number of concussions, number of diagnoses of conditions of interest by age at incident concussion and other descriptive results can be found in online supplementary results appendix 2.

Results for analyses controlling for SEFI2 and CCI will be presented in this section. Full results can be found in tables 2–5.

Concussion was associated with an increased risk of diagnosis of ADHD (HR=1.39; 95% CI 1.32 to 1.46), MADs (HR=1.72; 95% CI 1.69 to 1.76; p<0.001), dementia (HR=1.72; 95% CI 1.61 to 1.84; p<0.001) and PD (HR=1.57; 95% CI 1.41 to 1.75; p<0.001). Concussed women had a higher risk of diagnosis of ADHD and MADs by 28% (table 2) and 7% (table 3), respectively, as compared with concussed men. No effect of sex was noted for diagnosis of dementia or PD in concussed individuals. Multiple concussions had no additive effect on

Table 5 Hazard ratios for risk of Parkinson's disease diagnosis

Age of diagnosis			
	Mean±SD		
Control	62.0±17.5		
Concussion	59.6±17.3		
Model 1a		**Model 1b**	
HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
1.61 (1.45 to 1.80)	<0.001	1.57 (1.41 to 1.75)	<0.001
Model 2a		**Model 2b**	
0.94 (0.76 to 1.16)	0.56	0.94 (0.76 to 1.16)	0.55
Model 3a		**Model 3b**	
1.58 (1.42 to 1.76)	<.001*	1.54 (1.38 to 1.72)	<.001*
1.11 (0.70 to 1.76)	0.67†	1.11 (0.70 to 1.76)	0.67†
2.91 (1.28 to 6.65)	0.01‡	2.96 (1.29 to 6.77)	0.01‡
Model 4a		**Model 4b**	
1.31 (1.17 to1.46)	<0.001	1.28 (1.15 to 1.44)	<0.001
Model 5a		**Model 5b**	
0.98 (0.98 to 1.02)	0.81	0.98 (0.98 to 1.02)	0.88

Model 1a, Cox proportional HR adjusted for age, sex and geographical location via stratified analysis. Model 1b, model 1a plus adjustment for socioeconomic status and comorbidities. Model 2a, sex-interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 2b, model 2a plus adjustment for socioeconomic status and comorbidities. Model 3a, multiple concussion HR adjusted for age, sex and geographical location via stratified analysis. Model 3b, model 3a plus adjustment for socioeconomic status and comorbidities, Model 4a, control for occurrence of other outcomes of interest between index date and date of outcome of interest in question adjusted for age, sex and geographical location via stratified analysis. Model 4b, model 4a plus adjustment for socioeconomic status and comorbidities. Model 5a, time under study interaction HR adjusted for age, sex and geographical location via stratified analysis. Model 5b, model 5a plus adjustment for socioeconomic status and comorbidities.
For both models 3a and 3b: *HR of 1 concussion vs 0 concussions; †HR of 2 concussions vs 1 concussion; ‡HR of 3+ concussions vs 2 concussions.

associations with risk of diagnosis of ADHD, whereas a second concussion further increased the strength of association with risk of diagnosis of dementia above a single concussion (HR for 2 vs 1 concussion: 1.62; 95% CI 1.25 to 2.10) (table 4). Exposure to more than 3 concussions increased the strength of association with risk of diagnosis of MADs (HR for >3 vs 1 concussion: 1.22; 95% CI 1.01 to 1.47) and PD (HR for >3 vs 1 concussion: 3.27; 95% CI 1.63 to 6.59) beyond the risk induced by a single concussion (online supplementary results appendix 2). Controlling for diagnosis of any of the three remaining conditions of interest between the index date and diagnosis of the condition in question lowered the concussion-associated risk of diagnosis of ADHD by 9% (table 2), MADs by 0.6% (table 3), dementia by 10% (table 4) and PD by 18% (table 5) (these numbers were derived from tables 2-5 by subtracting model 1b from model 4b and dividing by model 1b). There was an effect of time under study (time between index date and diagnosis of the condition in question) on the association between concussion and subsequent diagnosis of MADs (HR=0.96; 95% CI 0.95 to 0.96; table 3), and dementia (HR=0.97; 95% CI 0.97 to 0.98; table 4). Time under study did not alter the association between concussion and risk of diagnosis of ADHD, or PD. Results from the first sensitivity analysis revealed similar associations between concussion and risk of diagnosis of MADs among all age groups, whereas younger age groups appear to be at greater risk of ADHD, and older age groups more at risk for dementia and PD (online supplementary results appendix 2). Results from the final sensitivity analysis showed an effect of year of diagnosis of incident concussion on the association between concussion and risk of diagnosis of MADs and dementia, such that those with incident concussion diagnosed during or after 1998 had a higher risk of diagnosis for either condition of interest compared with those with incident concussion diagnosed before 1998 (online supplementary results appendix 2).

DISCUSSION

The major findings from this retrospective population-based cohort study are the associations between the occurrence of concussion and an increased risk of diagnosis of ADHD, MADs, dementia and PD by factors of 1.4, 1.7, 1.7 and 1.6, respectively. Moreover, these findings were minimally affected when controlling for socioeconomic status (SEFI-2) and overall health status (CCI).

Comparisons are difficult to make with other studies, given the limited number of studies using similar methodologies. Nevertheless, our results are similar to those from studies with a focus on concussion-specific injuries that

were identified from medical registries.[8 12 13 30] However, our study includes individuals of all ages and not select age groups.[8 13 30] Our results, which suggest stronger associations between concussion and risk of diagnosis of ADHD and MADs for women than for men, are difficult to compare with previous research given the paucity of information in this area. The increased strength of association between multiple concussions and risk of diagnosis of MADs, dementia and PD as compared with a single concussion are similarly difficult to compare with previous research.

Earlier findings indicate that comorbidity exists between the conditions of interest included in the present study,[31–36] owing, in part, to a commonality in symptoms.[37–40] Thus, our results indicating a decrease in strength of association between concussion and risk of diagnosis of the condition in question by up to 19% when adjusting for the diagnosis of one of the other conditions of interest in the time to follow-up are not unexpected. While these findings support the idea of comorbidity between conditions, concussion continued to be associated with an increased risk of diagnosis for all four conditions of interest, suggesting that concussion may therefore be a risk factor for ADHD, MADs, dementia and PD, regardless of the presence of comorbid conditions. Unfortunately, the specific mechanisms resulting in these changes in strength of association are unknown, but it remains possible that dysregulation of pathways of various biomarkers involved in the conditions of interest in the present study—namely, cortisol, may also be affected following a concussion.[41–43]

Previous research has identified a decrease in strength of association between mild traumatic brain injuries and subsequent risk of diagnosis of either MADs[12] or dementia[13] as the time between diagnoses increases. We report similar findings, although specific for concussions and with a more gradual decrease in association over time, likely attributable to the differences in injury severity between studies.

The results from the first sensitivity analysis indicating that concussion-associated risk of diagnosis of ADHD was stronger for younger age groups and that older age-groups had stronger associations between concussion and risk of diagnosis of either dementia or PD are not unexpected. Indeed, ADHD is more prevalent in younger people,[27] whereas dementia and PD typically affect older individuals.[26] Results from the second sensitivity analysis revealed stronger associations between concussion and risk of diagnosis of MADs and dementia for incident concussions diagnosed during or after 1998 compared with those diagnosed before 1998. These differences are probably a byproduct of an increased number of diagnoses in recent years— namely, in adolescents,[1 40] which itself may be partially attributed to improved awareness and knowledge of concussions and their associated signs and symptoms.[44] It is also possible that advancements in clinical diagnostic parameters have contributed to these findings.[6 45]

Limitations

One of the limitations with the present study is that ICD-9-CM codes from the Medical Services database are restricted to the first three digits. It is therefore possible that some individuals may have experienced injuries more severe than a concussion. In order to mitigate any effect this might have had on our results, medical records indicating a concussion were limited to in-office visits, where the likelihood of a serious traumatic event is minimal.

Another limitation is that medical data was restricted to the years 1990–1991 to 2014–2015 (inclusive). We were therefore limited in our ability to account for each individual's previous medical history. Thus, CCI was included as a surrogate measure of health status and included in our analyses as a confounding variable.

The authors acknowledge the potential genetic and familial aspects of concussion[46] and the various outcomes discussed in the present study,[47–51] but the assessment of such factors was beyond the scope of this study.

The data in this study do not include post-mortem diagnoses. Although it is possible that various conditions may be diagnosed after death, it is believed that the number of diagnoses made post mortem would not significantly change our results.

Some of the data included in our study may pertain to individuals who were not born in the Province of Manitoba but moved to Manitoba later in life, potentially leading to an under-reporting of concussions and/or conditions of interest. Follow-up analyses have shown that the date of health insurance coverage was the same as an individual's date of birth for ~50% of individuals in both the matched control and concussion groups, mitigating any impact on our findings.

CONCLUSION

The findings from this study demonstrate an association between the occurrence of concussion and an increased risk of diagnosis of ADHD, MADs, dementia and PD later in life. As our results are specific to the administrative health data used for the present study, future studies exploring the relationships between concussion and ADHD, MADs, dementia and PD in other populations are warranted. Moreover, future studies could expand on our findings by including chart reviews to confirm clinical diagnoses of concussion, adjusting for familiality of conditions of interest, and long-term prospective follow-up of individuals following incident concussion.

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