Physical Trauma and Demyelinating Diseases: A Systematic Review and Meta-Analysis

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Abstract

Background: Although several observational studies investigated the relationship between physical trauma and demyelinating diseases, the relationship is still controversial in the literature. Thus, we decided to conduct a systematic review and meta-analysis to investigate this relationship.

Methods: On the 22nd of June 2023, PubMed, Scopus, Web of Sciences, and CENTRAL were searched using terms about demyelinating diseases and physical trauma. Studies were included if they investigated the association between physical trauma and the development of a demyelinating disease.

Results: The total number of the included participants was 2,411,312 from 57 articles. The analysis showed that physical trauma was significantly associated with higher odds of demyelinating disease development (OR=2.51; 95%CI: 1.87-3.37). In addition, both childhood and premorbid traumas were significantly associated with increased risk of demyelinating diseases (OR=2.97; 95%CI: 2.64-3.35, OR=3.51; 95%CI: 2.97-4.14). Fractures (OR=3.17; 95%CI: 2.85-3.52), head (OR=3.61; 95%CI: 2.84-4.59), and spinal traumas (OR=9.06; 95%CI: 1.21-68.01) were significantly associated with increased risk of demyelinating diseases as well.

Conclusion: In conclusion, we found a significant association between physical trauma and the risk of developing demyelinating diseases. However, several gaps in the literature should be addressed by future studies including the low number of studies investigating demyelinating diseases other than MS.

Introduction

Physical trauma is considered one of the largest contributors to the global burden of disease as it accounts for around 12% of the worldwide disease burden [1]. Moreover, injury was demonstrated by several studies to be a substantial cause of morbidity and mortality in the developed and developing world [2-5]. This burden predominantly impacts low- and middle-income countries as the injury-related mortality in these countries is approximately twice that found in high-income countries [1]. Moreover, trauma contributes up to 16% of the global prevalence of disability [6]. Despite the well-established knowledge regarding its significance and the advancements made in trauma prevention programs, injury and its related mortality are still on the rise [1]. Several studies linked trauma to many chronic neuro-

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logical diseases including Parkinson disease, dementia and demyelinating disorders [7-9]. Demyelinating diseases are group of diseases sharing the same pathophysiologic mechanism which mainly involves loss of myelin with relative preservation of the axons [10]. These diseases are considered to evolve due to an interaction between genetic and environmental risk factors [11]. Global surveys showed that the number of people with demyelinating diseases continues to increase. For example, the number of people diagnosed with Multiple Sclerosis (MS), which is considered the most common condition among demyelinating diseases, increased from 2.3 million in 2017 to 2.8 million in 2020 [12]. The clinical manifestations of these diseases are diverse and include weakness, paresthesia, focal sensory loss, optic neuritis, diplopia, ataxia, and vertigo. As a result, these diseases are associated with significant disability and mortality [13]. In addition, they are also associated with high psychological burden as they impact the quality of life across work, school, social, and physical functioning [14]. Several studies evaluated the relationship between premorbid and childhood trauma, and the development of demyelinating diseases [14, 15]. However, the relationship is still controversial as the studies investigating the topic are still evolving [14]. A study conducted in Norway among women with MS included 14,477 patients and found that physical trauma during childhood was associated with increased risk of developing MS [9]. Similarly, a study which was conducted in Germany and included 234 patients with MS demonstrated that childhood trauma was associated with the development of MS [16]. On the other hand, in a study conducted in the US including data from several population-based large cohort studies such as the Minnesota Population with MS found no correlation between childhood trauma and the development or exacerbation of MS [15]. As a result, we decided to conduct this systematic review and meta-analysis aiming to evaluate the association between history of physical trauma and demyelinating diseases. The hypothesis of this study is that the history of physical trauma is significantly associated with the development of demyelinating diseases.

Methods

Protocol and Registration

This study was conducted in concordance with the Cochrane Collaboration Handbook, and it was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [17, 18]. We have registered this study in the International Prospective Register of Systematic Reviews PROSPERO (CRD#42023437938).

Search Strategy

The search was done using the following databases: PubMed, Scopus, Web of Sciences, and The Cochrane Central Register of Controlled Trials (CENTRAL) up to the 22nd of June, 2023. Terms about trauma, and demyelinating diseases were used in the search process. To enhance words selection, the Medical Subject Headings (MeSH) library was used. Moreover, the complete search strategy is described in Methods. The search was performed by AAT and TNA independently and any disagreement regarding the search results was solved by discussion until a consensus was reached. The studies were included if they were: • Observational studies that investigated the association between physical trauma and the development of a demyelinating disease. Non-English articles were also included and translated into English using ChatGPT 3.5. • Clinical trials that investigated the impact of trauma prevention methods on the development of demyelinating diseases. Review studies, editorials and cellular articles were excluded from this study. In addition, any study which did not describe the criteria for diagnosing the demyelinating disease or wherein the diagnosis was not made by

a neurologist was also excluded. Moreover, studies that did not include a description of physical trauma, such as studies with general childhood abuse, were also excluded. Also, articles investigating the association between demyelinating diseases and the risk of subsequent trauma were excluded as they were considered irrelevant to the study aims. The search results and references were imported to Rayyan (https://www.rayyan.ai/), which is an artificial intelligence-powered tool for conducting systematic reviews, where the study selection was done. After deduplication of the articles, the study selection was performed by AAT and TNA independently and any discrepancy in the selection process was solved by discussion until a consensus was reached.

Main Outcomes

The population of interest is adults above the age of 18 years. The exposure of interest was physical trauma while the outcome of interest was the development of demyelinating diseases. Trauma was defined as any physical trauma occurring during childhood (¡20 years of age) or prior to the onset of disease development (premorbid) including head, extremity, and trunk trauma, as well as burns and fractures. Demyelinating disease was defined as any condition involving the loss of myelin with relative preservation of axons, including but not limited to, Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Neuromyelitis Optica (NMO), and Guillain Bare Syndrome (GBS), among others. A prerequisite of the diagnosis of a demyelinating disease was that it must have been done by a neurologist or used one of the clinical criteria to be reached.

Data Extraction and Quality Assessment

The data extraction was done on a preformed spread sheet. The following variables were extracted; title, year of publication, study design, country of origin (referring to the location of the study), primary outcome measure, trauma type, statistical analysis of the primary outcome, and any other noteworthy results. No authors were contacted to obtain additional data from the included articles. The data extraction process was conducted by the same two independent researchers (AAT and TNA), and any disagreements were resolved through discussion until a consensus was reached. To assess the risk of bias in the included studies, the Newcastle-Ottawa Scale (NOS) for observational studies was utilized [19]. This scale provides a framework for evaluating the quality and potential biases in observational study designs. The scale includes 3 components which assess the quality of the study design including selection, comparability, and outcome. The selection component focuses on the sampling procedure and the assessment of the exposure, whereas the comparability component assesses the methods of adjustment for confounding variables in the study. In addition, the outcome component primarily focuses on the assessment of the outcomes. The maximum score which can be achieved in NOS is 9, with any study scoring 7 or higher to be considered of high quality.

Data Analysis

The Odds Ratio (OR) and its related 95% Confidence Intervals (95% CIs) were used as an effect measure to assess the relationship between the exposure and the outcome. Owing to the diversity of the included studies in terms of the study population and methods, the studies were pooled using the random effect model. Sub-group analyses according to the type of physical trauma, onset of trauma, type of demyelinating disease, ethnicity, and high-quality studies (NOS=7–9) were conducted across the outcomes. Statistical heterogeneity was assessed using Cochran's Q heterogeneity test and the I^2 statistic. A funnel plot and Doi plot were used to visually assess publication bias. FinFinally, R and R studio version 4.3.1 were utilized for data analysis using the

following packages: tidyverse, meta, metafor, and dmetar.

Results

Search Results

The search yielded 3,583 articles, of which 994 articles were duplicates. The remaining 2,589 articles were screened using their title and abstract and 2,315 articles were excluded on the grounds of being reviews, editorials, cellular studies or irrelevant. The rest of the articles (274 articles) were tested against the inclusion criteria using their full-text form and 217 article were excluded due to not reporting any data regarding the outcome of interest. Ultimately, 57 studies were included in this systematic review and meta-analysis. The references of the included articles are available as References. Figure 1 describes the detailed selection process.

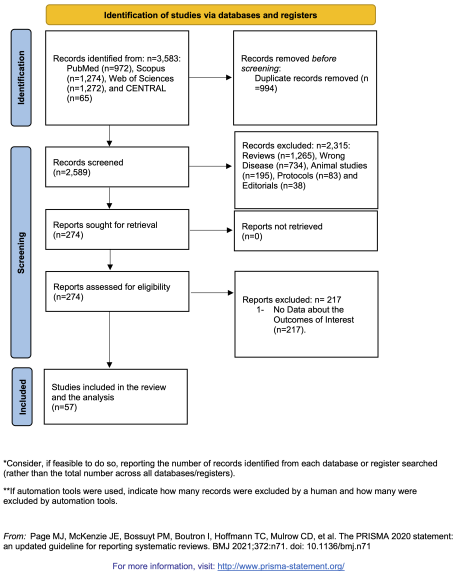

Figure 1: Details of the selection process.

Characteristics of the Included Studies

The total number of the included participants was 2,411,312 from 57 articles. Of those, 5.2% were cases of demyelinating diseases while the rest were healthy controls. Most of the studies were conducted in Europe (46.6%) followed by the Americas (31.0%) and Asia (22.4%). No studies were done in Africa. Forty-seven studies were case control in design while only 9 were cohort studies. Moreover, 44.8% of the studies investigated both premorbid and childhood trauma while 41.4% and 13.8% of the studies individually investigated either premorbid or childhood trauma, respectively. The majority of the studies investigated the impact of trauma on the development of MS (94.8%), whereas only 2 studies investigated its impact on ALS and 1 investigated the relationship between trauma and NMO. No other demyelinating diseases were investigated in the included studies. The female to male ratio among patients with demyelinating diseases was 2.02 while the mean age of diagnosis was 29.23. Table 1 in supplementary material summarizes the characteristics of the included studies.

Quality Assessment

According to NOS, 42.3% of the studies were of high quality (score=7-9) while the rest were of low quality (57.7%). The studies of low quality mainly lost points due to lack of adjustment for confounding bias (96.7%), while 76.6% lost points to poor assessment of the exposure, and 46.7% of them lost points to lack of comprehensive assessment of the outcome. The detailed quality assessment of the included studies is available in Table 2 in supplementary material.

Main Analysis

Regarding the association between physical trauma and the development of demyelinating diseases, 57 articles were included in the

analysis. The analysis showed that physical trauma was significantly associated with higher odds of demyelinating disease development (Figure 2: OR=2.51; 95%CI: 1.87-3.37); the model had insignificant heterogeneity (I2=0%, P-value=1.00).

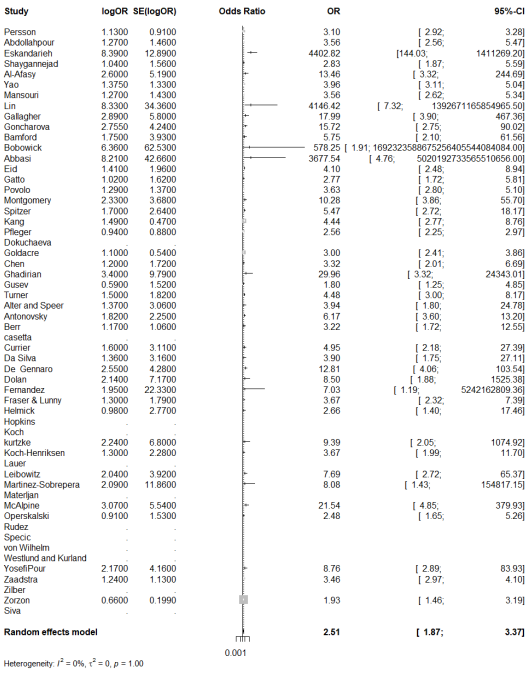

Figure 2: The association between physical trauma and the development of demyelinating diseases

Onset of Trauma

Eleven studies investigated the association between childhood physical trauma and the development of demyelinating diseases. The model that pooled these studies demonstrated that childhood trauma was significantly associated with higher odds of developing demyelinating diseases (Figure 3: OR=2.97; 95%CI: 2.64-3.35); the model had insignificant heterogeneity (I2=0%, P-value=0.57).

Moreover, 30 studies assessed the relationship between premorbid physical trauma and the risk of demyelinating diseases. The model that combined these studies demonstrated a significant association (Figure 4: OR=3.51; 95%CI: 2.97-4.14); the model also had significant heterogeneity (I2=38%, P-value=0.02).

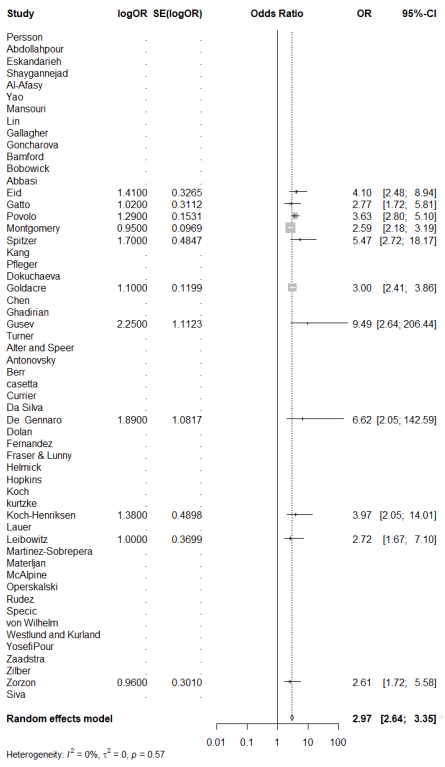

Figure 3: The association between childhood physical trauma and the development of demyelinating diseases

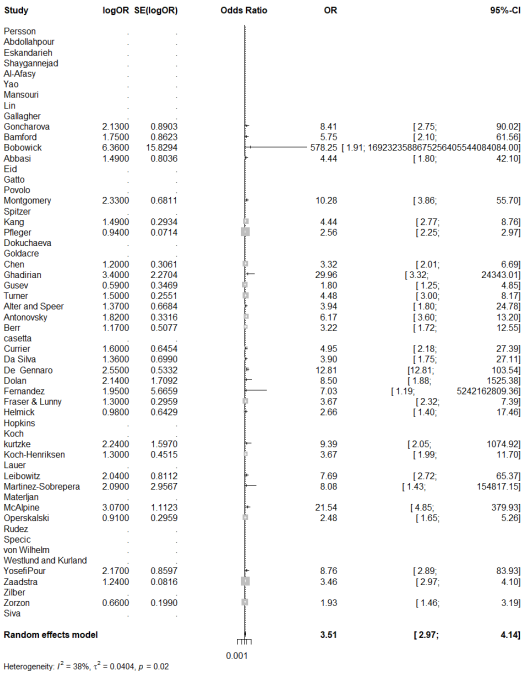

Figure 4: The relationship between premorbid physical trauma and the risk of demyelinating diseases.

Type of Trauma

Eight studies investigated the association between fractures and the development of demyelinating diseases. The model pooling these studies showed that fractures were associated with higher odds of demyelinating disease development (Figure 5: OR=3.17; 95%CI: 2.85-3.52); the model had insignificant heterogeneity (I2=20%, P-value=0.27).

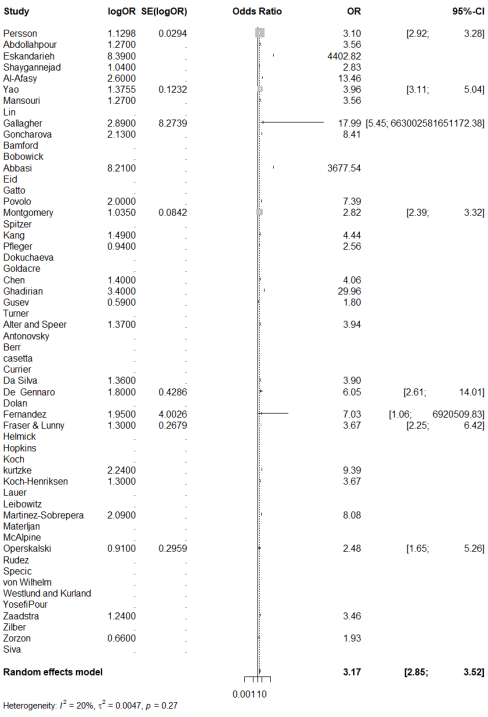

Figure 5: The association between fractures and the development of demyelinating diseases

Furthermore, the model investigating the association between head trauma and the development of demyelinating diseases included 24 studies. This model demonstrated a significant association between the two (Figure 6: OR=3.61; 95%CI: 2.84-4.59) with significant heterogeneity (I2=20%, P-value=0.27).

Five studies assessed the relationship between spinal trauma and the development of demyelinating diseases. The model that pooled these studies demonstrated a significant association (Figure 7: OR=9.06; 95%CI: 1.21-68.01); and had insignificant heterogeneity (I2=32%, P-value=0.21).

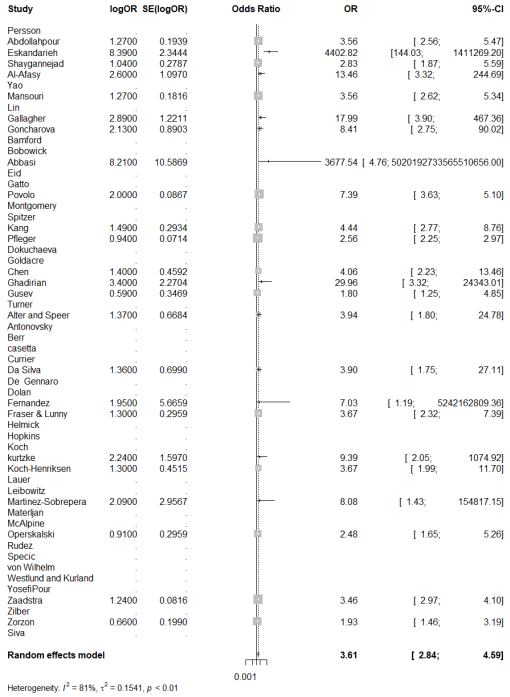

Figure 6: The association between head trauma and the development of demyelinating diseases

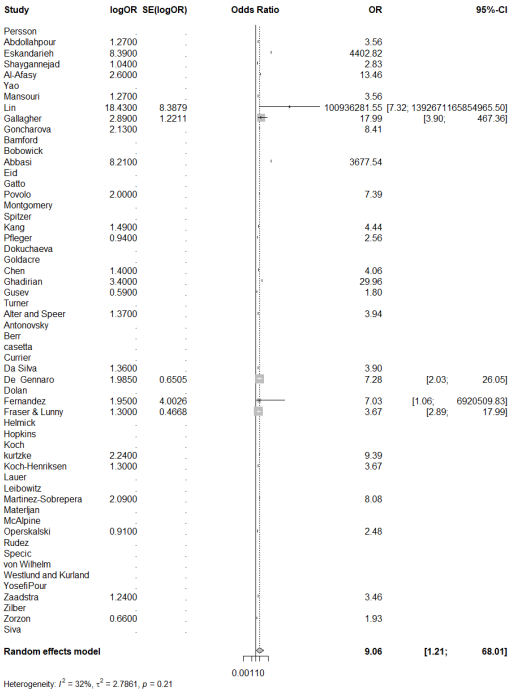

Figure 7: The relationship between spinal trauma and the development of demyelinating diseases.

Sub-group Analysis

Sub-group analysis according to disease type showed that physical trauma was significantly associated with higher odds of MS development (Figure 1: OR=3.26; 95%CI: 3.04-3.51), with insignificant heterogeneity in the model (I2=15%, P-value=0.21). Similarly, physical trauma was significantly associated with increased odds of ALS (OR=5.13; 95%CI: 1.21-21.83); the model had insignificant heterogeneity (I2=45%, P-value=0.18). Eskandarieh et al showed that physical trauma was also associated with increased odds of NMO development. A significant difference in the association between the 3 sub-groups was found with MS having the strongest and largest association (P-value¡0.01). Regarding the sub-group analysis according to ethnicity, physical trauma was associated with increased odds of demyelinating diseases development among patients from Mediterranean (Figure 2: OR=6.50; 95%CI: 2.59-16.32), Asian (Figure 2: OR=4.01; 95%CI:3.21-5.02), Caucasian (Figure 2: OR=3.14; 95%CI: 2.63-3.76), and Latino (Figure 2: OR=4.08; 95%CI: 1.09-15.23) ethnicities with no significant differences across the sub-groups (P-value=0.14). Sub-group analysis according to the quality of the studies demonstrated that both high-quality (7) (Figure 3: OR=3.46; 95%CI: 2.87=4.17) and low-quality studies (Figure 3: OR=3.77; 95%CI: 3.15=4.51) showed significant association between physical trauma and demyelinating diseases. Testing for sub-group differences revealed no significant difference between the two groups (P-value=0.51).

Publication Bias

Funnel and Doi plots showed significant major asymmetry indicating a significant publication bias (Figures 4 5).

Discussion

Demyelinating diseases are common neurological diseases with significant morbidity and disability. The aim of this study was to investigate the association between physical trauma and demyelinating diseases. After analyzing the data of around 2.5 million patients from 57 articles, this study revealed several key findings. First, physical trauma was significantly associated with increased risk of demyelinating diseases. This relationship was further confirmed when an analysis among high quality studies was done and showed results like those found in the main analysis. Second, analysis according to the onset of trauma demonstrated that both childhood and premorbid trauma were associated with increased risk of demyelinating diseases. Moreover, several specific trauma types were associated with increased risk of demyelinating diseases including fractures, head trauma and spinal trauma. However, only a few studies investigated other types of traumas such as extremity trauma, electrical shock, and burns. Thus, the evidence was less certain in their regard. Third, sub-group analysis according to demyelinating disease types revealed that only MS, ALS, and NPO were investigated in the literature, all of which had a significant association with physical trauma. The strongest evidence about the relationship between physical trauma and demyelinating diseases was among patients with MS, in whom a significant difference was found compared to other diseases. Additionally, sub-group analysis according to the ethnicity of the patients demonstrated that analysis among all ethnic backgrounds showed similar results to the primary analysis with no significant differences according to ethnic backgrounds. It is important to note that no studies were done regarding this topic in Africa which is considered an area with high risk of physical trauma due to the low socioeconomic status as well as the high rates of war, conflict, and child abuse [20, 21]. Thus, we recommend global initiatives to conduct future studies investigating this topic in the African region. Moreover, after reviewing the literature, only 3 demyelinating diseases were investigated including MS, ALS and NPO with only 2 studies and 1 study for

each of the latter two illnesses, respectively. As a result, future studies should focus on investigating the association between physical trauma and other demyelinating diseases including NPO and ALS, in addition to investigating it in understudied areas such as Africa. A previous meta-analysis which investigated the association between physical trauma and multiple sclerosis showed that both premorbid and childhood trauma were significantly associated with increased risk of multiple sclerosis [14]. According to the type of trauma, only head trauma was significantly associated with increased risk of the disease [14] On the other hand, our study also showed that premorbid and childhood trauma were associated with increased risk of demyelinating diseases. However, in addition to the association of increased risk of demyelinating disease development with head trauma we also demonstrated similar findings with other types of traumas including spinal trauma and fractures as well. This contradiction between our study and the previous meta-analysis might be due to the inclusion of more studies and a larger sample size, as we included over 2 million participants from 57 studies, while the previous meta-analysis only included around 340 thousand participants from 40 studies [14]. Thus, our analysis is considered more robust with lower confidence intervals resulting in more reliable and valid conclusions. Moreover, our results were further confirmed with a sub-analysis of high-quality studies. In addition, we conducted a sub-analysis according to the disease type which showed that each of MS, NPO and ALS were associated with physical trauma. On the other hand, the previous meta-analysis did not investigate demyelinating diseases other than MS [14]. The literature suggests important differences in the prevalence of demyelinating diseases according to ethnic background [22]. Studies showed that Caucasian ethnicity has the highest prevalence of MS followed by Mediterranean, Asian, and Hispanic ethnicities [22]. However, our subgroup analysis according to ethnicity revealed no differences according to ethnic background in the association between physical trauma and demyelinating diseases. We found significant asymmetry in the funnel plot and major asymmetry in the Doi plot indicating a significant publication bias. This contradicts the previous meta-analysis which did not find a significant publication bias [14]. In addition, there was no significant heterogeneity in the main analysis models or in the childhood trauma model. However, significant heterogeneity was found in the model assessing the impact of premorbid trauma, which raises a question as to whether premorbid trauma truly poses a risk to the diagnosis of demyelinating disease. Thus, future articles should focus on conducting studies that investigate this association. The poor definition of trauma among the included studies was a challenge for this study and will be remain one for future reviews. All the included studies either did not clarify how they defined trauma, or defined trauma inconsistently, which might introduce bias in the results. Future studies are recommended to examine trauma using validated scales such as the traumatic brain injury scale [23]. Moreover, in case-control studies using a self-report, medically validated trauma would be the preferred source of trauma definition. Nevertheless, if that is not available, having a parent or older sibling confirm the event would help minimize recall bias. Previous epidemiologic studies revealed that bias due to subjective outcomes increases heterogeneity in meta-analyses [24]. However, the study also showed that confirming the subjective outcome by clinician or medical records reduces bias and heterogeneity [24]. Furthermore, several studies failed to account for environmental factors associated with both childhood trauma and MS development including social status, adult socioeconomic factors, smoking and obesity [25-28]. From a pathophysiologic point of view, the studies linking the association between physical trauma and demyelinating diseases, mainly MS, go back as far as the middle of the 18th century [29]. Although several observational studies showed a significant association, the

biological link between trauma and demyelinating diseases has not been fully established [30]. Studies proposed that trauma to the brain or spinal cord might disrupt the blood brain barrier exposing the CNS as a target to the immune system. This would result in the immune cells attacking the CNS resulting in demyelinating lesions or plaques, especially among genetically susceptible individuals [31]. In addition, childhood trauma can cause dysregulation of the hypothalamic-pituitary-adrenal axis leading to oxidative stress and induce proinflammatory state before adulthood [32-34]. Moreover, some studies hypothesized that breaking the blood-brain barrier is a necessary initial process for the development of demyelinating diseases [35]. On the other hand, other researchers highlight that the high rate of blood-barrier disruption among patients with demyelinating disease in the absence of history of trauma contradicts the aforementioned evidence [15]. However, due to the long latency of demyelinating diseases and the unexpected nature of physical trauma, this association is considered challenging to be examined in the setting of clinical trials. It is important to note that physical trauma during childhood was associated with several neurological and non-neurological autoimmune diseases including Parkinson disease, dementia, rheumatoid arthritis and inflammatory bowel diseases [36]. Also, some studies suggested a dose-response relationship between abuse and the prevalence of chronic disease [37]. The accumulative evidence regarding the association between trauma and immune related diseases suggests central role of systematic inflammation [36]. Moreover, studies demonstrated that the rate of maltreatment among MS patients is high and ranges between 7% for physical trauma and 24.8% for emotional abuse [38]. . On top of that, studies also showed that traumatic stress during childhood increased the risk of immune disease exacerbations and hospitalizations [39]. The literature highlights the importance of incorporating trauma-informed care into clinical practice to reduce the harms associated with adverse childhood experiences including physical, emotional and sexual abuse [40]. This includes screening for adverse childhood experiences, addressing trauma-related events, and ensuring appropriate support. Consequently, this can help reduce the risk the of immune diseases in the future as well as reduce their severity and progression [40]. However, several limitations should be acknowledged. First, the low the quality of some of the included studies, predominantly due to poor assessment of the exposure and lack of accounting for confounding bias might reduce the reliability of our results. However, we conducted a sub-group analysis according to the study quality which exhibited results similar to those in the primary analysis. Also, since the individual data of the patients was not available to analyze, our results might have been impacted by confounding bias. Second, the poor definition of trauma in the included studies is another limitation. Additionally, the inconsistent definition of trauma in the studies which did provide an adequate definition adds to the limitations. Moreover, some of the models had high heterogeneity, which also might affect our results. Finally, although we performed several sensitivity analyses to reduce publication bias, the funnel and Doi plots still demonstrated significant publication bias.

Conclusion

In this systematic review and meta-analysis, we found that childhood and premorbid physical trauma was significantly associated with demyelinating diseases. Moreover, fractures, head trauma and spinal trauma were associated with increased risk of demyelinating diseases. These results remained significant when sub-group analyses were performed according to ethnicity, disease type and high-quality studies. However, several gaps in the literature which require further examination were also revealed. For instance, very few studies investigated the relationship between physical trauma and demyelinating diseases

other than MS. In addition, no studies were conducted in the African region which is an area with a high rate of physical trauma. Also, the poor and inconsistent definition of trauma was a main limitation in our review. Thus, we recommend conducting future prospective, well-controlled studies that utilize an adequate, consistent definition of trauma and investigate this association in the understudied areas as well as among different demyelinating disease types.

Conflict of Interest

The authors declare that they have no competing interests.

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