Concussion in adolescence and risk of multiple sclerosis

Running head: Concussion and MS

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Character count: title (46); running head (15)
Word count: abstract (249); introduction (425); discussion (1721); body (3587)
Number of tables: 2

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/ana.25036

Objective: To assess whether concussion in childhood or adolescence is associated with subsequent multiple sclerosis risk. Previous research suggests an association but methodological limitations included retrospective data collection and small study populations.

Methods: The national Swedish Patient (hospital diagnoses) and Multiple Sclerosis registers were used to identify all MS diagnoses up to 2012 among people born from 1964, when the Patient Register was established. The 7292 patients with multiple sclerosis were matched individually with 10 people without MS by sex, year of birth, age/vital status at multiple sclerosis diagnosis, and region of residence (county), resulting in a study population of 80212. Diagnoses of concussion and control diagnoses of broken limb bones were identified using the Patient Register from birth to age 10 years or from ages 11 to 20 years. Conditional logistic regression was used to examine associations with multiple sclerosis.

Results: Concussion in adolescence was associated with a raised risk of multiple sclerosis, producing adjusted odds ratios (and 95% confidence intervals) of 1.22 (1.05-1.42, p=0.008) and 2.33 (1.35-4.04, p=0.002) for one diagnosis of concussion, or more than one diagnosis of concussion, respectively, compared with none. No notable association with multiple sclerosis was observed for concussion in childhood, or broken limb bones in childhood and adolescence.

Interpretation: Head trauma in adolescence, particularly if repeated, is associated with a raised risk of future multiple sclerosis, possibly due to initiation of an autoimmune process in the central nervous system. This further emphasises the importance of protecting young people from head injuries.

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS), where genetic and environmental factors conspire to influence risk. One suggested trigger for the pathological process is non-specific damage to the nervous system such as brain concussion or head trauma,[1] including as a result of participation in boxing,[2] liberating CNS components such as neurofilament light (NFL) into the cerebrospinal fluid, which eventually may reach the systemic compartment including lymph nodes; then adaptive immunity to CNS components can be activated either in CNS draining lymph nodes or in the CNS itself.[3]

Two systematic reviews and meta-analysis of physical trauma and MS risk reported statistically significant associations from high quality case-control studies,[1] but the pooled results from cohort studies are not statistically significant.[1 4] In one review exclusion of lower quality case-control studies resulted in non-statistically significant pooled odds ratios, leading the authors to conclude the evidence was insufficient to confirm a causal link between traumatic injury and MS.[4] There is therefore clearly a need for further high-quality studies with prospectively recorded exposure data that have sufficient power. There have been relatively few studies of trauma up to age 20 years[1 5-10] and as far as we are aware all have relied on retrospective reporting of earlier trauma, potentially limiting their accuracy. The majority involved substantially fewer than 700 cases and controls, and the largest study was of 5550 participants.[7] Head trauma up to age 20 years is worthy of further study for other reasons: it is more likely to pre-date clinical onset of MS, which tends to occur after age 20 years, while earlier onset is uncommon.[11] There may be age-specific differences in susceptibility to some exposures as childhood and adolescence represent distinct developmental phases of the CNS; and the importance of other specific environmental MS risks appears to vary between childhood and adolescence.[12]

To the best of our knowledge, this is the largest study of traumatic head injury before age 20 years and subsequent MS risk; and notably, the first to use prospectively recorded data thus enhancing accuracy. We used Swedish register data, separating traumatic brain injury between childhood (from birth to age 10 years) and adolescence (ages 11 to 20 years). Rather than examining all head trauma, we focused on a diagnosis of concussion as this is more likely to identify involvement of the CNS. We also identified multiple episodes of trauma to determine if there is a dose-dependent association. To estimate the possible importance of non-CNS trauma in the same age groups, we used control diagnoses of broken limb bones.

Subjects and Methods

Ethics statement

The study was approved by the research ethics committee of Karolinska Institutet.

All diagnoses of MS in Sweden recorded in the Patient Register or the MS Register were identified between 1964 and 2012 using ICD codes (ICD-10 G35; ICD-9 and ICD-8 340). In this population, the majority of individuals with MS appeared in both sources so the first diagnosis was used. The Patient Register has recorded inpatient diagnoses since 1964 and outpatient diagnoses since 2001, with complete national coverage achieved by 1987.[13 14] The coverage of the MS Register has increased steadily since its initiation in 1996[15] and has a high degree of diagnostic accuracy for MS:[16] informed consent is required for inclusion in this register. Men and women with a first MS diagnosis after age 20 years were matched individually with 10 people without MS by year of birth and age/vital status at MS diagnosis (the comparators were alive when the diagnosis was made), sex and region of residence (county). Those with and without MS were only included if they did not immigrate or

emigrate to or from Sweden between birth and MS onset, as indicated by the Total Population Register,[17] which provides information on demographic characteristics, including migration, vital status and region of residence. The study comprises 7,292 with MS and 72,920 without.

Exposure Measures

Concussion was identified from hospital inpatient and outpatient diagnoses using ICD codes (ICD-10 S06.0; ICD-8 and ICD-9 850; ICD-7 852). Upper and lower limb fractures were identified similarly (ICD-10 S42, S52, S62, S72, S82 and S92; ICD-7, ICD-8 and ICD-9 810-819, 820-829). Diagnoses were characterised as occurring in childhood from birth to age 10 years, or in adolescence between ages 11 and 20 years. The number of diagnoses was summed in each group and categorised as none, one and two or more. To be considered as a separate episode, diagnoses had to be at least three months apart during the relevant age-range.

Potential Confounding Factors

Age, sex and region of residence are taken into account by the matched structure of the data and the analysis. Level of education measured nearest in time to first MS diagnosis (and the same date in the individually matched comparators) was obtained from national census data, from 1980 or 1985, and subsequently data were obtained on an annual basis from the LISA database (*Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier*: Longitudinal integrated database for sickness insurance and labour market studies). Educational level was categorised into compulsory education or below; post-compulsory secondary school education; post-compulsory further or higher education (post-school college or university); and education data not available.

Statistical Analysis

The distributions of the variables of those with and without MS were investigated using cross-tabulation and statistical significance assessed using the χ^2 test. The main analysis used conditional logistic regression, taking into account the risk-set structure, to examine the associations of concussion and broken limb bones in childhood and adolescence with MS diagnosed after age 20 years. The adjusted model included the measures of concussion and limb trauma for ages birth to 10 years and 11 to 20 years, as well as level of education.

A sensitivity analysis was performed to assess whether associations with MS for exposures in adolescence were due to injuries in late adolescence resulting in neurological examinations that uncovered MS incidentally, resulting in an MS diagnosis in the early twenties thus creating a spurious association resulting from surveillance bias. Therefore, patients with MS diagnoses by age 30 years were excluded. The model contained the other covariates used in the analysis.

Duration of hospital admission for concussion was used as marker of severity. Diagnoses in outpatient settings were combined with inpatient admissions of up to one day; and longer hospital admission was categorised based on the distribution, as two days, and three days or longer. These three categories were compared with the group who did not have a concussion diagnosis. Number of concussion diagnoses was not taken into account and this analysis was only performed for concussion between ages 11 and 20 years. To assess trend for duration of hospital admission for concussion with MS risk, those without concussion were excluded and trend for MS risk was estimated among those with MS onset after age 20 years and their matched controls.

Statistical significance was defined as 95% confidence intervals not including 1.00 or $p<0.05$. The analysis was conducted using Stata statistical software, version 14).[18]

Results

The study population is characterised by a higher proportion of women consistent with the sex ratio in MS (table 1). The distributions of year of birth and age at MS diagnosis are consequences of the design to identify exposures in childhood and adolescence and MS diagnoses after age 20 years, as well as the initiation date for Swedish registers used here. Each of the 7292 patients with MS was successfully matched with 10 individuals without MS, so that there is no difference in the distributions for sex, year of birth and year of diagnosis/matching. There is some difference in level of education, such that further/higher education is associated with a lower MS risk, but this is not statistically significant.

Table 2 shows that neither concussion nor limb trauma in childhood (birth to age 10 years) were associated with MS. However, concussion but not limb trauma, in adolescence (ages 11 to 20 years) is statistically significantly associated with subsequent MS and demonstrates a dose-dependent association, with a higher magnitude association with MS for two or more diagnoses of concussion in adolescence, with adjusted odds ratios (and 95% confidence intervals) of 1.22 (1.05-1.42, p=0.008) for one diagnosis of concussion and 2.33 (1.35-4.02, p=0.002). The influence of incomplete coverage by the Patient Register during the earlier part of the study period was assessed by examining for those born before and after 1970. For those born in 1970 or before (n=34,419), the unadjusted odds ratios for the association of concussion in adolescence with MS are 1.29 (1.01-1.66, p=0.046) for one concussion and

1.89 (0.55-6.49, p=0.311) for two or more. For those born after 1970 (n=45,793) the odds ratios are 1.19 (1.00-1.44, p=0.057) for one concussion and 2.47 (1.34-4.52, p=0.004) for two or more. Lower statistical significance is due largely to dividing the study population into two. Compared with post-compulsory school education, further/higher education is associated with a non-statistically significant reduced MS risk, and the adjusted odds ratio is 0.95 (0.91-1.00, p=0.071). Lower educational level is associated with a modest increased risk of head trauma (in adolescence) and also with raised MS risk, so it represents a potential confounding factor. Adjustment for educational level has only a modest impact on odds ratio for the association of concussion in adolescence with MS.

A sensitivity analysis examined whether the association with MS differs for concussion between ages 11 to 15 years or 16 to 20 years: the unadjusted odds ratios for the earlier age are 1.28 (1.05-1.58, p=0.017) for one concussion and 2.94 (1.27-6.82, p=0.012) for two concussions; and at older ages, 1.23 (1.01-1.50, p=0.044) for one concussion and 2.23 (0.76-6.59, p=0.147) for two concussions. Another analysis excluded those who had concussion with limb injuries, but did not alter the results for the association of limb injuries with MS notably (data not shown). Some 64 people had a concussion diagnosis both in adolescence and in earlier childhood: there was no evidence of an interaction influencing MS risk (data not shown).

Another analysis was performed to assess whether exposures in adolescence are associated with MS diagnosed from age 30 years. Despite the notable reduction in statistical power from excluding those with MS diagnosed by age 30 years (and their matched comparators), the association of concussion in adolescence with MS remains statistically significant, with odds ratios of 1.25 (1.03-1.51, p=0.023) and 2.37 (1.15-4.91, p=0.020) for one and two diagnoses

of concussion, respectively, compared with none. There were no other notable changes in the associations (data not shown), except for level of education, which attained statistical significance. Compared with post-compulsory school education, further/higher education is associated with a reduced MS risk, with an adjusted odds ratio of 0.89 (0.79-0.99, p=0.042).

The distribution of hospital admission duration associated with a diagnosis of concussion shows that 1,430 were examined or admitted for up to one day, 323 for two days and 182 for three days or longer. Compared with no diagnosis of concussion, the odds ratios for MS are 1.15 (0.97-1.37, p=0.105), 1.55 (1.12-2.14, p=0.008) and 1.75 (1.16-2.64, p=0.007), respectively. Among those admitted to hospital with concussion, trend testing across the three categories for duration of hospital admission produces a p value of 0.027, constant with an increasing magnitude of association with MS by increasing duration of hospital admission.

Discussion

Using prospectively recorded longitudinal data, concussion in adolescence, particularly among those with more than one concussion diagnosis, was found to be associated with a raised risk of subsequent MS in a dose-dependent manner. Concussion in childhood up to age 10 years was not associated with MS risk. Broken limb bones were examined to eliminate the possibility that all physical trauma represents a raised MS risk, but neither broken limb bones in childhood nor adolescence were associated with MS.

It is plausible that head injuries affecting the CNS can increase the risk of MS. The evidence includes experimental results showing primarily non-inflammatory insults to the nervous system can lead to expansion of myelin-antigen-specific T cells which been show to result in encephalomyelitis if the genetic requirements for autoimmune disease are present.[19 20] Non-

specific insults such as stroke or even peripheral nerve biopsy is accompanied by expanded numbers of myelin-antigen reactive T cells producing pro-inflammatory cytokines such as interferon-γ.[21 22] It has been demonstrated that interferon-γ may induce apoptosis of oligodendrocytes and this is consistent with the pattern of damage to the CNS in MS.[23] However, a study of experimental autoimmune encephalomyelitis indicated that the main influence of interferon-γ is severe suppression of re-myelination, through its influence on re-myelinating oligodendrocytes, rather than on developing or mature oligodendrocytes.[24] Interferon-γ expression following CNS trauma could in theory be implicated in the pathogenesis of MS, but its precise role is not entirely clear.

This study did not have a systematic measure of concussion severity, but used duration of hospital admission as an indicator: however, this is a crude indicator as other trauma-related injuries will influence medical care. Despite this, greater severity signalled by duration of admission was associated with greater MS risk. Concussion results in neuroinflammation that can persist after the injury.[25] Despite the indication of greater risk of MS associated with more severe trauma, more minor CNS trauma may still increase risk as there are ongoing inflammatory and cerebral injury processes that occur even after mild head trauma resulting from sporting participation.[26] This, coupled with the evidence from sports with a high risk of head trauma such as boxing,[2] indicate the potential role of sporting injuries in adolescence as a risk for MS. In theory, it may be possible to reduce the risk of delayed adverse outcomes, such as MS, following a traumatic injury to the CNS through therapies to reduce inflammation.[27]

To test the hypothesis that traumatic injuries of the CNS by age 20 years influence MS risk, we focused on diagnoses of concussion in childhood and adolescence. Concussion is a

relatively common diagnosis and more specific to the CNS than general head injuries. Concussion is less likely than more severe forms of brain injury to require long-term follow-up and neuroimaging, reducing the possibility of incidental diagnoses of subclinical MS in the years after the injury. To investigate the possible role of non-CNS trauma we examined the association of limb bone fractures with MS risk. While a broken leg or arm bone does not exclude entirely contemporaneous head injury and an influence on the CNS, this is less likely than for a head injury that may (or may not) involve the brain. We also modelled limb injury and concussion separately and together (in the unadjusted and adjusted analysis, respectively) and found no evidence that trauma to the limbs in childhood or adolescence was associated with subsequent MS risk. It is important to rule out the possibility of reverse causation as milder physical manifestations of preclinical MS that may exist in adolescence[28] could potentially increase the risk of accidents and trauma. As there is no risk associated with broken limb bones, reverse causation seems to be an unlikely explanation for the association with concussion. An important strength of our approach is that we examined exposures at an age prior to typical MS onset, making it more likely that they could influence pathogenesis. Another significant methodological advantage of this study, unlike previous studies of exposures at these ages,[1 5-10] is use of prospectively recorded diagnoses retrieved from general population registers. This will have reduced problems of reporting bias, where cases invest more effort in reporting prior events and recall bias, which can be a particular problem for poorly remembered events from early childhood.

Surveillance bias may potentially influence the results, where concussion results in neurological examinations leading to a diagnosis of subclinical MS, even if the resulting diagnoses is some months after the injury due to time required for diagnostic work-up and referrals. In the main analysis, the first diagnosis of MS occurred from age 21 years, but a

sensitivity analysis excluded all those with an MS diagnosis up to age 30 years. Despite the loss of statistical power resulting from exclusion of over 40% of the study population, concussion in adolescence remained statistically significantly associated with increased MS risk in later adulthood, suggesting that this potential source of surveillance bias is unlikely to explain the results. As always with observational studies the possibility of other potential sources of confounding exists. Lower level of education has been associated with an increased risk of MS, and this is not fully explained by known risk factors such as smoking, lower vitamin D status history of infectious mononucleosis and body mass.[29] As educational level is associated many lifestyle factors, potentially including behaviour relevant to trauma risk, we adjusted for education in our analysis, but it had little influence on the results. An advantage of education over measures of material and cultural circumstances based on employment, is that education in the majority is completed at a relatively young age likely to pre-date MS onset after age 20 years as investigated here and thus less likely to be a consequence of MS.

The association with MS for concussion in adolescence but not childhood deserves consideration. This could be because the number of children who had any diagnoses of concussion by age 10 years was lower than during adolescence and there may also be differences in severity of trauma between the age groups. Another possibility is that adolescence represents periods of greater susceptibility to concussion than earlier childhood. Such an age-specific pattern is observed for other exposures such as Epstein-Barr virus infection, which tends to be asymptomatic in childhood, but associated with infectious mononucleosis and a raised risk of MS when the infection occurs in adolescence and subsequently.[30] Other evidence that adolescence represents a period of raised susceptibility for some exposures includes for adolescent obesity[31] which, particularly in interaction with HLA risk genes,[32] is associated with subsequent MS. It is speculated that inflammation

associated with adipose tissue may influence disease pathogenesis.[32] In a sensitivity analysis, concussion in early and late adolescence was examined separately, but provided no clear evidence of a difference in MS risk.

The magnitude of MS risk associated with a single episode of concussion in adolescence is modest, although persuasively statistically significant. Two or more episodes of concussion are rather infrequent in this population but represent a higher magnitude risk for MS, possibly due to exacerbation of the process initiated by the first trauma. However, it should be noted that only a small proportion of MS risk is explained by our measure of hospital-treated concussion, even though this does not rule out the possibility of far commoner milder head injuries not identified here influencing MS risk.

This study has some potential limitations. We chose concussion as is a distinct diagnostic entity, but other diagnoses for CNS trauma were not included, so our estimates of risk associated with head trauma are conservative. Also, we did not investigate other types of potentially relevant injuries, such as to the spinal cord,[33] again, probably underestimating the role of trauma as a risk for MS. Similarly, people with concussion receiving specialised hospital care may identify a subset of diagnoses with the possibility of bias associated with severity or comorbidity and as even mild head trauma is associated with ongoing inflammatory processes.[26] We are likely to have incomplete ascertainment of potentially relevant injuries as many episodes of CNS trauma would not have been diagnosed formally and not included in the Patient Register. Such undiagnosed CNS trauma may be overrepresented among those with broken limb bones, so adjustment could in theory reduce the observed magnitude of association with concussion (this does not appear to represent a substantial influence in this study). MS has an insidious onset with a subclinical period, so

even though we examined trauma prior to age 20 years and excluded earlier-onset MS, some individuals may have experienced trauma after the disease process had begun, but as discussed above there is no evidence that this produced a spurious association. We focused on exposures in childhood and adolescence, but cannot exclude the possibility that similar exposures at a later age are relevant to MS risk. National Patient Register coverage was incomplete during the earliest portion of the study period, so some exposures in childhood and adolescence will have been missed (reducing the precision of our estimates), although a high proportion of the study population were born at a later date when coverage was more complete. When the sample was split for births up to 1970 or subsequently, by when the majority of Swedish counties (*län*) were covered by the Patient Register,[14] the magnitude of association between concussion in adolescence and MS was somewhat higher for the later period, which is consistent with underestimation of the number of concussion diagnoses during the earlier period. Inpatient treatment for fractures will have been more likely for long bone or more complicated fractures, thus tending to identify more severe injuries than during the later period when outpatient treatment was included; but this is unlikely to have masked an association of general trauma with MS risk. While the Patient Register has some inaccuracies, it is considered acceptable for diagnoses that are not exceedingly rare,[13] and it allowed use of exposure information that was recorded prospectively, often many years prior to MS diagnosis.

Traumatic brain injury signalled by a diagnosis of concussion in adolescence is associated with a raised risk of MS in subsequent adulthood, possibly by causing an expansion of myelin-antigen specific T cells. Repeated mild head trauma has been associated with other delayed neurological outcomes[34] and this study provides yet further evidence of the

importance of protecting young people from traumatic head injury, for example during participation in sports.

Acknowledgements

Funding to obtain and analyse the data was provided by a research grant from F. Hoffmann-La Roche Ltd. and Novartis Pharma AG.

Author Contributions: T. O., L. A., S. Ba. and S. M. specified the hypothesis and developed the study design with A. H. S. Ba., S. Bu., and S. M. acquired the data. The statistical analysis was conducted by A. H., S. Bu., and S. M. The first draft of the manuscript was written by SM, which was then edited by all authors.

Potential Conflicts of Interest: None declared.

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Table 1. Characteristics of the study population

	With MS n (%)	Without MS n (%)	p
Sex			1.000
Male	2166 (29.7)	21660 (29.7)	
Female	5126 (70.3)	51260 (70.3)	
Year of birth			1.000
1961-1970	3129 (42.9)	31290 (42.9)	
1971-1980	3045 (41.8)	30450 (41.8)	
1981-1990	1095 (15.0)	10950 (15.0)	
1991-2000	23 (0.3)	230 (0.3)	
Age at MS diagnosis/matching (years)			1.000
21-30	3000 (41.1)	30000 (41.1)	
31-40	3318 (45.5)	33180 (45.5)	
41-50	974 (13.4)	9740 (13.4)	
Educational level			0.243
Compulsory school	622 (8.5)	6327 (8.7)	
Post-compulsory school	3395 (46.6)	33078 (45.4)	
Further/higher education	3220 (44.2)	32904 (45.1)	
No information on education	55 (0.8)	611 (0.8)	
Total	7292 (100)	72920 (100)	

Table 2. Association with MS after age 20 years for concussion and broken limb bones in childhood and adolescence

	With MS n (%)	Without MS n (%)	Unadjusted OR* (95% CI; p)	Adjusted OR*# (95% CI; p)
Concussion: birth-age 10 years				
None	7179 (98.5)	71747 (98.4)	Reference	Reference
One	109 (1.5)	1127 (1.6)	0.97 (0.79-1.18; 0.735)	0.95 (0.78-1.16; 0.626)
Two or more	4 (0.1)	46 (0.1)	0.86 (0.31-2.41; 0.787)	0.85 (0.31-2.37; 0.761)
Concussion: ages 11-20 years				
None	7075 (97.0)	71202 (97.6)	Reference	Reference
One	201 (2.8)	1649 (2.3)	1.23 (1.06-1.42; **0.007**)	1.22 (1.05-1.42; **0.008**)
Two or more	16 (0.2)	69 (0.1)	2.33 (1.35-4.02; **0.002**)	2.33 (1.35-4.02; **0.002**)
Broken limb bones: birth-age 10 years				
None	7200 (98.7)	72141 (98.9)	Reference	Reference
One	89 (1.2)	757 (1.0)	1.18 (0.94-1.47; 0.145)	1.18 (0.94-1.47; 0.152)
Two or more	3 (0.0)	22 (0.0)	1.37 (0.41-4.56; 0.613)	1.42 (0.42-4.75; 0.570)
Broken limb bones: ages 11-20 years				
None	7100 (97.4)	71043 (97.4)	Reference	Reference
One	177 (2.4)	1703 (2.3)	1.04 (0.89-1.22; 0.625)	1.02 (0.87-1.20; 0.799)
Two or more	15 (0.2)	174 (0.2)	0.86 (0.51-1.46; 0.585)	0.83 (0.49-1.41; 0.495)

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; p, p value.

*The matched analysis accounts for, year of birth, age at MS diagnosis, sex and region of residence.

#Adjustment was for all measures in the table and level of education.