Archives of Clinical Neuropsychology, 2024, **00**, 1–9
https://doi.org/10.1093/arclin/acae040
Original Empirical Article

Self-Reported Executive Functioning in Young Adult Survivors of Childhood Bacterial Meningitis

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ABSTRACT

Objective: This study investigated executive functions (EFs) in young adult survivors of childhood bacterial meningitis (BM). These skills are important for normal development, and their potential vulnerability in early years suggests that childhood BM could affect executive functions in the longer term.

Method: The adult self-report Behavior Rating Inventory of Executive Function was administered to 474 young adult survivors of childhood BM who participated in the 20|30 Dutch Postmeningitis study. Average scores were compared to population-norm group scores. Subgroup scores were compared according to causative pathogen and age at onset.

Results: Young adult survivors of childhood BM scored lower on overall metacognition than the age-matched population norm group. Young adult survivors of childhood BM caused by *Streptococcus pneumoniae*, *S. agalactiae*, or *Escherichia coli* had lower scores than cases caused by *Neisseria meningitidis*. Survivors with age-at-onset below 12 months had a higher (worse) overall EF score than survivors with age-at-onset above 12 months.

Conclusions: Young adult survivors of childhood BM experience difficulties in EF. However, most of the self-reported EF scores were within the norm. Future studies need to additionally assess EF in adult survivors of childhood BM using performance-based tests.

Keywords: Childhood bacterial meningitis; Long-term sequelae; Executive functioning

INTRODUCTION

Acute bacterial meningitis (BM) is a serious inflammatory condition involving the membranes (meninges) covering the brain and spinal cord with peak incidence in neonates and elderly. In the Netherlands, the incidence of BM has decreased between 1989–1993 and 2014–2019 from 6.37 to 1.58 episodes per 100.000 population per year (Bijlsma et al., 2016). BM can rapidly become fatal and lead to devastating lifelong morbidity in survivors (Liu et al., 2016). Due to the improvement of the mortality rate and decreased incidence rates as a result of immunization programs targeting the major bacterial pathogens—*Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae*—research interest has shifted to the likelihood and the patterns of residual disability in survivors of BM.

About 50% of survivors suffer from one or more long-term neurological sequelae after childhood BM (Chandran et al., 2011). Most frequently reported sequelae are hearing loss, focal neurologic deficits, cognitive deficiencies, and epilepsy (Baraff et al., 1993; Grimwood et al., 1995; Lucas et al., 2016). These sequelae are associated with invasion of the central nervous system by bacteria, causing inflammation and disruption of the meninges and subarachnoid space (Gerber & Nau, 2010). The inflammation can also involve the brain cortex and parenchyma (van de Beek et al., 2016). Cognitive deficiencies often involve deficits in short-term memory, attention, processing speed, learning, and deficiencies in executive functioning (EF) (Anderson et al., 2004; Baraff et al., 1993; Koomen et al., 2004; Viner et al., 2012). Considering long-term outcome, deficiencies in EF after childhood BM are of particular concern.

Received: March 1, 2024. **Revised:** April 15, 2024. **Accepted:** May 9, 2024

EF refers to the goal-directed control of thought, action, and emotion (Lewis et al., 2011; Munro et al., 2018; Nowrangi et al., 2014). It includes significant neuropsychological functions that enable the control and monitoring of our behavior such as thought flexibility, emotional control, and planning (Munro et al., 2018). EF has been associated with the prefrontal cortex and parietal and cerebellar lobes (Munro et al., 2018; Nowrangi et al., 2014). The latest imaging and neuropsychological studies show that the cerebellum modulates prefrontal functions via reciprocal neural loops connecting the two cortices (Darki et al., 2020; Munro et al., 2018). EF develops stepwise from childhood to adolescence in parallel to the myelination of the white matter of these neural loops (Anderson, 2001; Munro et al., 2018). Histopathological and rat model studies document a wide range of brain injuries associated with BM including loss of myelinated fibers in the white matter (Gerber et al., 2009; Gerber & Nau, 2010; Nau et al., 2004). Thus, damage by childhood BM to the developing neural loops could leave survivors vulnerable to experience deficiencies in EF (Anderson et al., 2004).

Commonly, morbidity in survivors of childhood BM varies with causing pathogen, age at onset and socioeconomic status (SES) (Collaborators, 2018; Edmond et al., 2010). Children or infants who suffer from pneumococcal meningitis (BM caused by *Streptococcus pneumoniae)* or neonatal meningitis (BM during first 28 days of life mainly caused by *S. agalactiae, Escherichia coli or Listeria monocytogenes)* have the highest risk of developing neurological sequelae (Baraff et al., 1993; Kim, 2010; Koopmans et al., 2017; Ouchenir et al., 2017). Neurological sequelae in pneumococcal meningitis and neonatal meningitis are substantially caused by serious complications that often occur in these types of meningitis such as cerebral infarction, cerebral edema, hydrocephalus, ventriculitis, hemorrhages, and secondary ischemic injury because of decreased brain perfusion (Barichello et al., 2013; Baud & Aujard, 2013; Mao et al., 2018). Young age at onset, especially below 12 months, is a well-known risk factor for both early neurologic complications and long-term sequelae of bacterial meningitis in children (de Jonge et al., 2010; Grimwood et al., 1996; Grimwood et al., 2000; Hudson et al., 2013; Namani et al., 2013). Regarding EF, age at onset below 12 months was related to poor language and executive skills (Anderson et al., 2004).

Low SES was associated with higher morbidity and mortality in survivors of childhood BM (Collaborators, 2018; Edmond et al., 2010; Koelman et al., 2020; Wright et al., 2021). In addition, coma, seizures, prolonged fever for at least 7 days, low white blood cell count, history of symptoms longer than 48 hr before admission, male gender, and absence of petechiae were identified as important prognostic factors for poor neurologic outcome (de Jonge et al., 2010). Adjunctive dexamethasone treatment in childhood BM has proven to have a beneficial effect on neurologic outcome beyond the neonatal age, especially in the case of sensorineural hearing loss (de Gans, van de Beek, & European Dexamethasone in Adulthood Bacterial Meningitis Study, 2002).

Despite several longitudinal studies on neurobehavioral outcomes in survivors of childhood BM, potential deficiencies in EF have not been extensively investigated in survivors of childhood BM (Anderson et al., 2004; Chandran et al., 2011; Grimwood et al., 2000). The purpose of the present study was to study EF in two large and unique historical cohorts of young adult survivors of childhood BM. EF was investigated using the Behavioral-Rating-Inventory-of-Executive-Functioning Adult Self-Report (BRIEF-A) because it is related to quality of life and adaptive functioning (Cushman et al., 2021; Perna et al., 2012). We hypothesized that deficiencies in EF are prevalent in young adult survivors of childhood BM and that prognostic factors for poor neurologic outcome were associated with deficiencies in EF. Especially, survivors who suffered from pneumococcal meningitis or neonatal meningitis and survivors with age of onset below 12 months were expected to be at risk of deficiencies in EF.

METHODS

Sample and Procedure

A total of 947 survivors of childhood BM were contacted and received a letter to participate in the present study, as part of the Dutch 20|30 Postmeningitis study. The Dutch 20|30 Postmeningitis study was initiated to investigate long-term outcomes after childhood BM. In brief, the Dutch 20|30 Postmeningitis study investigated executive and behavioral functioning, mood and sleeping disorders, subjective hearing, health-related quality of life, academic performance, and economic self-sufficiency (de Jonge et al., 2013; El Tahir et al., 2019; Koomen et al., 2005).

The cohort of survivors used in the Dutch 20|30 Postmeningitis study were composed of two independent, comparable historical cohorts (de Jonge et al., 2013; Koomen et al., 2003). For the first cohort, files of the Netherlands Reference Laboratory for BM (NRLBM) were searched in 1999 for children born between January 1986 and December 1994 who survived non-hemophilus influenzae type b (Hib) BM between January 1990 and December 1995. For the second cohort, the files of the NRLBM were searched again in 2005 for Dutch children born between January 1993 and December 1999 who suffered from non-hemophilus influenzae type b (Hib) BM between January 1997 and December 2001. The diagnosis BM was based on the isolation of bacteria in the cerebrospinal fluid (CSF). Exclusion criteria included a complex onset of meningitis (defined as: meningitis secondary to immunodeficiency states, Central nervous system (CNS) surgery, cranial trauma, and CSF shunt infections of relapsing meningitis).

Self-Reported Executive Functions With the BRIEF-A

The Behavioral-Rating-Inventory-of-Executive-Functioning Adult Self-Report (BRIEF-A) was used to assess everyday EF (Gioia et al., 2000). Using the BRIEF-A, the participants indicated the frequency of issues by rating 75 statements on a three-point Likert scale ranging from 1 (never) to 3 (often).

Raw sum scores were used to compare survivors of childhood BM to the norm group with same age range as survivors of childhood BM in the present study (only raw scores were available). For the comparison of survivors of childhood BM with a clinically normal versus clinically elevated score on the BRIEF-A, raw sum scores were transformed into age-adjusted norm scores that followed a *t*-distribution with mean = 50 and standard deviation (*SD*) = 10. A higher T-score score indicated a higher number of reported issues by the questionnaire respondent. A T-score of

65, or 1.5 *SD* above the mean, was used as the threshold for a clinically elevated score indicating deficiencies in executive functioning (Aita et al., 2023; Reynold de Seresin et al., 2023). The nine BRIEF-A subscales were merged into two broader indexes and an overall global executive composite score (GEC). The first broad index, the behavior regulation index (BRI), included the following subscales: inhibit, shift, emotional control, and self-monitor.

The second broad index, the metacognition index (MI), includes the following subscales: initiate, working memory, task completion, planning/organizing, and organizing materials. The reliability coefficients of the BRIEF-A scales in the present study ranged from 0.75 to 0.96 and were comparable to the reliability values of a normative sample (0.72–0.96) (Scholte, 2011).

Self-reported EF was digitally collected between April 2018 and October 2019. A normative population sample of Dutch and Flemish adults ($N = 1{,}600$) was included to compare EF scores (Scholte, 2011). Only the two broad indexes and the GEC score of the normative population sample were available. Part of the normative sample ($N = 444$) was matched by age to the cohort of survivors of childhood BM because scores of individual subscales were available for this group (Scholte, 2011). The medical ethical committee of VU University Medical Center Amsterdam (now Amsterdam UMC) approved the Dutch 20|30 Postmeningitis study, and written active consent was obtained from all participants.

Statistical Analyses

Incomplete questionnaires were excluded. For descriptive analyses, categorical variables are presented as number (%) while continuous variables are presented as mean (*SD*) or as median. Chi-square tests (or Fisher exact tests, when cell sizes were small) and Mann–Whitney U tests were used to assess differences between the clinically elevated GEC group (T-score of ≥65 for GEC) and clinically normal GEC group (T-score of <65 for GEC). One sample *t*-tests were used to compare average EF raw sum scores of survivors of childhood BM with those of the age-adjusted norm sample. Subgroup analyses of executive function were calculated with multivariate analysis of variance (MANOVA) for BM subtypes with gender, age-at-onset (≤12 vs. >12 months of age) and causative pathogen (*S. pneumoniae*, *N. meningitidis,* and *S. agalactiae or E. coli*) as between-subject factors. Further analysis with multivariate analysis of covariance (MANCOVA) also controlled for coma, seizures, prolonged fever for at least 7 days, low white blood cell count, history of symptoms longer than 48 hr before admission, male gender and absence of petechiae, average educational level (as indication of SES) of both parents, and current age as covariates.

RESULTS

Demographic Characteristics

A total of 488 participants were included in the Dutch 20|30 Postmeningitis study after deduplication and exclusion of participants who did not complete any of the questionnaires. A subsample of 474 participants fully completed the BRIEF-A (Fig. 1). Demographic and clinical characteristics are reported in Table 1. The median age of the survivors was 26.00 years (range 22.00–28.00), and the median time since meningitis was 23.1 years (range 19.4–25.4). Educational outcomes were significantly different between the GEC ≥ 65 (group with a clinically elevated level of problems in EF) and the GEC < 65 group (group with a clinically normal level EF). The number of survivors with a lower educational level, academic retention, and special needs in primary or secondary school were higher in the GEC ≥ 65 (group with a clinically elevated level of problems in EF). Other demographic and clinical factors were not significantly different between the GEC ≥ 65 and the GEC < 65 group.

Executive Functioning

Figure 2 summarizes the descriptive statistics on all scales of the BRIEF-A (Scholte, 2011) and outcomes of *t*-tests comparing the survivors of childhood BM with an established age-matched norm group sample. Compared to the established norm group, survivors of childhood BM scored significantly higher (worse) on the themes of inhibition, working memory, and organizing materials, indicating increased levels of issues. Conversely, survivors of childhood BM scored significantly lower (better) on emotional control and self-monitor. Considering the broader indexes, survivors of childhood BM scored significantly higher (worse) on the MI than the established norm group (*Ms* 61.7 vs. 59.8, 95% CI: 0.55–3.25, $p < .01$) and significantly lower (better) on the BRI (*Ms* 45.1 vs. 46.3, 95% CI: −2.12 to −0.17, $p = .02$). The GEC scores for survivors of childhood BM and the established norm group were not significantly different (*Ms* 106.8 vs. 106.1, 95% CI: −1.41 to 2.92 $p = .47$). Figure 2 also shows greater variation in EF within the group of survivors of childhood BM.

Difference in Executive Functioning Across Subgroups According to Causative Pathogen, Gender and Age-At-Onset

The outcomes of the three (causative pathogen) × two (age-at-onset) and two (causative pathogen) × two (age-at-onset) MANOVA examining EF differences in BM subtypes can be found in Table 2 and Table S1 and S2 (Supplementary materials). A significant main effect was found for causative pathogen, with univariate main effects on working memory and planning/organizing. Specifically, survivors of childhood BM caused by *S. pneumoniae* and *S. agalactiae/E. coli* scored higher (worse) on working memory and planning/organizing than survivors of childhood BM caused by *N. meningitidis* (see Table S1, Supplementary materials). For age-at-onset, a main effect was found, with univariate main effect on Initiate. The interaction between age-at-onset and causative pathogen was not significant. The MANCOVA for causative pathogens and age-at-onset adjusted for educational level of parents, current age, absence of petechiae, coma, low white blood cell count, male gender, prolonged fever, seizures, and symptoms >48 h also revealed a significant main effect for causative pathogen with a univariate main effect for working memory indicating remaining increased levels of issues with working memory when controlled for these factors. The results of age-at-onset were similar to the MANOVA outcomes. Thus, survivors with age-at-onset below 12 months had a higher (worse) overall EF score than survivors with age-at-onset above 12 months, although there were no significant differences in the nine BRIEF subscale scores.

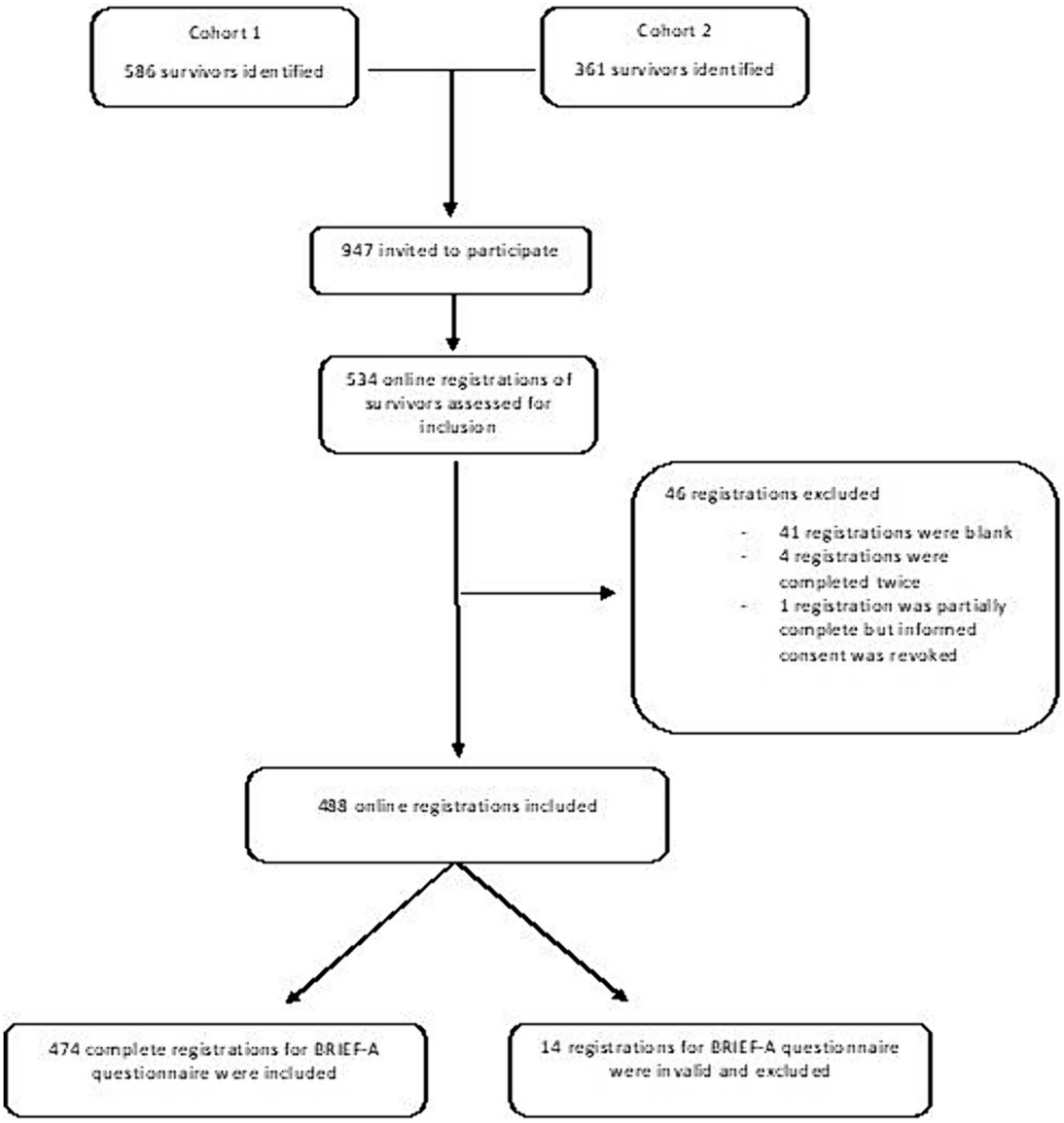


Fig. 1. Flowchart demonstrating the selection of participants for the Dutch 20|30 Post meningitis study.

The outcomes of the two (gender) × two (age-at-onset) MANOVA (Table S3 and S4, Supplementary materials) examining EF differences in gender subgroups show a significant main effect for gender. This was characterized by univariate main effects on inhibition, shift, emotional control, self-monitor, initiate, and planning/organizing. Men scored significantly higher (worse) on inhibition, initiate, self-monitor, and planning/organizing than women, while women scored significantly higher (worse) on shift and emotional control than men. No significant multivariate main effect was found for age-at-onset, but a univariate main effect for initiate was found. Survivors of childhood BM with age-at-onset below 12 months scored higher (worse) on initiate than survivors of childhood BM with age of onset above 12 months. The interaction between gender and age-at-onset was not significant.

The outcomes of the three (causative pathogen) × two (age-at-onset) MANCOVA adjusted for dexamethasone, educational level of parents, current age, absence of petechiae, coma, low white blood cell count, male gender, prolonged fever, seizures, and symptoms >48 h (Table S5, Supplementary Materials) revealed a significant main effect for causative pathogen but no main effect for age-at-onset. No univariate main effects were found. The interaction between causative pathogen and dexamethasone was not significant.

The outcomes of the three (causative pathogen) × two (age-at-onset) and the two (causative pathogen) × two (age-at-onset) MANCOVA adjusted for dexamethasone, educational level of parents, current age, absence of petechiae, coma, low white blood cell count, male gender, prolonged fever, seizures, and symptoms >48 h (Tables S5 and S6, Supplementary materials) revealed a significant main effect for causative pathogen but no main effect for age-at-onset. No univariate main effects were found. The interaction between causative pathogen and dexamethasone was not significant.

Table 1. Demographic and clinical characteristics of survivors of childhood bacterial meningitis

	Total sample $N = 474$	GEC[a] ≥ 65 $N = 75$	GEC < 65 $N = 399$	Cramer's Φ	p
Male, *n* (%)	212 (45)	32 (43)	180 (45)	0.02	.70
Current age (years), median (IQR)	26.0 (22.0–28.0)	25.0 (21.0–27.0)	26.0 (23.0–28.0)	n.a.	.09[d]
Low[b] educational level, *n* (%)	298 (63)	59 (79)	239 (60)	0.14	<.01
Academic retention in primary or secondary school, *n* (%)	95 (20)	22 (29)	73 (18)	0.10	.04
Special needs in primary or secondary school, *n* (%)	166 (35)	37 (49)	129 (32)	0.13	<.01
Employment status (unemployed), *n* (%)	61 (12)	19 (25)	42 (11)	0.16	<.01
Age at admission (months), median (IQR)	25.0 (9.0–46.0)	22.0 (7.0–40.0)	26.0 (9.0–47.3)	n.a.	.18[d]
Age ≤ 12 months at admission, *n* (%)	147 (31)	26 (35)	121 (30)	0.03	.46
Time since meningitis (years), median (IQR)	23.1 (19.3–25.4)	22.9 (18.9–25.1)	23.2 (19.4–25.4)	n.a.	.38[d]
Causing pathogen, *n* (%)					
E. coli	6 (1)	0 (0)	6 (2)	0.05	.60[e]
N. meningitidis	361 (76)	55 (73)	306 (77)	0.03	.53
S. agalactiae	16 (3)	4 (5)	12 (3)	0.05	.30[e]
S. pneumoniae	90 (19)	15 (20)	75 (19)	0.01	.81
Dexamethasone (administered during admission), *n* (%)	106 (22)	17 (23)	89 (22)	0.01	.87
Prognostic factors and complications, *n* (%)[f]					
Absence of petechiae	157 (45)	29 (46)	128 (45)	0.02	.77
Coma	278 (84)	36 (59)	183 (67)	0.07	.21
Focal neurologic signs	31 (7)	8 (11)	23 (6)	0.09	.10
Hearing impairment[g]	41 (9)	5 (7)	36 (9)	0.03	.51
Low white blood cell count[h]	24 (7)	18 (6)	6 (9.7)	0.05	.31
Prolonged fever	219 (66)	48 (53)	230 (84)	0.01	1.00
Seizures	55 (12)	12 (16)	43 (11)	0.08	.16
Symptoms >48 h	84 (24)	10 (16)	74 (25)	0.09	.09
Health-related quality of life, median (IQR)[i]					
Global Physical Health	51.5 (32.7–62.5)	46.6 (33.0–62.5)	51.5 (32.7–62.5)	0.51	<0.01
Global Mental Health	48.9 (21.3–67.6)	40.3 (21.3–60.6)	50.4 (30.7–67.6)	0.65	<0.01
Global02 (overall quality of life)	4 (1–5)	3 (1–5)	4 (1–5)	0.34	<0.01
Depression	41.0 (41.0–75.6)	57.1 (41.0–75.6)	41.0 (41.0–69.6)	0.63	<0.01
Anxiety	51.4 (40.3–81.4)	59.7 (40.3–81.4)	48.1 (40.3–71.4)	0.66	<0.01
Sleep disturbance	45.1 (32.0–68.3)	52.2 (32.0–68.3)	45.1 (32.0–68.2)	0.61	<0.01
Fatigue	46.1 (33.0–75.8)	53.2 (33.7–75.8)	46.0 (33.7–70.3)	0.51	<0.01

[a]Global Executive Composite; GEC ≥ 65 refers to survivors of childhood BM with a clinically elevated score; GEC < 65 refers to survivors of childhood BM with a clinically normal score; [b]Educational level was dichotomized as low (secondary and intermediate vocational education) and high (at least higher vocational education); [d]Mann–Whitney U test; [e]Fisher's exact test; [f]Symptoms >48 h before presentation. [g]Hearing impairment was defined as unilateral or bilateral perceptive loss of >25 dB. [h]Low blood cell count corresponds to a value less than 5,000/mm^3. [i]PROMIS Profile-29 and PROMIS Global Health domains.

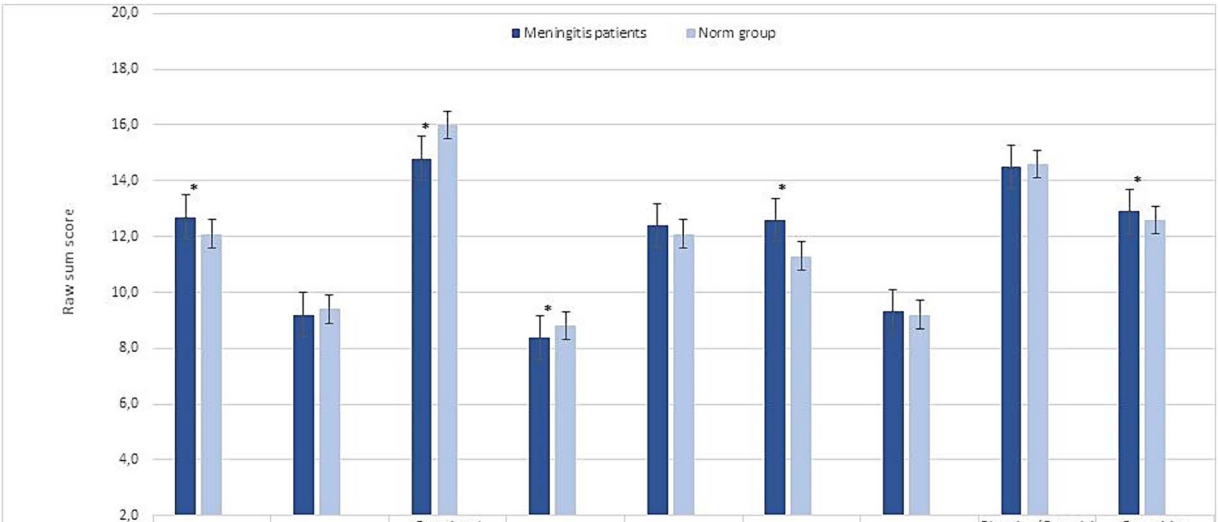
DISCUSSION

This nationwide cohort study investigated EF in young adult survivors of childhood BM. Findings suggest that childhood BM might lead to deficiencies in EF. About 15% ($N = 75$) of survivors of childhood BM in the present study showed a clinically elevated overall EF score.

Survivors of childhood BM primarily reported problems on the metacognition scale. Specifically, these were in the initiate, working memory, planning/organizing, organization of materials, and task-completion scales. Of these scales, working memory and organizing of materials ability seemed particularly vulnerable. Interestingly, survivors of childhood BM reported less problems with emotional control and self-monitor than the age-matched norm group. This finding is puzzling but might be due to sequelae following BM being adequately managed, promoting maturation of emotional control and self-regulation.

The results of this study are in line with previous findings, at 4–10 years post-illness (Koomen et al., 2004) and in a study with longitudinal data on neurobehavioral outcomes in children who recovered from childhood BM (Anderson et al., 2004), EF was not severely impaired but it was consistently below normative developmental expectations. Moreover, age-at-onset of childhood BM below 12 months was related to poor academic scores and poor performance on tasks requiring executive skills in these studies. Survivors of childhood BM in the present study with age-at-onset below 12 months also reported more problems with EF compared to those with age-at-onset above 12 months. Scores on the nine EF subscales were similar for survivors of childhood BM with age-at-onset above and below 12 months. This last finding might be explained by the influence of age-at-onset becoming less substantial on EF or cognitive outcome with time since illness (Anderson, 2001; Anderson et al., 2004; Bedford et al., 2001).

The variation in all EF subscales was greater in survivors of childhood BM than in the age-adjusted norm group, suggesting that the group of survivors of childhood BM is more heterogeneous concerning EF. The number of survivors that required special educational needs was higher in the group



	Inhibition	Shift	Emotional control	Self-monitor	Initiate	Working Memory	Task monitor	Planning/Organizing	Organizing materials
Meningitis patients	12,7	9,2	14,8	8,4	12,4	12,6	9,3	14,5	12,9
Norm group	12,1	9,4	16	8,8	12,1	11,3	9,2	14,6	12,6
Cohen's d	0,20	0,07	0,26	0,16	0,09	0,37	0,04	0,03	0,08

Fig. 2. Average BRIEF subscales scores of survivors of childhood bacterial meningitis ($N = 474$) compared to norm group scores ($N = 444$). Note. $^{*}p < .05$.

of survivors with a clinically elevated level of problems in EF. Furthermore, the number of unemployed survivors and survivors with lower education attainment was also higher in the group of survivors with a clinically elevated level of problems in EF. As, neurological sequelae can vary with causing pathogen, we explored differences in EF scores between causing pathogen subgroups. Survivors of childhood BM caused by *S. pneumoniae, S. agalactiae*, or *E. coli* reported more problems in EF than survivors of childhood BM caused by *N. meningitidis*. This finding is consistent with literature on pathogen-specific outcome. Childhood BM caused *by S. pneumoniae*, *S. agalactiae*, and *E. coli* is associated with high mortality and neurological disability (Bijlsma et al., 2016; Ouchenir et al., 2017; van de Beek et al., 2016).

Our results should be considered in light of some methodological limitations. Firstly, the effect sizes in the present study were small implicating that not all these differences might be clinically relevant. Also, statistical differences in the present study are heavily dependent on the included sample size. In large sample sizes, even small differences in EF scores can appear statistically significant. But, values for statistical significance do not evaluate clinical significance; often, it is the judgment of the clinician and the patient that decides whether a result is clinically significant or not. Secondly, only the BRIEF was used to measure EF in the present study. In order to obtain full insight into EF in young adult survivors additional studies with performance-based measures are needed for a more comprehensible interpretation of the results found in the present study. A number of studies indicate low concordance between objective measures to assess neuropsychological functions and subjective self-reported measures in this domain (Biederman et al., 2008; Stanovich, 2009; Toplak et al., 2013). However, the BRIEF is a widely used measure to assess EF and self-report scales and questionnaires like the BRIEF have been shown to have a higher ecological validity than results obtained in a structured test environment (Isquith et al., 2013; Lewis et al., 2011). Ecological validity refers to the association between a particular measure and everyday behavior. Ecological validity is important because cognitive performance in functional contexts can vary significantly from underlying impairment. In addition, acquired strategies or other cognitive functions might compensate for underlying neuropsychological difficulties in survivors of childhood BM. Important aspects in the present study that might have influenced EF scores and the interpretation of these scores are: the fact that young adult survivors may lack self-awareness considering everyday functioning and the fact that no information from a proxy was obtained. Thirdly, another limitation of the current study was the fact that normative psychological test measures were used instead of a control group. Another important aspect of this study is that self-reported problems might be underestimated due to selection bias. This might have occurred because we used an online version of the BRIEF-A questionnaire that possibly restricted participation of patients with more severe sequelae. Finally, no information on the progression of self-reported EF difficulties over time could be obtained because of the cross-sectional design of this study.

CONCLUSION

Young adult survivors of childhood BM experience difficulties in EF. The percentages of survivors who required special educational needs, survivors with low educational attainment, and unemployed survivors were higher in the group of survivors with a clinically elevated level of problems in EF compared to the group of survivors with a clinically normal level of EF. Future studies using performance-based measures are needed for a more

Table 2. Outcomes of MAN(C)OVAs investigating differences in BRIEF-subscales across causing pathogen and age at onset subgroups ($N = 473$)

	MANOVA				MANCOVA			
	Pilai's trace	***F***	***p***	η_p^2	**Pilai's trace**	***F***	***p***	η_p^2
Causative pathogen (*N. meningitidis*, *S. pneumoniae*, *S. agalactiae*/*E. coli*[a]) × Age-at-onset (≤12 months of age, >12 months of age)								
Causative pathogen	0.05	2.51	0.001	0.03	0.15	2.39	0.001	0.07
Inhibit		0.14	0.873	0.01		1.46	0.235	0.10
Shift		1.58	0.207	0.01		1.02	0.363	0.01
Emotional control		2.40	0.092	0.01		1.81	0.308	0.01
Self-monitor		1.10	0.333	0.01		0.97	0.379	0.01
Initiate		1.77	0.172	0.01		0.72	0.487	0.01
Working memory		3.91	0.021	0.02		5.00	0.007	0.03
Task completion		1.16	0.313	0.01		2.49	0.084	0.02
Planning/organizing		3.31	0.038	0.01		5.12	0.007	0.03
Organizing materials		0.10	0.907	0.01		0.95	0.497	0.04
Age-at-onset	0.04	1.91	0.049	0.04	0.04	1.36	0.207	0.04
Inhibit		0.76	0.382	0.01		0.13	0.719	0.01
Shift		0.02	0.900	0.01		3.24	0.073	0.01
Emotional control		2.03	0.155	0.01		0.59	0.442	0.01
Self-monitor		0.92	0.761	0.01		0.03	0.870	0.01
Initiate		0.61	0.436	0.01		4.2	0.042	0.02
Working memory		3.47	0.063	0.01		0.71	0.401	0.01
Task completion		0.25	0.616	0.01		3.13	0.078	0.01
Planning/organizing		0.24	0.622	0.01		1.00	0.369	0.01
Organizing materials		0.01	0.986	0.01		1.75	0.187	0.01
Causative pathogen × Age-at-onset	0.04	1.14	0.307	0.02	0.02	0.76	0.656	0.02
Covariates								
Current age					0.05	2.80	0.003	0.05
Educational level of parents[c]					0.04	1.1	0.363	0.04
Absence of petechiae					0.04	1.37	0.200	0.04
Coma					0.05	1.64	0.105	0.05
Low white blood cell count[d]					0.04	1.26	0.262	0.04
Male gender					0.23	8.9	0.001	0.23
Prolonged fever					0.01	0.43	0.920	0.01
Seizures					0.03	0.92	0.510	0.03
Symptoms >48 h					0.02	0.70	0.713	0.02

[a]Patients with *S. agalactiae* and *E. coli* were combined due to small sizes. The only patient with *L. monocytogenes* was excluded from the analysis; [b]Educational level of both parents was dichotomized as low (educational level was secondary school and/or intermediate vocational education) or high (educational level was at least higher vocational education). [d]Low blood cell count corresponds to a value less than 5,000/mm^3.

comprehensible interpretation of the results found in the present study and more widely investigation of neurobiological effects associated with childhood BM.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Archives of Clinical Neuropsychology* online.

FUNDING

This work was supported by GlaxoSmithKline Biologicals SA [HE-NEISSERIA-001 to AMvF]. GlaxoSmithKline Biologicals SA was involved in establishing the contents of the Dutch 20|30 Postmeningitis Study. The final responsibility for this study rests with the authors.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We thank all survivors of childhood bacterial meningitis for their participation in the Dutch 20|30 Post Meningitis study and Heleen Maurice Stam for assistance with statistical analyses.

AUTHOR CONTRIBUTIONS

Omaima El Tahir (Conceptualization, writing— original draft, editing final draft), Julia Groenveld (Conceptualization, Writing—original draft), Rogier de Jonge (Investigation, Project administration, Supervision, Writing—original draft, Writing—review & editing), Kim Oostrom (Conceptualization, Formal analysis, Investigation, Methodology, Supervision), Sui Lin Goei (Conceptualization, Methodology, Supervision), Jeroen Pronk (Methodology, Supervision, Writing—original draft), and Marceline van Furth (Conceptualization, Funding acquisition, Methodology, Project administration, Supervision).

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