Emotional or sexual abuse in childhood may increase risk of multiple sclerosis (MS) in women, and risk may increase further with exposure to multiple kinds of abuse, according to the first prospective cohort study of its kind.

More research is needed to uncover underlying mechanisms of action, according to lead author Karine Eid, MD, a PhD candidate at Haukeland University Hospital, Bergen, Norway, and colleagues.

"Trauma and stressful life events have been associated with an increased risk of autoimmune disorders," the investigators wrote in the *Journal Of Neurology, Neurosurgery, & Psychiatry*. "Whether adverse events in childhood can have an impact on MS susceptibility is not known."

The present study recruited participants from the Norwegian Mother, Father and Child cohort, a population consisting of Norwegian women who were pregnant from 1999 to 2008. Of the 77,997 participating women, 14,477 reported emotional, sexual, and/or physical abuse in childhood, while the remaining 63,520 women reported no abuse. After a mean follow-up of 13 years, 300 women were diagnosed with MS, among whom 24% reported a history of childhood abuse, compared with 19% among women who did not develop MS.

To look for associations between childhood abuse and risk of MS, the investigators used a Cox model adjusted for confounders and mediators, including smoking, obesity, adult socioeconomic factors, and childhood social status. The model revealed that emotional abuse increased the risk of MS by 40% (hazard ratio [HR] 1.40; 95% confidence interval [CI], 1.03-1.90), and sexual abuse increased the risk of MS by 65% (HR 1.65; 95% CI, 1.13-2.39).

Although physical abuse alone did not significantly increase risk of MS (HR 1.31; 95% CI, 0.83-2.06), it did contribute to a dose-response relationship when women were exposed to more than one type of childhood abuse. Women exposed to two out of three abuse categories had a 66% increased risk of MS (HR 1.66; 95% CI, 1.04-2.67), whereas women exposed to all three types of abuse had the highest risk of MS, at 93% (HR 1.93; 95% CI, 1.02-3.67).

Eid and colleagues noted that their findings are supported by previous retrospective research, and discussed possible mechanisms of action.

"The increased risk of MS after exposure to childhood sexual and emotional abuse may have a biological explanation," they wrote. "Childhood abuse can cause dysregulation of the hypothalamic-pituitary-adrenal axis, lead to oxidative stress, and induce a proinflammatory state decades into adulthood. Psychological stress has been shown to disrupt the blood-brain barrier and cause epigenetic changes that may increase the risk of neurodegenerative disorders, including MS.

"The underlying mechanisms behind this association should be investigated further," they concluded.

### Study Findings Should Guide Interventions

Commenting on the research, Ruth Ann Marrie, MD, PhD, professor of medicine and community health sciences and director of the multiple sclerosis clinic at Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, said that the present study "has several strengths compared to prior studies – including that it is prospective and the sample size."

Marrie, who was not involved in the study, advised clinicians in the field to take note of the findings, as patients with a history of abuse may need unique interventions.

"Providers need to recognize the higher prevalence of childhood maltreatment in people with MS," Marrie said in an interview. "These findings dovetail with others that suggest that adverse childhood experiences are associated with increased mental health concerns and pain catastrophizing in people with Affected individuals may benefit from additional psychological supports and trauma-informed care."

Tiffany Joy Braley, MD, associate professor of neurology, and Carri Polick, RN and PhD candidate at the school of nursing, University of Michigan, Ann Arbor, who published a case report last year highlighting the importance of evaluating stress exposure in MS, suggested that the findings should guide interventions at both a system and patient level.
"Although a cause-and-effect relationship cannot be established by the current study, these and related findings should be considered in the context of system level and policy interventions that address links between environment and health care disparities," they said in a joint, written comment. "Given recent impetus to provide trauma-informed health care, these data could be particularly informative in neurological conditions which are associated with high mental health comorbidity. Traumatic stress screening practices could lead to referrals for appropriate support services and more personalized health care."

While several mechanisms have been proposed to explain the link between traumatic stress and MS, more work is needed in this area, they added.

This knowledge gap was acknowledged by Marrie.

"Our understanding of the etiology of MS remains incomplete," Marrie said. "We still need a better understanding of mechanisms by which adverse childhood experiences lead to MS, how they interact with other risk factors for MS (beyond smoking and obesity), and whether there are any interventions that can mitigate the risk of developing MS that is associated with adverse childhood experiences."

The investigators disclosed relationships with Novartis, Biogen, Merck, and others. Marrie receives research support from the Canadian Institutes of Health Research, the National Multiple Sclerosis Society, MS Society of Canada, the Consortium of Multiple Sclerosis Centers, Crohn’s and Colitis Canada, Research Manitoba, and the Arthritis Society; she has no pharmaceutical support. Braley and Polick reported no conflicts of interest.

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