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School performance and psychiatric morbidity 6 years after pediatric acute disseminated encephalomyelitis: A nationwide population-based cohort study

Magnus Spangsberg Boesen[a,b,*], Annika Langkilde[c], Alfred Peter Born[a], Melinda Magyari[d,e], Morten Blinkenberg[d], Tanuja Chitnis[f], Lau Caspar Thygesen[g], Frank Eriksson[h]

[a] Department of Pediatrics, Rigshospitalet, University of Copenhagen, Denmark
[b] Department of Neurology, Herlev Hospital, Denmark
[c] Department of Radiology, Diagnostic Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[d] Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark
[e] Danish Multiple Sclerosis Registry, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark
[f] Partners Pediatric Multiple Sclerosis Center at the Massachusetts General Hospital for Children, Boston, MA, USA
[g] National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark
[h] Section of Biostatistics, Department of Public Health, University of Copenhagen, Denmark

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) can cause cognitive impairment in children. However, long-term consequences for school performance and psychiatric morbidity have never been characterized. Our aim was to investigate long-term school performance and psychiatric morbidity after pediatric ADEM (< 18 years).

Methods: We identified all children with ADEM 2008–2015 in Denmark using hospital diagnostic codes for acquired demyelinating syndromes. We reviewed all medical records to validate ADEM including blinded MRI review. Reference children were the entire pediatric (< 18 years) population or randomly sampled sex and age-matched reference children. Outcomes were from nationwide population-based registers on special needs assistance, grade point average, highest completed education, in-hospital psychiatric hospital diagnoses, out-of-hospital psychiatric consultations or psychopharmacological drug prescriptions.

Results: 52 children had ADEM (median onset age: 5.5 years; median age at follow-up end: 13.4 years). Secondary school grade point average was similar among children with ADEM and reference children; however, children with ADEM had increased psychiatric morbidity (hazard ratio = 2.4; 95% confidence interval = 1.2–5.1; $p = 0.02$), primarily due to increased drug prescriptions for sleep problems and depression.

Conclusion: Children with prior ADEM have increased sleep problems and possibly also depression; however, school performance is seemingly unaffected. Clinicians should consider problems with sleep and mood at follow-up.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a rare autoimmune disease of the CNS. (Krupp et al., 2013; Boesen et al., 2018b, 2018a) It peaks in the first decade of life and is the commonest acquired demyelinating syndrome (ADS) at this age. (Boesen et al., 2018b, 2018a) A diagnosis of ADEM includes encephalopathy, multifocal neurological deficits, and an abnormal magnetic resonance imaging (MRI) showing poorly demarcated white-matter lesions. (Krupp et al., 2013)

ADEM is usually a transitory disease; however, one-third of these children do not recovery fully, and residual demyelinating brain lesions

Abbreviations: ADEM, acute disseminated encephalomyelitis; ADS, acquired demyelinating syndrome; MRI, magnetic resonance imaging; ICD-10, International Classification of Diseases version 10; ON, optic neuritis; NMOSD, neuromyelitis optica spectrum disorder; IPMSSG, International Pediatric MS Study Group

* Corresponding author at: Department of Neurology, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark.
E-mail addresses: magnus.spangsberg.boesen@regionh.dk (M.S. Boesen), Annika.Langkilde@regionh.dk (A. Langkilde), alfred.peter.born@regionh.dk (A.P. Born), melinda_magyari@dadlnet.dk (M. Magyari), Morten.Blinkenberg@regionh.dk (M. Blinkenberg), tchitnis@rics.bwh.harvard.edu (T. Chitnis), lct@si-folkesundhed.dk (L.C. Thygesen), eriksson@sund.ku.dk (F. Eriksson).

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may be present years after the ADEM episode. (Boesen et al., 2018b) Further, cognitive impairment in children with ADEM is well-established using neuropsychological testing. (Sunnerhagen et al., 2003; Hahn et al., 2003; Jacobs et al., 2004; Kuni et al., 2012; Rostásy et al., 2009; Deery et al., 2010; Beatty et al., 2016) However, the impact on long-term academic performance is not clear. Further, psychiatric morbidity following ADEM has not been well characterized, although ADEM may signal the onset of pediatric MS which carries a high rate of psychiatric co-morbidity. (Krupp et al., 2013; Boesen et al., 2017)

To investigate the long-term academic and psychiatric consequences of pediatric ADEM, we undertook a nationwide population-based multicenter cohort study of all children (< 18 years) with ADEM during 2008–2015 in Denmark. Our aim was to explore whether children with ADEM had poorer academic performance (i.e. school grades or special needs education) or increased psychiatric morbidity (i.e. increased prescriptions of drugs for sleep problems and depression, or outpatient psychiatric consultations).

2. Materials and methods

2.1. Children with incident ADEM during 2008–15 (exposed children)

The ADEM cohort was nationwide and population-based from January 1, 2008, to December 31, 2015, in children younger than 18 years in Denmark, as described previously. (Boesen et al., 2018b) Briefly, we reviewed the medical records in children registered in the National Patient Register with codes of the following hospital discharge diagnoses (International Classification of Diseases 10 [ICD-10] codes in parentheses): optic neuritis (ON, H46), transverse myelitis (G37.3), neuromyelitis optica spectrum disorder (NMOSD, G36.0), and other acute demyelination (G04.0, G04.8, G04.9, G36.8, G36.9, G37.8, G37.9). A review committee consisting of a resident neurologist (MSB) and a senor pediatric neurologist (APB) confirmed ADEM as the most likely diagnosis by reviewing the medical records including all case notes and paraclinical data (i.e. MRI and laboratory data).

2.1.1. Blinded MRI review

In children with ADEM, we undertook blinded reevaluation of the baseline and one follow-up MRI by a senior neuroradiologist (AL). A resident neurologist (MSB), a senior neurologist (MB), and a senior neuroradiologist (AL) constructed the MRI evaluation scheme prior to the MRI review (Table 1).

During the MRI review, AL was aware that the MRIs belonged to children with ADS but was blinded to all other data, including the ADS phenotype. The blinded MRI review was not part of the review committee's confirmation of the ADEM diagnosis.

2.2. Reference children (non-exposed children)

We used two reference cohorts:

1) Sex and age-matched reference children: All residents in Denmark have a unique personal identification number in the Civil Registration System, allowing unambiguous linkage between registers in Denmark. (Thygesen et al., 2011) The number contains information on date of birth and sex; accordingly, for each child with ADEM, we selected ten non-ADEM children matched by sex and date of birth using random sampling from the Danish population. (Pedersen, 2011) The control children did not acquire ADEM during 2008–15. The non-ADEM children were assigned an index date identical to the date of ADEM onset. We used this sex and age-matched cohort of reference children for comparing special needs education and psychiatric morbidity among children with ADEM and reference children (time-to-event data).
2) Entire non-ADEM pediatric population: For the analysis of grade point average, we used the entire pediatric population in Denmark who had obtained a grade point average from 9th (age 15 years) or 10th grade (age 16 years) during 2008–18 and who had not experienced ADEM.

2.3. Outcomes

2.3.1. Educational data

Compulsory schooling in Denmark covers one year of preschool followed by nine years of schooling, corresponding to primary and lower secondary school. Children normally start in school at 6 years old. All state and private schools in Denmark report administrative data to Statistics Denmark, which generates the nationwide Student Register. We chose the following three outcome categories for school performance:

a) Special needs assistance during 0–9 grade

Data were available from the Student Register since 2011. We defined this as a binary variable if the child had received special needs assistance during 0–9 grade. We estimated length of exposure as time from age 6 years to graduation (age 16 years) or end of follow-up (September 29, 2017).

b) Grade Point average after 9–10 grade

The School Grade Register contains data on grades from 9–10 grade, and marks are given on a scale ranging from −3 to 12, with a minimal sufficiency at 2. We calculated the mean of the four grades in Danish and Math (oral and writing). Children needed to have ADEM onset before the examination to be included in the estimate.

c) Current or highest completed degree

We included data on initiated, ongoing or completed education from the Population's Education Register, which holds annually recorded information on the highest achieved and current education for every individual. We grouped ADEM children into pre-school, 0–9 grade, high school (10–12 grade), collage/university, non-academic career (e.g. carpentry).

2.3.2. Psychiatric morbidity

Onset of psychiatric morbidity was defined by the first registration of one of the following outcomes:

a) Hospital diagnostic code of psychiatric disease

The National Patient Register contains nationwide information on all hospital admissions and outpatient visits such as demographic characteristics (i.e. age, sex), administrative details (e.g. date of admission, hospital), and diagnoses. (Lynge et al., 2011) We retrieved data on hospital diagnostic codes on “mental and behavioral disorders” (F-diagnoses in ICD-10), including depression, anxiety and attention deficit hyperactivity disorder.

b) Outpatient consultations at psychiatrist or psychologist clinics

Private consultant psychiatrists and psychologists are reimbursed by reporting to the Danish healthcare authorities, and we retrieved data on these consultations through the Danish National Health Service Register. (Andersen et al., 2011)

c) Outpatient psychopharmacological drug prescriptions

The National Prescription Database contains data on all drug prescriptions dispensed from pharmacies in Denmark. We collected data on drugs for mood disorders and attention deficits (Anatomical

Table 1
Blinded reevaluation of the baseline and one follow-up MRI in children with ADEM.

	Baseline MRI	Follow-up MRI
Children with ADEM (n = 52)	52/52 (100%)	48/52 (92%)
Time from baseline to follow-up MRI, y, mean ± SD (range)	1.0 ± 0.8 (0.02–3.8)	
Contrast given	45/52 (87%)	23/47 (49%)
Brain MRI		
Contrast enhancement	10/45 (22%)	1/23 (4%)
T1 hyperintensity (basal ganglia, thalamus, or dentate nucleus)	0/33 (0%)	0/29 (0%)
T2 lesions		
0	1/52 (2%)	20/48 (42%)
1–9	30/52 (58%)	22/48 (46%)
10–20	11/52 (21%)	4/48 (8%)
> 20	10/52 (19%)	2/48 (4%)
Complete or partial T2 resolution on follow-up MRI	–	40/47 (85%)[a]
T1 lesions		
0	17/52 (33%)	39/47 (82%)
1–9	28/52 (54%)	6/47 (13%)
10–20	5/52 (10%)	1/47 (2%)
> 20	2/52 (4%)	1/47 (2%)
Complete or partial T1 resolution on follow-up MRI	–	28/32 (88%)[a]
Lesion site		
Basal ganglia or thalamus	30/52 (58%)	4/47 (9%)
Frontal	37/52 (71%)	20/48 (42%)
Parietal	29/52 (58%)	8/48 (17%)
Occipital	25/52 (48%)	9/48 (19%)
Temporal	21/52 (40%)	7/48 (15%)
Cerebellum	19/52 (37%)	5/48 (10%)
Brainstem	27/52 (52%)	3/48 (6%)
Body of corpus callosum	14/52 (27%)	2/48 (4%)
Criteria-specific lesions		
Lesions perpendicular to long axis of corpus callosum	12/52 (23%)	5/48 (10%)
Sole presence of well-defined lesions	6/52 (12%)	8/48 (17%)
Number of periventricular lesions		
0	15/52 (29%)	36/48 (75%)
1	10/52 (19%)	5/48 (10%)
2	9/52 (17%)	3/48 (6%)
3	9/52 (17%)	3/48 (6%)
> 3	9/52 (17%)	1/48 (2%)
Juxtacortical or cortical lesions	29/52 (56%)	8/48 (17%)
Presence of diffuse, poorly demarcated, large (> 1–2 cm) lesions involving predominantly the cerebral white matter	36/52 (69%)	5/48 (10%)
ADEM is the most likely radiological diagnosis	–	47/52 (90%)
Simultaneous presence of gadolinium-enhancing and non-enhancing lesions	9/45 (20%)	1/23 (3%)
Dissemination in time on MRI (McDonald 2017 criteria)	9/52 (17%)	1/48 (4%)
Dissemination in space on MRI (McDonald 2017 criteria)	31/52 (60%)	2/48 (4%)
Optic nerve lesion[b]	2/27 (7%)	1/20 (5%)
Black holes[c]	6/52 (12%)	3/46 (7%)
Extensive, confluent leukodystrophy-like pattern[d]	4/19 (21%)	1/5 (20%)
Large, ill-defined lesions in the cerebellar peduncle[d]	11/19 (57%)	1/5 (20%)
Medullary MRI		
Medulla scanned	16/52 (31%)	18/43 (42%)
Contrast enhancement	13/15 (87%)	14/18 (78%)
T2 or STIR lesions	12/15 (80%)	1/14 (7%)
T2 or STIR lesion resolution on follow-up MRI	–	11/14 (78%)

(*continued on next page*)

Table 1 (*continued*)

	Baseline MRI	Follow-up MRI
T1 lesions	4/16 (25%)	0/17 (0%)
Longitudinal extensive transverse myelitis	10/16 (63%)	0/17 (0%)
Lesion location in spinal cord[e]		
Only central	8/16 (50%)	0/6 (0%)
Central and lateral	1/15 (7%)	0/6 (0%)

[a] Only assessed in children with lesion on baseline MRI who also had a follow-up MRI.
[b] Few children were investigated with optic nerve specific MRI sequence.
[c] Black holes were defined as hypointense, non-enhancing lesions, resembling cerebrospinal fluid on T1 weighted images and being concordant with hyperintense lesions on T2 weighted images.
[d] Only assessed in children with cerebellum lesions.
[e] Lesion location in spinal cord could be assessed in few patients only.
Abbreviations: ADEM, acute disseminated encephalomyelitis; SD, standard deviation; STIR, Short-TI Inversion Recovery; y, year.

Therapeutic Chemical in parentheses): psycholeptics (N05), psychoanaleptics (N06), and guanfacine (C02AC02). We excluded the following drug prescriptions because they are generally used for epileptic seizures: diazepam (N05BA01), midazolam (N05CD08) and clobazam (N05BA09). In Denmark, all sleep medicine (including melatonin) requires a prescription, and, in general, only pediatricians and child and adolescent psychiatrists prescribe sleep medicine for children in Denmark.

2.4. Statistical analyses

We used linear regression adjusted for sex and date of birth to compare the mean grade point average between ADEM children and all non-ADEM children in Denmark with a grade point average in 9th or 10th grade during 2008–18.

For time-to-event data, we calculated hazard ratios (HR) by using a Cox regression model with ADEM as exposure and psychiatric co-morbidity or special needs education as outcome stratified for the age- and sex-matched groups. We excluded children with psychiatric morbidity before the ADEM onset or index date. For psychiatric morbidity, follow-up time started at ADEM onset or the index date, and children were followed until the date of psychiatric co-morbidity, migration, death, or end of follow-up (December 31, 2017). For special needs education, follow-up started at ADEM onset or the index date, when the register was established (January 1, 2011), or at age 6 years (when children start primary school), and children were followed until the date of special needs education, 9-10 grade graduation, death, or end of follow-up (September 29, 2017).

2.5. Ethics

The study was approved by the Danish Data Protection Agency (case number: 30-1423/03567) and the Danish Health Data Authority (FSEID: 00003621/DST: 707103). The Danish Health and Medicines Authority waived the requirement to obtain patient informed consent to access medical records including MRIs (case number: 3-3013-896/1), and chief physicians of the relevant hospital departments approved access to patient records from their hospital.

3. Results

3.1. Characteristics of children with ADEM

A thorough description of the 52 children with ADEM has previously been published. (Boesen et al., 2018b) Briefly, the median age at onset was 5.5 years (range: 0.8–17.2) and the median age at follow-up end was 13.4 years (range: 3.6–25.9). Sixty-two percent were boys. All children with ADEM had an abnormal baseline MRI, but encephalopathy or polyfocal neurological deficits were not required; accordingly, 71% had encephalopathy, 50% had polyfocal neurological deficits, and, thus, only 35% fulfilled the International Pediatric MS Study Group (IPMSSG) criteria for ADEM. (Krupp et al., 2013)

Table 2
Grade point average in Danish and Math in 9–10 grade among children with ADEM and control children.

	ADEM[a]	Control children	Mean difference [95% CI]	p-value
Children[a], n	17	815,182	–	–
Mean (SD)	6.5 (2.6)	6.6 (2.7)	−0.12 [−1.4;1.2][b]	0.86[b]

[a] Only ADEM children with onset before 9th grade graduation were included. One child with prior ADEM, who was 17 years of age at the end of follow-up, was not registered with grades in Danish and Math.
[b] Linear regression adjusted for sex and age comparing the mean difference in grades in Danish and Math among children with ADEM and control children.
Abbreviations: ADEM, acute disseminated encephalomyelitis; n, number; CI, confidence interval; SD, standard deviation.

We undertook blinded review of MRIs in all ADEM children, and ADEM was the most likely radiological diagnosis in 47/52 (90%) of children with ADEM (Table 1). MRI findings in the five children diagnosed with ADEM on clinical criteria whose blinded MRI diagnoses were not ADEM: one child had cerebellitis, one child did not have resolution of MRI lesions on follow-up, and three children had MS-like lesions at baseline. Importantly, none of the children progressed to multiphasic ADEM or MS during follow-up by the IPMSSG criteria. (Krupp et al., 2013) However, only 7/52 (13%) were tested for anti-MOG antibodies, and 3/7 (43%) were tested positive; for anti-aquaporin-4 antibodies, 15/52 (10%) of children were tested, and 1/15 (7%) tested positive.

3.2. No difference in school performance between children with ADEM and reference children

During a median time at risk of 3 years (range: 1 month–6.7 years), special needs education was given to 6 children with ADEM (162 years at risk) and 45 reference children (1597 years at risk); this difference was not statistically significant (HR = 1.40; 95% confidence interval [CI] = 0.57 − 3.42; $p = 0.46$). Further, as shown in Table 2, the mean difference in grade point average for children with ADEM (17 children) compared with reference children was not significantly different between the two groups (mean difference = [−0.12]; 95% CI = [−1.4] − 1.2; $p = 0.86$). At the end of follow-up, 7 children with ADEM and 70 sex- and age-matched reference children were at least 20 years of age; among the ADEM children, 6/7 (86%) attended or had completed high school, whereas the proportion was 56/70 (80%) among the reference children. Further, 4 children with ADEM were at least 22 years of age at the end of follow-up, and 1/4 (25%) of children attended university; the proportion was 25/40 (63%) in the reference children.

Table 3
Hazard ratios for psychiatric morbidity after ADEM onset or index date for ADEM children compared with control children.

	ADEM[a]	Reference children[a]	HR (CI)[b]	p-value
Psychiatric outcomes combined, number of events/years at risk	9/281	37/2875	2.4 (1.2–5.1)	0.02
Psychiatric hospital diagnostic code, events	4	23	1.8 (0.6–5.4)	0.27
Psychopharmacological drug prescriptions, events	6[c]	14	4.5 (1.7–12.0)	0.003
Out-of-hospital psychiatry or psychologist visit, events	3	15	1.9 (0.5–6.5)	0.33

[a] Two ADEM and 30 non-ADEM children were excluded due to psychiatric exposure before ADEM onset or the index date. One control child died before the index date.

[b] Increased hazard for psychiatric morbidity in ADEM children compared with non-ADEM children.

[c] Five children were prescribed sleep medicine (melatonin), and one child was prescribed an anti-depressant (escitalopram). Three of these children had additional registrations: Two children had psychiatric hospital diagnostic codes for a reaction to severe stress and adjustment disorders (F43), and one of these children had a cannabis use disorder and was followed in psychiatry. One child was also followed in psychiatry.

Abbreviations: ADEM, acute disseminated encephalomyelitis; CI, confidence interval; HR, hazard ratio.

3.3. Children with ADEM had increased psychiatric co-morbidity

Psychiatric co-morbidity was present in 9 children with prior ADEM (281 years at risk) and in 37 reference children (2875 years at risk, Table 3) at the end of follow-up. Accordingly, the rate of psychiatric co-morbidity was statistically significantly higher in children with ADEM compared with reference children (Table 3: HR = 2.4; 95% CI = 1.2−5.1; $p = 0.02$). Accordingly, the hazard for psychiatric morbidity was 2.4 times higher in children with ADEM compared with reference children, although our data support an increased hazard of psychiatric morbidity ranging from 20% to 410%. This difference was primarily due to an increased prescription of drugs for sleep problems or depression (Table 3: HR = 4.5; 95% CI = 1.7−12.0; $p = 0.003$).

4. Discussion

In this nationwide population-based study, we found a seemingly similar school performance among children with ADEM and reference children. However, children with ADEM had a 2.4 increased hazard for psychiatric morbidity (HR = 2.4; 95% CI = 1.2−5.1; $p = 0.02$) compared with reference children, and this was mainly due to sleep problems and depression.

The strengths of our study are that the ADEM cohort was large and population-based with precise case ascertainment by review of the medical records, including blinded review of the baseline and one follow-up MRI. Further, the reference groups were population-based. Lastly, we used outcomes for school performance and psychiatric morbidity independently collected from nationwide, population-based registers.

Several limitations need to be addressed. (1) It is possible that children who have experienced an ADEM episode have poorer school performance than their peers, and that we did not detect this difference due to a type II error because the ADEM cohort was small and still young at the end of follow-up and, thus, not all children with ADEM had acquired the relevant register-based outcome. For example, only 17/52 (33%) of children had graduated 9–10 grade. (2) The length of exposure in the registers was not complete. (3) Few children with ADEM were tested for anti-MOG antibodies. (4) Children with prior ADEM may be more inclined to seek medical advice and treatment for psychiatric co-morbidity than would the reference children (surveillance bias). (5) Not all children with ADEM fulfilled the IPMSSG criteria for ADEM, but we thoroughly evaluated the children with ADEM by medical records and blinded review of the MRIs by an experienced neuroradiologist (Table 1). (Krupp et al., 2013) (6) The matching criteria excluded control children who acquired ADEM during 2008–2015. This means that all estimated parameters were conditioning on no ADEM events in the control group until 2015. Because ADEM is extremely rare, this conditional parameter was presumably close to the unconditional parameter which was the target of our inference. We did not have information on ADEM before 2008 when sampling reference children, and a child with an ADEM event before 2008 was misclassified as ADEM-free. As ADEM is rare, the possible bias resulting from selecting misclassified children into the reference group is small. (7) We did not have data on neuropsychological testing in children with ADEM and the reference children; instead, we used a proxy for cognitive impairment (e.g. school grades and special needs education).

Several smaller studies using neuropsychological evaluation in children with prior ADEM have demonstrated intelligence and cognition within the normal ranges, (Sunnerhagen et al., 2003; Hahn et al., 2003; Beatty et al., 2016; Suppiej and Cainelli, 2014) although other studies have pointed to persisting cognitive deficits. (Jacobs et al., 2004; Kuni et al., 2012; Rostásy et al., 2009) However, children with prior ADEM seem to have problems in attention, behavior and emotions, particularly those children with onset before 5 years of age. (Sunnerhagen et al., 2003; Jacobs et al., 2004; Beatty et al., 2016) Nevertheless, children with prior ADEM have a more favorable psychosocial and cognitive prognosis than do children with MS. (Hahn et al., 2003; Deery et al., 2010) Further, cognitive impairment and mood-related difficulties have been consistently found in children with MS. (Amato et al., 2016) In addition, MRI lesions in right thalamus, middle and posterior corpus callosum, and bilateral parieto-occipital white-matter lesions have been correlated with cognitive impairment in pediatric MS. (Rocca et al., 2014) To the best of our knowledge, studies have not investigated academic achievements after ADEM in a real-world setting using grade point average and current education as outcomes, and our findings suggest normal long-term cognitive outcome after ADEM.

Our data support the notion that ADEM should be regarded as a monophasic disease that does not impact long-term academic performance; (Boesen et al., 2018b) however, awareness of the increased psychiatric morbidity is important for counseling parents and tailoring an appropriate follow-up. We plan a follow-up study of the ADEM cohort to examine school performance at high school and university. Further, we plan to investigate the impact of pediatric MS on school performance and psychosocial outcomes in future studies. We also plan to examine baseline and follow-up MRI abnormalities as predictors of these outcomes.

In conclusion, children with prior ADEM have increased sleep problems and possibly also depression; this does seemingly not impact school performance. Clinicians should consider problems with sleep and mood at follow-up.

CRediT authorship contribution statement

Magnus Spangsberg Boesen: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Annika Langkilde:** Writing - review & editing. **Alfred Peter Born:** Conceptualization, Writing - review & editing. **Melinda Magyari:** Conceptualization, Writing - review & editing. **Morten Blinkenberg:** Conceptualization, Writing - review & editing. **Tanuja Chitnis:** Writing - review & editing.

Lau Caspar Thygesen: Conceptualization, Formal analysis, Writing - review & editing. **Frank Eriksson:** Conceptualization, Formal analysis, Writing - review & editing.

Declaration of Competing Interest

Dr. Boesen has served on a scientific advisory board for Teva; has received speaker honoraria for lecturing from Novartis and support for congress participation from Teva, Novartis and Roche.

Dr. Langkilde has received honoraria for lecturing from Biogen.

Dr. Born has received speaker honoraria from Novartis and has served on an advisory board for Biogen.

Dr Magyari has served on the scientific advisory board for Biogen, Sanofi, Teva, Roche, Novartis, and Merck; has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, and support for congress participation from Biogen, Genzyme, Teva, and Roche.

Dr. Blinkenberg has served on scientific advisory boards for Genzyme, Roche, Biogen, Merck, Novartis and Teva; has received speaker honoraria from Genzyme, Biogen, Merck, Novartis, Teva and Roche; has received consulting honoraria from the Danish Multiple Sclerosis Society, Biogen, Teva, Roche and Merck; and has received funding for travel from Genzyme, Roche and Biogen.

Dr. Chitnis has served as an advisor for Biogen-Idec, Novartis, and Alexion and serves on clinical trial advisory boards for Novartis and Sanofi Aventis. She has received research support from the Department of Defense, NIH, National MS Society, Guthy Jackson Charitable Foundation, Verily, EMD-Serono and Novartis.

Dr. Thygesen has received honoraria for lecturing from Rigshospitalet (Copenhagen, Denmark), Statistics Denmark and Sanofi Aventis.

Dr. Eriksson reports no disclosures.

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