Stress and the risk of multiple sclerosis

T. Riise, PhD
D.C. Mohr, PhD
K.L. Munger, ScD
J.W. Rich-Edwards, PhD
I. Kawachi, MD
A. Ascherio, MD

Address correspondence and reprint requests to Dr. T. Riise, Department of Public Health and Primary Health Care, University of Bergen, Kalfarveien 31, N-5018 Bergen, Norway

ABSTRACT

Objective: Several studies have shown that stressful life events are associated with a subsequent significant increase in risk of multiple sclerosis (MS) exacerbations. We wanted to study prospectively whether stress can increase the risk of developing the disease itself.

Methods: We studied 2 cohorts of female nurses: the Nurses' Health Study (NHS) (n = 121,700) followed from 1976 and the Nurses' Health Study II (NHS II) (n = 116,671) followed from 1989. The risk of MS after self-report on general stress at home and at work in the NHS in 1982 was studied prospectively using Cox regression. Logistic regression was used to retrospectively estimate the effects of physical and sexual abuse in childhood and adolescence collected in the NHS II 2001. We identified 77 cases of MS in the NHS by 2005 and 292 in the NHS II by 2004. All analyses were adjusted for age, ethnicity, latitude of birth, body mass index at age 18, and smoking.

Results: We found no increased risk of MS associated with severe stress at home in the NHS (hazard ratio 0.85 [95% confidence interval (CI)] 0.32–2.26). No significantly increased risk of MS was found among those who reported severe physical abuse during childhood (odds ratio [OR] 0.68, 95% CI 0.41–1.14) or adolescence (OR 0.77, 95% CI 0.46–1.28) or those having been repeatedly forced into sexual activity in childhood (OR 1.47, 95% CI 0.87–2.48) or adolescence (OR 1.21, 95% CI 0.68–2.17).

Conclusions: These results do not support a major role of stress in the development of the disease, but repeated and more focused measures of stress are needed to firmly exclude stress as a potential risk factor for MS. *Neurology*® 2011;76:1866–1871

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **MS** = multiple sclerosis; **NHS** = Nurses' Health Study; **OR** = odds ratio.

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the CNS with unknown causes. It appears that the etiology is multifactorial, including both genetic and environmental components.^{1–3}

Exposure to stress has long been suspected as a factor that can aggravate MS. There are many studies showing that among people diagnosed with MS, stressful life events are associated with a significant increase in risk of MS exacerbation in the weeks or months following onset of the stressor.⁴ A number of mechanisms have been proposed, including mediation between stressful events and the immune system via the glucocorticoid and the β -adrenergic pathways.^{5,6} But it is not known whether stressful life events could increase the risk of developing the disease itself.

In spite of a general concern of such a relation particularly among many patients who report that they had been going through a stressful period prior to their first symptom of their disease, few studies have addressed this question. One prospective study found that among people without MS a traumatic stressor, the death of a child, significantly increased the risk of subsequent diagnosis with MS.⁷ Moreover, the effect was strongest for parents who lost their child

From the Department of Public Health and Primary Health Care (T.R.), University of Bergen, Bergen; The Norwegian Multiple Sclerosis Competence Centre (T.R.), Haukeland University Hospital, Bergen, Norway; Department of Preventive Medicine (D.C.M.), Feinberg School of Medicine, Northwestern University, Chicago, IL; Departments of Nutrition (K.L.M., A.A.), Epidemiology (J.W.R.-E., A.A.), and Society, Human Development & Health (I.K.), Harvard School of Public Health, Boston; and Connors Center for Women's Health and Gender Biology (J.W.R.-E.) and Channing Laboratory (A.A.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Study funding: Supported by the NIH/NINDS (NS042194 and NS046635).

Disclosure: Author disclosures are provided at the end of the article.

suddenly, as compared with those who did not, suggesting a possible dose effect. This suggests that stress not only can affect pathogenic processes in patients with MS, but that traumatic stressors can affect the risk of ever developing clinically diagnosable MS.

Therefore, we estimated the risk of developing MS related to major stress at work and at home and sexual and physical trauma in childhood in 2 large cohorts of US women.

METHODS Study population. The study population comprised women participating in 2 prospective studies of female registered nurses living in the United States: the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II). The NHS was established in 1976 and recruited 121,700 nurses aged 30 to 55 years; the NHS II was established in 1989 and recruited 116,671 nurses aged 25 to 42 years. Every 2 years, women in these cohorts update lifestyle factors and are asked to report to us any major disease diagnoses, including MS. The procedure for ascertainment of the MS cases in these cohorts and the validity of this approach have previously been reported.^{8,9} Briefly, women reporting a new diagnosis of MS are asked for permission for study investigators to contact their neurologists. The neurologists completed a questionnaire regarding the diagnosis including the certainty of the diagnosis (definite, probable, possible, not MS, based on Poser criteria), clinical history (including date of MS diagnosis and date of the first symptoms of MS), and the results of laboratory tests including MRI. The diagnosis was supported by positive MRI findings in 76% (NHS) and 89% (NHS II) of the cases, reflecting a higher proportion of cases with recent onset in the NHS II. By June 2004, we documented 94 cases of definite and probable MS in the NHS with onset of symptoms after baseline in 1982 (when the exposure to stress was assessed). In the NHS II, there were 509 definite and probable cases by the end of 2005 with onset of symptoms during the study period, of whom 460 cases had had onset before the information on childhood trauma was ascertained in 2001.

Stress measurements. In 1982, a total of 110,282 of the participants of NHS were sent a questionnaire including questions on stress at home and at work. A total of 94,185 of the nurses responded to this questionnaire, including 77 nurses who later developed MS. They were asked "How would you rate the amount of stress in your daily life? i) at home ii) at work" with "minimal," "light," "moderate," or "severe" as the response categories. This measure of stress has previously been shown to be a major predictor for suicide in this cohort.¹⁰

The 2001 questionnaire sent to the participants of the NHS II included 22 questions on physical and sexual abuse in childhood and adolescence. Such traumas can fundamentally alter systems that mediate the effect of stress (e.g., sensitization of neuroendocrine response), reduce neuroendocrine regulation of inflammation (e.g., glucocorticoid resistance), and increase inflammatory activity.¹¹ These effects can extend into adulthood, suggesting that these systems are permanently altered by childhood trauma.¹²

Child and adolescent sexual abuse was measured by questions regarding unwanted sexual touching and forced sexual activity adapted from a national survey conducted in 1995,^{13,14}

while the questions on physical abuse were adapted from the Revised Conflict Tactics Scale.¹⁵ A total of 68,505 women responded to this questionnaire (response rate of 75%) including 292 individuals who had developed MS between 1989 and 2001 or after the survey in 2001. Physical abuse was measured querying whether a participant's parent, stepparent, or adult guardian ever did the following to them: pushed, grabbed, or shoved; kicked, bit, or punched; hit with something that hurt; choked or burned; or physically attacked in some other way. For each type of physical abuse, respondents were asked about the frequency of the event (never, once, a few times, more than a few times). Questions were asked separately for childhood (up to age 11 years) and adolescence (ages 11–17 years). As described elsewhere,⁶ a categorical physical abuse severity scale for childhood and adolescence was created ranging from a minimum score of 0 = no physical abuse, 1 = mild physical abuse, 2 = moderate physical abuse, and 3 = severe physical abuse. Those who had abuse experiences in several categories (e.g., those who experienced both mild and severe abuse) were classified as having the highest severity category.

Items on sexual abuse in childhood and adolescence included a question on forced sexual touching: "Were you ever touched in a sexual way by an adult or an older child or were you forced to touch an adult or an older child in a sexual way when you did not want to?" and a question on forced sexual activity: "Did an adult or older child ever force you or attempt to force you into any sexual activity by threatening you, holding you down, or hurting you in some way when you did not want to?" Respondents could answer "no, this never happened"; "yes, this happened once"; or "yes, this happened more than once." These questions on early physical and sexual abuse have previously been shown to be a predictor of diabetes and of an early start of smoking in the same study population.^{16,17}

For both studies, information on smoking (never/past/current, pack-years: <10 packs/y, 10–24, 25+), body mass index (BMI) at age 18 (in kg/m²: <18.5, 18.5–21, 21–23, 23–25, 25–27, 27–30, 30+), ethnicity (Scandinavian, Southern European, other Caucasians, others), and latitude at birth (south tier, middle tier, north tier) was available. The distribution of these covariates in the 2 cohorts has previously been reported.^{9,18,19}

The marked difference in the number of MS cases in the 2 cohorts reflects the prospective design in the NHS compared to the use of all prevalent cases in the NHS II. Further, the NHS II is also a younger cohort of women—they were 25–42 years old at baseline compared with 30–55 in the NHS. Thus, the NHS women were largely past the age of peak MS incidence.

Standard protocol approvals and patient consents. Approval was received from the Brigham and Women's Hospital institutional review board, and written informed consent was obtained from all patients participating in the study.

Statistical methods. Analyses in the NHS were completely prospective (i.e., women who already had developed MS at the time level of stress was assessed [1982] were excluded from the analysis) and Cox proportional hazards models, conditioned on age and follow-up cycle, were used to estimate the risk of MS in the subgroups of reported stress at home or at work. Logistic regression was used to conduct a bidirectional analysis (retrospective considering cases from 1989 to 2001 and prospective considering cases from 2001 to 2005) of the associations of physical and sexual abuse on the risk of MS in the NHS II. All analyses in both cohorts were adjusted for age, ethnicity, latitude of birth, BMI at age 18, and smoking.

Table 1 Incidence rates and hazard ratios of multiple sclerosis by levels of home and work stress in the Nurses' Health Study 1982-2003 (n = 94,185)

	Total cohort, n (%)	MS cases, n (%)	IR ^a	HR ^b	HR ^c (95% CI)
Home stress					
Minimal	17,498 (19)	13 (17)	3.6	1	1
Light	27,447 (29)	25 (32)	4.4	0.91	0.88 (0.44-1.73)
Moderate	40,856 (43)	32 (42)	3.8	0.78	0.75 (0.39-1.45)
Severe	7,309 (8)	6 (8)	4.0	0.87	0.85 (0.32-2.26)
Missing	1,075 (1)	1 (1)	4.6	1.18	1.23 (0.16-9.48)
Work stress					
Minimal	7,862 (8)	6 (8)	3.7	1	1
Light	15,172 (16)	21 (27)	6.6	1.67	1.64 (0.66-4.07)
Moderate	40,967 (44)	30 (39)	3.5	0.91	0.90 (0.38-2.18)
Severe	10,296 (11)	4 (5)	1.9	0.52	0.52 (0.15-1.85)
Missing	19,888 (21)	16 (21)	4.0	1.33	1.38 (0.54-3.54)

Abbreviations: HR = hazard ratio; IR = incidence rate; MS = multiple sclerosis.

^a Crude incidence rates per 100,000 person-years of follow-up.

^b Hazard ratios adjusted for age in 5-year groups.

^c Hazard ratios adjusted for age, ethnicity, latitude of birth, body mass index at age 18, and smoking (never, <10 packs/year, 10-24 packs/year, 25+ packs/year).

Based on the known distribution of the stress variables and the number of cases in the cohorts, we estimated a statistical power of 0.54 to detect a relative risk of 2.0 for comparing severe stress (prevalence = 10%) with little/no stress (90%) in the NHS and 0.90 for comparing severe physical/sexual abuse (7%) with less/no abuse (93%) in the NHS II.

Table 2 Odds ratios and 95% confidence intervals of risk of multiple sclerosis by severity of physical abuse in childhood (n = 68,321) and adolescence (n = 68,325)^a

	No. (%) noncases	No. (%) MS cases	OR ^b	95% CI	p Value
Severity of physical abuse in childhood (<11 y)					0.22
None	34,655 (51)	162 (55)	1		
Mild	11,130 (16)	39 (13)	0.74	0.52-1.05	
Moderate	17,505 (26)	75 (26)	0.90	0.68-1.19	
Severe	4,739 (7)	16 (5)	0.68	0.41-1.14	
Severity of physical abuse during adolescence (11-17 y)					0.28
None	45,848 (67)	200 (69)	1		
Mild	9,900 (15)	35 (12)	0.79	0.55-1.14	
Moderate	7,812 (11)	41 (14)	1.17	0.83-1.64	
Severe	4,473 (7)	16 (5)	0.77	0.46-1.28	

Abbreviations: CI = confidence interval; MS = multiple sclerosis; NHS = Nurses' Health Study; OR = odds ratio.

^a Questions included in the 2001 questionnaire in the Nurses Health Study II followed from 1989 to 2004. Separate logistic regression model for each variable.

^b Adjusted for age in 10-year groups, ethnicity, latitude of birth, body mass index at age 18, and smoking (never, <10 packs/year, 10-24 packs/year, 25+ packs/year).

RESULTS A total of 93,110 of the 94,185 (99%) nurses who responded to the 1982 questionnaire in the NHS had answered the questions on stress at home, while a lower percentage, 79% (74,297 out of 94,185), responded to the question on stress at work. A total of 87% (n = 17,399) of the women who did not answer the question on stress at work reported to be "homemakers" at the time of study. Further, the distribution of stress at home for the individuals not responding to the question of stress at work was very similar to that of the rest of the respondents. The vast majority of those who responded to the question of stress at home in the total study population reported minimal to moderate stress, while only 8% reported severe stress at home (table 1). The corresponding figure for severe stress at work was 14%.

Stress measurements were available for 77 of the 94 women who had developed MS after 1982. Adjusting for age, ethnicity, latitude at birth, BMI at age 18, and biannually updated smoking status, there were no significant differences in the risk of MS between any of the levels of stress at home or at work (table 1). A total of 93,938 cases were included in these multivariate analyses after exclusion of cases with missing values on the covariates. Further, there was no trend of increasing risk associated with increased levels of stress. The levels with the highest risk were those who reported minimal stress at home and those who reported light stress at work.

To study whether there could have been a short-term effect, we repeated the analyses with end of follow-up in 1992, i.e., 10 years later. The results were similar with no effect of the stress variables on the MS risk (data not shown).

In the NHS II, the scales on physical abuse in childhood (n = 68,321) and adolescence (n = 68,325) could be calculated for 99.7% of the women who responded to the questionnaire in 2001 including 292 of the 509 women who had developed MS in the total cohort. A total of 7% of the women reported severe physical abuse in childhood and a similar figure was reported for adolescence. There was no increased risk of MS for those who reported various levels of physical abuse during childhood or adolescence, adjusting for age, ethnicity, latitude of birth, BMI at age 18, and smoking (table 2).

The 4 questions on sexual abuse were answered by 99.2% of the women. The number of women included in the analyses was 68,242, 68,255, 68,240, and 68,264 for having been touched in a sexual way in childhood, in adolescence, and being forced into sexual activity in childhood and in adolescence, respectively. In childhood, approximately 10% reported having been touched in a sexual way several times, and 3% were forced into sexual activity several

Table 3 Odds ratios and 95% confidence intervals of risk of multiple sclerosis by type of sexual abuse during childhood and adolescence for each of the 4 questions included in the 2001 questionnaire in the Nurses Health Study II^a

Variable	No. (%) noncases	No. (%) MS cases	OR ^b	95% CI	p Value
As a child (<11 years) touched in a sexual way, when did not want to					0.05
No, never	53,906 (79)	231 (78)	1		
Yes, once	7,225 (11)	21 (7)	0.67	0.43-1.05	
Yes, more than once	6,820 (10)	39 (13)	1.30	0.92-1.83	
As a teenager (11-17 years) touched in a sexual way, when did not want to					0.29
No, never	54,314 (80)	241 (83)	1		
Yes, once	7,658 (11)	25 (9)	0.72	0.48-1.09	
Yes, more than once	5,992 (9)	25 (9)	0.92	0.61-1.39	
As a child (<11 years) forced into sexual activity					0.28
No, never	63,819 (94)	271 (93)	1		
Yes, once	1,811 (3)	6 (2)	0.76	0.34-1.71	
Yes, more than once	2,318 (3)	15 (5)	1.47	0.87-2.48	
As teenager (11-17 years) forced into sexual activity					0.76
No, never	62,487 (92)	266 (91)	1		
Yes, once	3,260 (5)	13 (4)	0.91	0.52-1.60	
Yes, more than once	2,226 (3)	12 (4)	1.21	0.68-2.17	

Abbreviations: CI = confidence interval; MS = multiple sclerosis; OR = odds ratio.

^a Separate logistic regression models for each variable.

^b Adjusted for age in 10-year groups, ethnicity, latitude of birth, body mass index at age 18, and smoking (never, <10 packs/year, 10-24 packs/year, 25+ packs/year).

times. Similar figures were reported for adolescence. Sexual touching in adolescence was not associated with MS risk, while a borderline significant effect was seen for sexual touching in childhood (table 3). However, there was no significant trend for this variable ($p = 0.42$), with the lowest risk for those who had experienced sexual touching once. There was an elevated but nonsignificant risk among women having been forced into sexual activity several times, both during childhood (odds ratio [OR] 1.51, confidence interval [CI] 0.90-2.55) and adolescence (OR 1.25, CI 0.70-2.23).

DISCUSSION In this study, general level of stress at home or at work in adulthood and physical and sexual traumas in childhood/adolescence were not associated with MS, although a slightly, nonsignificant elevated risk was found for those who reported to repeatedly have been forced into sexual activity.

Typical of large cohort studies, we had no objective measurements of stress or any biological markers of long-term effects of stress. We evaluated 2 differ-

ent types of stress: chronic daily home- and work-related stress and childhood trauma. Both these measures have limitations in estimating meaningful levels of stress. The self-report on general stress level in daily life in adulthood might reflect temporary conditions. Measurement at one timepoint may not reliably or validly assess the forms of chronic stress that could potentially alter the immune system. Still, we did not find different results when restricting the follow-up to the decade following the year of stress measurement. Further, the questions on daily stress used in our study have previously been found to be strongly associated with increased risk of suicide in the same study population.⁶ The increased risk for suicide was strongest for the 10 first years following measurement in 1982, but it was present also for the whole study period, suggesting that these measurements reflected a rather lasting level of stress or other factors related to stress perception in this cohort.

Physical and sexual traumas in childhood have been shown to be associated with marked neuroendocrine changes.¹¹ In addition to being stressful at the time, the effect of such traumas have also been shown to lead to higher stress reactivity later in life and an increased risk of psychiatric disorders.¹² But the long-term emotional impact of the early abuse was not assessed. Further, it could be that few traumatized individuals who had substantial negative health consequences from childhood abuse were in the study population, given the demanding nature of the nursing profession. We found no marked elevated risk for the groups of individuals who had been physically or sexually abused. There was a nonlinear borderline significant effect of sexual touching in childhood that is difficult to interpret, since the lowest risk of MS was found among women who had experienced sexual touching once. Further, the very small group of women who reported having experienced the most severe sexual abuse in childhood had a nonsignificant 50% increased risk. This prevents us from making firm conclusions regarding this exposure.

Our findings contradict the reports of a few previous studies. Two early case-control studies have reported a possible link between stress and the onset of MS. One study found that 79% of the patients reported stressful events 2 years prior to disease onset compared to 54% of the controls during a comparable period,²⁰ and another study reported similar findings for the 6 months preceding the first symptom.²¹ This could indicate that since stress increases the risk of new episodes, it could also induce the first episode; i.e., the onset. However, recall bias, a major problem for retrospective design used in these studies, could possibly have influenced the results. The findings

could also be an artifact in which the experience of stress is an early sign of underlying disease activity, which subsequently is expressed as a first symptom, i.e., stress being a marker of early disease activity.²² In any case, the effect of stress in these observations would rather point to stress being a contributing triggering factor, rather than stress over longer period of time playing a more causal role in the disease development that is likely initiated several years prior to first clinical symptoms.¹

A large prospective study of bereaved parents found that these individuals had a significantly increased risk of developing MS after the death of their child, particularly after a follow-up for more than 8 years.⁷ These results cannot be explained by recall bias or any other information bias, but, as the authors suggest, it is possible that unmeasured potential confounders, such as lifestyle factors or other environmental factors, could have explained part of the increased risk. Interestingly, in this particular cohort, bereaved parents also had an increased risk for myocardial infarction,²³ epilepsy,²⁴ cancers,²⁵ psychiatric hospitalization,²⁶ hospitalization for type II diabetes,²⁷ and total mortality,²⁸ and their later children (born after the death of the index child) had an increased risk of congenital malformations,²⁹ epilepsy,³⁰ and cerebral palsy.³¹ Although it is possible that the risk of all these conditions is related to severe stress, factors associated with the disease of the child or factors related to the sudden death not taken into account in the analyses may also have contributed.

A major challenge when studying this relation is to achieve unbiased measurement of stress. A prospective design can overcome biases related to the effects of MS symptoms on self-reported stress. However, because the disease is infrequent, initiating a prospective study specifically with this aim is not feasible. Existing cohorts such as the one used in the present study provide unique opportunities, but can also have some liabilities. One part of the present study employed a longitudinal design, but this part of the study has a relatively low power considering the low number of cases that were found during the follow-up period. Further, studying the relationship between stressful life events and disease endpoints is difficult due to the complexity of the process by which a hypothesized triggering event in the environment could result in a disease event. The assessments used in this survey, while having demonstrated validity for other outcomes, were not designed for this study. The possibility that these assessments were not sensitive to the stressors and stress mechanisms that might increase risk of developing MS cannot be ruled out. Further, only female nurses were studied in this cohort, limiting our interpretation to women.

The results of this study do not support a major role of stress in the development of the disease. However, future studies with more focused and frequently measured stress assessments are needed to preclude a firm exclusion of stress as a potential risk factor for MS.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. T. Riise and Dr. K. Munger.

DISCLOSURE

Dr. Riise has received funding for a 1-year research stay at Harvard School of Public Health from the Norwegian Research Council. Dr. Mohr receives research support from the NIH and US Department of Veterans Affairs/HSR&D. Dr. Munger has received funding for travel and speaker honoraria from the Consortium of MS Centers and the National MS Society. Dr. Rich-Edwards receives research support from the NIH and the Society for Epidemiologic Research Developmental Origins of Health and Disease. Dr. Kawachi serves as Senior Editor in Social Epidemiology for *Social Science & Medicine* and on the editorial board of the *American Journal of Epidemiology*. Dr. Ascherio served on a scientific advisory board for the Michael J. Fox Foundation; serves on the editorial boards of *Neurology*[®], *Annals of Neurology*, and the *American Journal of Epidemiology*; has received speaker honoraria from Merck Serono; and receives research support from the NIH, the US Department of Defense, the Michael J. Fox Foundation, and the National Multiple Sclerosis Society.

Received August 19, 2010. Accepted in final form February 18, 2011.

REFERENCES

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;343:938–952.
2. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis: part I: the role of infection. *Ann Neurol* 2007;61:288–999.
3. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis: part II: noninfectious factors. *Ann Neurol* 2007;61:504–513.
4. Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. *BMJ* 2004;328:731.
5. Mohr DC. Stress and multiple sclerosis. *J Neurol* 2007; 254(suppl 2):65–68.
6. Gold S, Mohr DC, Huitinga I, Schulz KH, Heesen C. The role of stress response systems in the pathogenesis and progression of multiple sclerosis. *Trends Immunol* 2005;26: 644–652.
7. Li J, Johansen C, Brønnum-Hansen H, Stenager E, Koch-Henriksen N, Olsen J. The risk of multiple sclerosis in bereaved parents: a nationwide cohort study in Denmark. *Neurology* 2004;62:726–729.
8. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004; 62:60–65.
9. Hernán MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. *Neurology* 1999;53:1711–1718.
10. Feskanich D, Hastrup JL, Marshall JR, et al. Stress and suicide in the Nurses' Health Study. *J Epidemiol Community Health* 2002;56:95–98.
11. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology* 2008;33:693–710.

12. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 2000;284:592–597.
13. Moore DW, Gallup GH, Schussel R. *Disciplining Children in America: A Gallup Poll Report*. Princeton, NJ: The Gallup Organization; 1995.
14. Finkelhor D, Moore D, Hamby SL, Straus MA. Sexually abused children in a national survey of parents: methodological issues. *Child Abuse Negl* 1997;21:1–9.
15. Straus MA, Gelles RJ. *Physical Violence in American Families: Risk Factors and Adaptations to Violence in 8,145 Families*. New Brunswick, NJ: Transaction Books; 1990.
16. Rich-Edwards JW, Spiegelman D, Lividoti Hibert EN, et al. Abuse in childhood and adolescence as a predictor of type 2 diabetes in adult women. *Am J Prev Med* 2010;39: 529–536.
17. Jun H-J, Rich-Edwards J, Boynton-Jarrett R, Austin SB, Lindsay Frazier AL, Wright R. Childhood abuse and adolescent smoking: the importance of severity, accumulation, and timing. *J Adolesc Health* 2008;43:55–63.
18. Hernán MA, Olek MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. *Am J Epidemiol* 2001;154: 69–74.
19. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology* 2009;73: 1543–1550.
20. Warren S, Greenhill S, Warren KG. Emotional stress and the development of multiple sclerosis: case-control evidence of a relationship. *J Chronic Dis* 1982;35:821–831.
21. Grant I, Brown GW, Harris T, McDonald WI, Patterson T, Trimble MR. Severely threatening events and marked life difficulties preceding onset or exacerbation of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1989;52:8–13.
22. Mohr DC, Pelletier D. A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. *Brain Behav Immun* 2006;20:27–36.
23. Li J, Hansen D, Mortensen PB, Olsen J. Myocardial infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. *Circulation* 2002;106: 1634–1639.
24. Christensen J, Li J, Vestergaard M, Olsen J. Stress and epilepsy: a population-based cohort study of epilepsy in parents who lost a child. *Epilepsy Behav* 2007;11:324–328.
25. Li J, Johansen C, Hansen D, Olsen J. Cancer incidence in parents who lost a child. *Cancer* 2002;95:2237–2242.
26. Li J, Laursen TM, Precht DH, Olsen J, Mortensen PB. Hospitalization for mental illness among parents after the death of a child. *N Engl J Med* 2005;24:352:1190–1196.
27. Olsen J, Li J, Precht DH. Hospitalization because of diabetes and bereavement: a national cohort study of parents who lost a child. *Diabet Med* 2005;10:1338–1342.
28. Li J, Precht DH, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003;361:363–367.
29. Hansen D, Lou HC, Olsen J. Serious life events and congenital malformations: a national study with complete follow-up. *Lancet* 2000;356:875–880.
30. Li J, Vestergaard M, Obel C, Precht DH, Christensen J, Lu M, Olsen J. Prenatal stress and epilepsy in later life: a nationwide follow-up study in Denmark. *Epilepsy Res* 2008;81:52–57.
31. Li J, Vestergaard M, Obel C, et al. Prenatal stress and cerebral palsy: a nationwide cohort study in Denmark. *Psychosom Med* 2009;71:615–618.

Career Moves Begin at Neurology Career Center

Job seekers: The AAN's Neurology Career Center is a one-stop shop for qualified candidates looking to make a career move in neurology. Search for opportunities in your state and area of interest and create a profile that you can share with only those employers in whom you're interested.

Advertising for a position in neurology? Reach more than 22,500 Academy members online, in print, and at special career events.

Make your next career connection with the Neurology Career Center!

www.aan.com/careers