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REVIEW

Quantitative Meta-analyses of Cognitive Abilities in Children With Pediatric-onset Multiple Sclerosis

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Abstract

Pediatric-onset multiple sclerosis (POMS), is the manifestation of multiple sclerosis in individuals before 18 years of age. About a third of children with POMS show some form of lower cognitive performance. The purpose of this study is to examine using quantitative meta-analyses the effect size of altered performance between children with and without POMS on overall intelligence quotient (IQ), information processing speed, and language functions. We searched the literature for studies that reported scores on cognitive tests administered to children with and without POMS. Studies were systematically reviewed using PRISMA guidelines. We analyzed data from 14 studies that examined 1283 children with and without POMS when cognitive categories consisted of five or more studies. Effect sizes, publication bias and potential confounds were considered. Significant cognitive differences are revealed for all categories with the strongest effect observed for overall IQ. A moderate effect is observed for information processing speed, and small effects for verbal fluency and verbal memory. Cognitive abilities present differently in children with POMS and a better understanding of this manifestation will inform intervention and remediation tools that can improve clinical and educational practice for the benefit of children with POMS.

Keywords Pediatric-onset multiple sclerosis · POMS · Cognitive abilities · Children · Meta-analysis

Introduction

Multiple sclerosis is a chronic inflammatory disease with progressive neurodegeneration. Pediatric-onset multiple sclerosis (POMS) is a rare form of multiple sclerosis, expressed when the manifestation of the disease starts before 18 years of age. POMS makes up 3 to 5% of all individuals with multiple sclerosis (Belman et al., 2016; Boiko et al., 2002; Chitnis et al., 2009, 2011; Duquette et al., 1987; Ghezzi et al., 1997; Yeh et al., 2009). The overall incidents range from 0.05 to 2.85 per 100 000 children and this number increases with age (Jeong et al., 2019).

Approximately 30% of all patients with POMS experience some form of cognitive impairment (Amato et al., 2008; Julian et al., 2013; MacAllister et al., 2005). Research demonstrates altered cognitive skills in individuals with POMS, such as intellectual functioning, language, information processing speed as well as attention, visuomotor and visuospatial abilities, memory, and executive functions (Blaschek et al., 2012; Bogdanova et al., 2020; MacAllister et al., 2013; Öztürk et al., 2020; Storm Van's Gravesande et al., 2019; Suppiej et al., 2014). Some studies conclude that impairment of language abilities is present for children with POMS, but not for adults with multiple sclerosis (Amato et al., 2008; Banwell & Anderson, 2005; MacAllister et al., 2005, 2007; Smerbeck et al., 2011; Till et al., 2011). Most studies show lower scores on overall intelligence tests in children with POMS compared to their typically developing peers (Carroll et al., 2019; Green et al., 2018; Pastò et al., 2016; Till et al., 2012; Wuerfel et al., 2018). But some results show the absence of these differences (Portaccio et al., 2009; Smerbeck et al., 2011). Studies on information processing speed demonstrate longer

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reaction times for children with POMS in comparison with the control group (Bethune et al., 2011; Brenton et al., 2019; Charvet et al., 2014; Pastò et al., 2016; Portaccio et al., 2009; Wuerfel et al., 2018), but not always (Till et al., 2013).

Studies with children that examined mean age at testing (Johnen et al., 2019) or age at POMS onset (Wuerfel et al., 2018), have attributed effects of altered performance to age, whereas others did not (Green et al., 2018; Pastò et al., 2016; Smerbeck et al., 2011). Quantitative meta-analyses with adults with multiple sclerosis also show the influence of age on processing speed and working memory (Johnen et al., 2017), but other meta-analyses did not identify effects of age (Prakash et al., 2008; Santangelo et al., 2019). Thus, it remains unclear which cognitive categories are most affected by POMS and whether age moderates these effects. Because no single study is definitive, systematic reviews and meta-analyses can serve as powerful tools for identifying overarching effects in the literature. In a series of meta-analyses, we examine, for the first time, effect sizes associated with overall intelligence quotient (IQ), speed of processing and language functions (i.e., verbal fluency and verbal memory) in children with and without POMS.

Methods

Literature Search and Systematic Review

To systematically review the literature, we used the established PRISMA 2020 guidelines and checklist (Page et al., 2021). Literature databases PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (www.webofknowledge.com) were searched between March 1st and April 1st, 2021 for articles written in English and Russian using keywords: (executive function OR inhibition OR memory OR information processing speed OR language OR verbal fluency OR cognition OR cognitive impairment OR cognitive decline OR cognitive reserve OR attention OR IQ OR intelligence) AND (multiple sclerosis) AND (children OR pediatric OR childhood OR adolescents OR adolescence OR youth). A supplementary manual search of references in relevant articles was also performed. This search yielded a total of 1590 papers. Figure 1 illustrates article yields and steps taken to identify eligible articles.

Selection Criteria

Eligible articles examined the cognitive performance of children (age < 18 years) with POMS and a matched control group; studies with other comorbidities in which participants had additional diagnosis were excluded. Excluded diagnoses were Hodgkin's lymphoma, and schizoaffective disorder. Eligible articles reported age and sample size, numerical values for means and standard deviations for each sample. Corresponding authors of some studies that examined eligible samples but did not report numerical scores needed for the meta-analyses were contacted. A total of 14 articles survived these criteria and were considered for the quantitative meta-analyses.

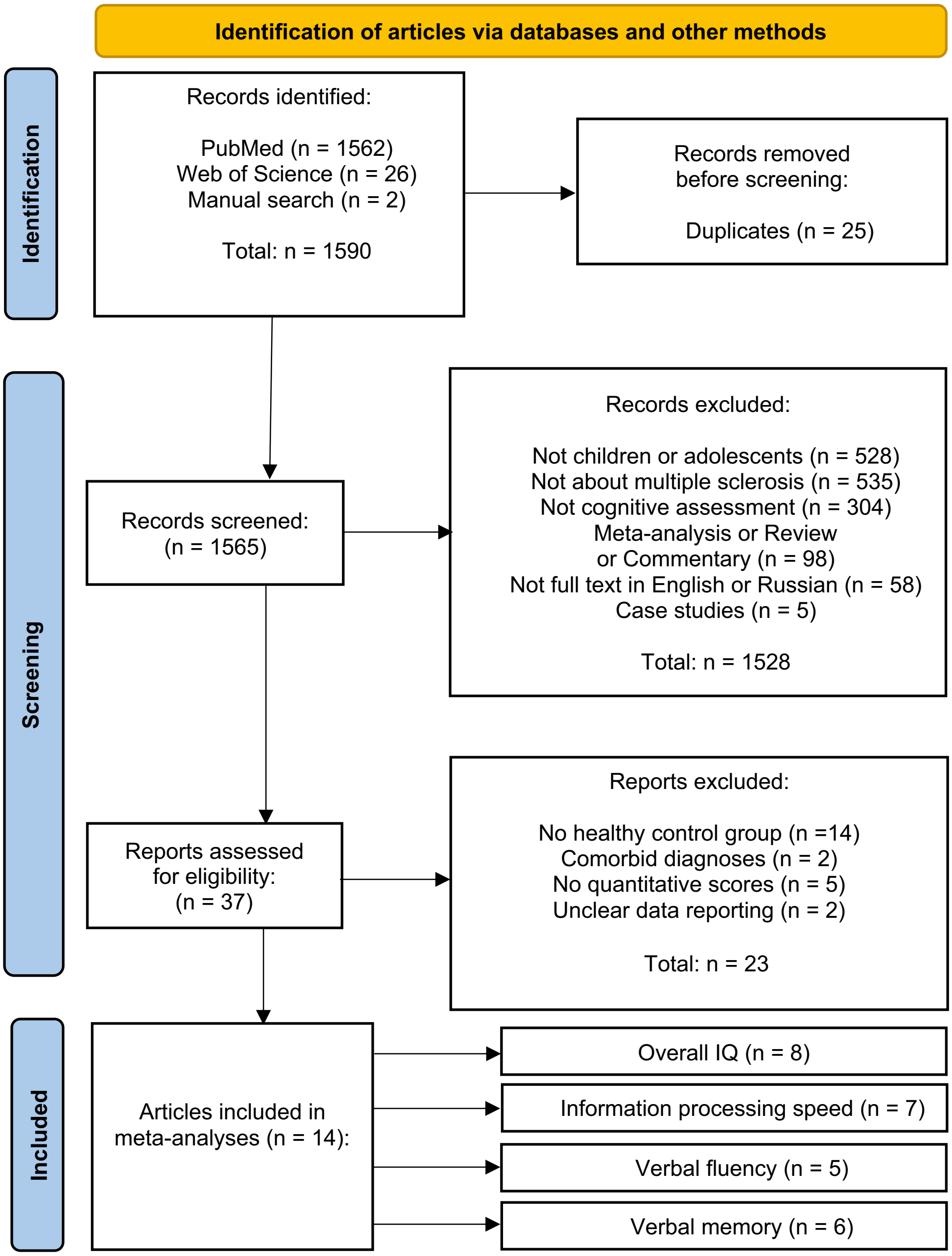
Data Extraction

Article information, sample demographics and author conclusion were organized by age, sex, clinical characteristics of POMS and cognitive categories (Table 1). We tabulated data from all eligible studies which used neuropsychological tests and organized them into cognitive categories. Although some suggest that quantitative meta-analyses can be performed using data from two studies (Valentine et al., 2010), others recommend that five or more studies can provide reasonable power for random-effects meta-analyses (Jackson & Turner, 2017). These considerations yielded four categories that contained five or more original studies with data from children with POMS and controls: (a) overall IQ, (b) information processing speed (i.e., reaction time) for oral and written versions, and only oral version, (c) verbal fluency (e.g., retrieving words from memory related to a category from memory), and (d) verbal memory (e.g., ability to memorize and retrieve verbal stimuli). Articles were screened, data were tabulated, and the final dataset was double-checked by Elena S. Lysenko and Mariia D. Bogdanova.

Statistical Analysis

Quantitative meta-analyses were performed using R studio. The metaphor (Viechtbauer, 2010) package in R programming language was used to perform statistical analyses for identifying weighted effect-sizes across cognitive categories; multilevel meta-analyses were used by calculating between-study variance τ^2 differences in effect-sizes within studies and between studies. Effect sizes for between-group scores were calculated as Hedges' g, representing mean differences between children with POMS and typically developing children, divided by the pooled standard deviation for each cognitive category. To evaluate the significance of the results, confidence intervals ($p < 0.05$) were considered. According to Cohen's conventions, effect-size, $d \geq 0.2$, $d \geq 0.5$ and $d \geq 0.8$ are interpreted to have small, medium, and large effects, respectively. Egger's regression tests were used for funnel plots construction (Higgins et al., 2003). Quality control associated with publication bias was also assessed (Bown & Sutton, 2010; Duval & Tweedie, 2000). Specifically, heterogeneity statistics measured the degree of interstudy heterogeneity (Q-test) and the proportion of different variation between samples (I^2). Values lower than 25% were considered as low interstudy heterogeneity, values around 50% were medium interstudy heterogeneity and

Fig. 1 PRISMA illustrating the screening and study selection process for meta-analysis



a value greater than 75% were considered high (Higgins et al., 2003). Using the package metameta in (Quintana, 2020, 2021) we performed power analyses by estimating the median of statistical power for each cognitive category for a range of true effect sizes. Mixed-effects meta-regression model was used to assess the influence of confounds as mean age and sex on cognitive categories (Viechtbauer, 2010).

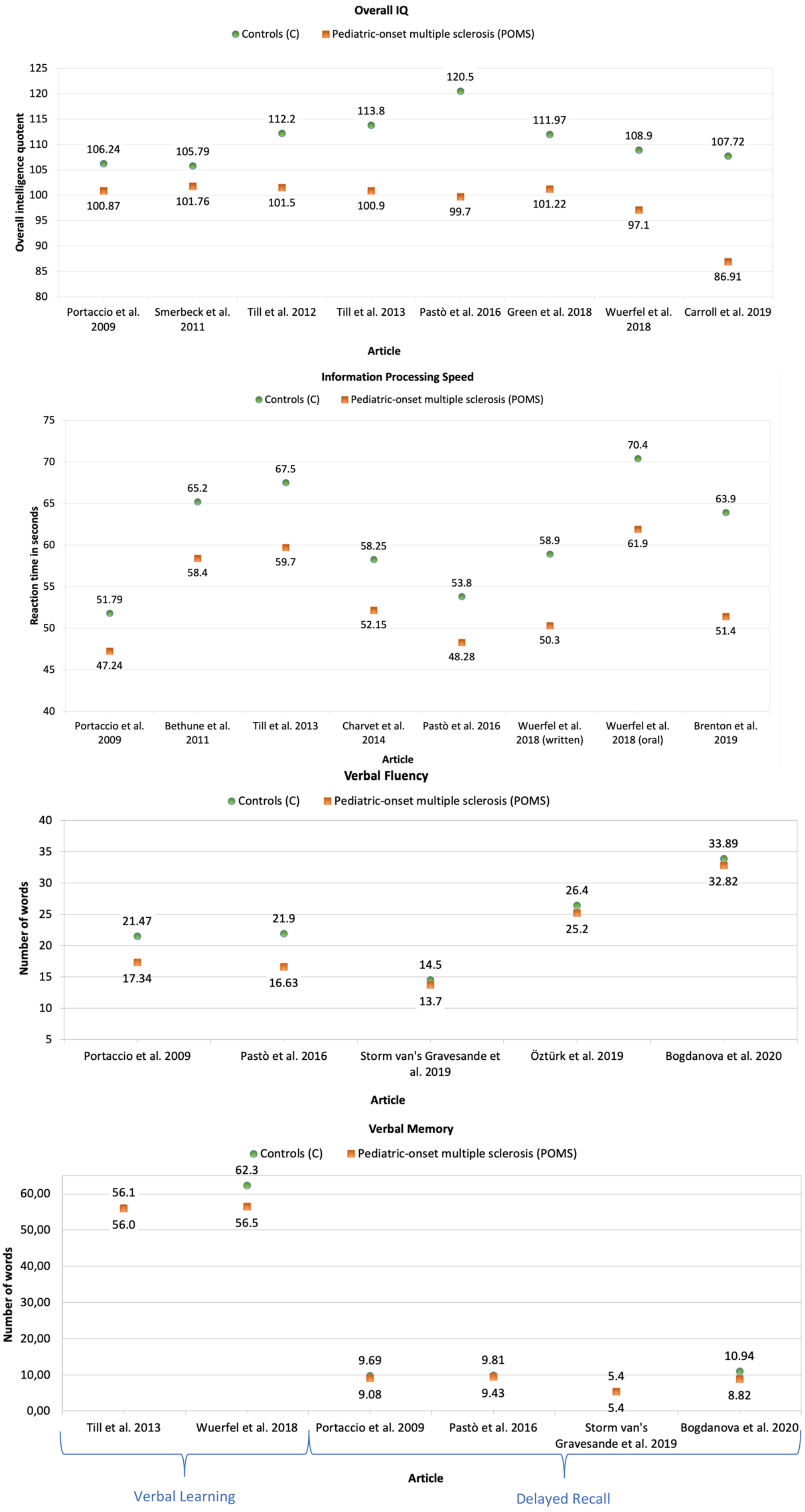
Results

The mean values by cognitive category are illustrated in Fig. 2. Table 1 shows scores by study. Overall IQ represents intelligence quotient scores. Information processing speed scores represent reaction time in seconds on the symbol

Table 1 Characteristics of primary studies and classification of neuropsychological tests for cognitive categories

Study	Group	N sample (M/F)	Age (M ± SD)	EDSS (Median ± SD), Range	Mean age at onset (M ± SD) (in years), Range	Disease duration (in years)	Information processing speed	Overall IQ	Verbal fluency	Verbal memory—Delayed Recall	Verbal learning
Portaccio et al. (2009)	Controls	58 (25/32)	14.8 ± 3.5				51.79 ± 9.25	106.24 ± 10.42	21.47 ± 7.47	9.69 ± 1.61	
	MS	61 (30/31)	15.4 ± 2.4	mean 1.4 ± 0.8	12.5 ± 3.5	3.0 ± 3.2	47.24 ± 12.68	100.87 ± 28.09	17.34 ± 9.56	9.08 ± 2.34	
Bethune et al. (2011)	Controls	29	15.6 ± 2				65.2 ± 10.1				
	MS	26	16.1 ± 2.3	1.0 (0–6.0)	12.2 ± 3.6	3.4 ± 3.5	58.4 ± 16				
Smerbeck et al. (2011)	Controls	43 (22/21)	14.87 ± 2.41					105.79 ± 13.71			
	MS	43 (22/21)	14.78 ± 2.51	1.50 (0.0–6.5)		2.70 ± 2.50		101.76 ± 13.36			
Till et al. (2012)	Controls	33 (6/27)	15.9 ± 2.14					112.2 ± 8.41			
	MS	34 (7/27)	16.1 ± 2.12	1.0 (0–4)		4.2 ± 3.22		101.5 ± 12.02			
Till et al. (2013)	Controls	26 (5/21)	16.19 ± 2.59				67.5 ± 11	113.8 ± 7.2			56.1 ± 8.9
	MS	28 (6/22)	16.06 ± 2.23	1.0 (0–4.0)	11.6 ± 3.8	4.4 ± 3.3	59.7 ± 18.8	100.9 ± 13.1			56 ± 7.4
Charvet et al. (2014)	Controls	8	16–17.9				58.25 ± 11.83				
	MS	39	16–17.9	1.0 (0–4.0)		2.34 ± 2.25	52.15 ± 13.1				
Pasto et al. (2016)	Controls	57 (25/32)	14.8 ± 3.5				53.8 ± 12.5	120.5 ± 16	21.9 ± 7.7	9.81 ± 1.72	
	MS	48 (23/25)	15.2 ± 2.6	1.5 ± 1.0		2.8 ± 3.4	48.28 ± 13.67	99.7 ± 20.2	16.63 ± 6.66	9.43 ± 2.31	
Green et al. (2018)	Controls	30 (6/24)	16.01 ± 2.43					111.97 ± 8.2			
	MS	32 (7/25)	16.28 ± 2.21	1.0 (0–4)	11.90 ± 3.87	4.35 ± 3.26		101.22 ± 12.36			
Wuerfel et al. (2018)	Controls	37 (10/27)	15.3 ± 1.7				58.9 ± 11.1 (written) 70.4 ± 14.9 (oral)	108.9 ± 12.9			62.3 ± 7.6
	MS	37 (10/27)	15.5 ± 1.8	mean 1.1 ± 1.1 (0–3.5)	13.7 ± 2.6 (7–17)	1.87 ± 1.41	50.3 ± 9.1 (written) 61.9 ± 14.2 (oral)	97.1 ± 18.8			56.5 ± 10.2
Brenton et al. (2019)	Controls	40 (8/32)	median 16				63.9 ± 11.0				
	MS	20 (4/16)	median 16	1.5 (1.5–2.0)	median 13 (13–14.5)	median 2 (1–3.5)	51.4 ± 11.9				
Carroll et al. (2019)	Controls	25	15.02					107.72 ± 10.74			
	MS	11	15.87		12.62 ± 3.47	2.87 ± 2.27		86.91 ± 16.2			
Ozturk et al. (2019)	Controls	53							26.4 ± 11.8		
	MS	46	14 ± 3.2	0 (0–3.5)	13 ± 2.6				25.2 ± 11		
Bogdanova et al. (2020)	Controls	65 (33/32)	13.37 ± 2.25						33.89 ± 5.89	10.94 ± 2.57	55.32 ± 7.52
	MS	38 (11/27)	14.95 ± 1.86	mean 1.5 ± 0.4	12 ± 3.0	3.0 ± 1.9			32.82 ± 7.32	8.82 ± 2.44	47.79 ± 8.3

Fig. 2 Graphs with mean scores for each cognitive category



digit modalities test. Verbal fluency scores correspond to the number of words generated for a semantic category within one minute. Verbal memory scores reflect performance on delayed recall and verbal learning. Forest plots and funnel plots are illustrated in Figs. 3 and 4, respectively. Effect-sizes for overall neuropsychological scores for each included study and summary of meta-analytic results are presented in Tables 2 and 3, respectively.

Overall IQ

Eight studies reported data on overall IQ. Wechsler Intelligence Scale for Children-Revised (WISC-R) was used by Portaccio et al. (2009), and Pasto et al. (2016), Wechsler Abbreviated Scale of Intelligence—2nd Edition (WASI-II) was used by Smerbeck et al. (2011), Till et al. (2012), Till et al. (2013), and Green et al. (2018). Carrol et al. (2019) used Wechsler Intelligence Scale for Children-4th Edition (WISC-IV) and Wechsler Adult Intelligence Scale—4th Edition (WAIS-IV), and Wuerfel et al. (2018) did not specify a version. A medium to large significant effect on overall IQ was observed between children with and without POMS (N = 603; Hedges'g = 0.85; 95% CI [0.54, 1.16]; $p < 0.01$), children with POMS have lower scores than the control group. Interstudy heterogeneity was significant ($Q = 23.94$, $df = 7$, $p < 0.01$; $I^2 = 69.62\%$) and publication bias was also significant ($z = 2.74$, $p = 0.01$). To address publication bias, we used the trim and fill method. After applying a trim and fill procedure the effect size decreased to 0.78, but remained significant and moderate Hedges'g = 0.78; 95% CI [0.47, 1.10]; $p < 0.01$; interstudy heterogeneity was moderate ($Q = 27.8$, $df = 8$, $p < 0.01$; $I^2 = 71.33\%$; Fig. 3) and with a nonsignificant publication bias ($z = 0.65$, $p = 0.52$).

Information Processing Speed

Seven studies reported scores on the symbol digit modalities test using information processing speed associated with oral and written responses. Five articles used the oral version (Bethune et al., 2011; Brenton et al., 2019; Charvet et al., 2014; Pastò et al., 2016; Portaccio et al., 2009; Till et al., 2013), one article used the written and oral version separately (Wuerfel et al., 2018), and one article used combined oral or written versions (Charvet et al., 2014). For information processing speed considering both oral and written versions, a significant medium effect size showing children with POMS performing slower than children in the control group was observed (N = 514; Hedges'g = 0.57; 95% CI [0.38, 0.75]; $p < 0.01$). Publication bias was not significant ($z = 0.99$, $p = 0.32$) according to Egger's regression combined with funnel plots. Interstudy heterogeneity was low ($Q = 5.99$, $df = 6$, $p = 0.42$; $I^2 = 1\%$; Fig. 3). For information processing speed considering only the oral version a significant medium effect size showing children with POMS performing slower than children in the control group was observed (N = 467; Hedges'g = 0.53; 95% CI [0.35, 0.72]; $p < 0.01$). Publication bias was not significant ($z = 1.47$, $p = 0.14$) according to Egger's regression combined with funnel plots. Interstudy heterogeneity was low ($Q = 4.53$, $df = 5$, $p = 0.48$; $I^2 = 0{,}01\%$; Fig. 3).

Verbal Fluency

This category includes data from five studies, in which verbal fluency is measured in its semantic aspect. Two studies used Semantic Verbal Fluency Test Expressive language (Pastò et al., 2016; Portaccio et al., 2009), one used Multiple Sclerosis Inventory of Cognition verbal fluency (Storm Van's Gravesande et al., 2019), one used K, A, S (letters) -Animal (Verbal Fluency in Turkish adaptation; Öztürk et al., 2020), and one used Delis-Kaplan Executive Function Verbal Fluency (Bogdanova et al., 2020). A small effect size was observed for group differences on tasks of verbal fluency (N = 742; Hedges'g = 0.36; 95% CI [0.18, 0.54]; $p < 0.01$), with a nonsignificant publication bias ($z = 0.02$, $p = 0.98$). A moderately relevant interstudy heterogeneity was observed ($Q = 6.16$, $df = 4$, $p = 0.19$; $I^2 = 28.4\%$; Fig. 3).

Verbal Memory

Verbal memory was examined using six studies that reported data from eight different participant groups that tested participant's immediate recall, delayed recall, and verbal learning. Delayed recall was examined by the Selective Reminding Test-Delayed used in two studies (Pastò et al., 2016; Portaccio et al., 2009), Multiple Sclerosis Inventory of Cognition word list A was used in one study (Storm Van's Gravesande et al., 2019), and the Auditory Verbal Learning Test A7 Delayed Recall in another (Bogdanova et al., 2020). Verbal learning was examined using the Test of Memory and Learning, 2nd ed.–Word Selective Reminding (Till et al., 2013) and Verbal Learning and Memory Test (Wuerfel et al., 2018). A small effect size was revealed between children with and without POMS on verbal memory tasks (N = 771; Hedges'g = 0.31; 95% CI [0.04, 0.58] $p = 0.02$), with a nonsignificant publication bias ($z = 0.85$, $p = 0.39$) according to Egger's regression combined with funnel plots. A moderately relevant interstudy heterogeneity is observed ($Q = 15.55$, $df = 5$, $p = 0.01$; $I^2 = 67.0\%$; Fig. 3).

Age and Sex As Moderators

To examine the influence of age and sex on cognitive functioning, moderator analyses were carried out. Age and sex were not significant moderators of cognitive differences for any of the categories.

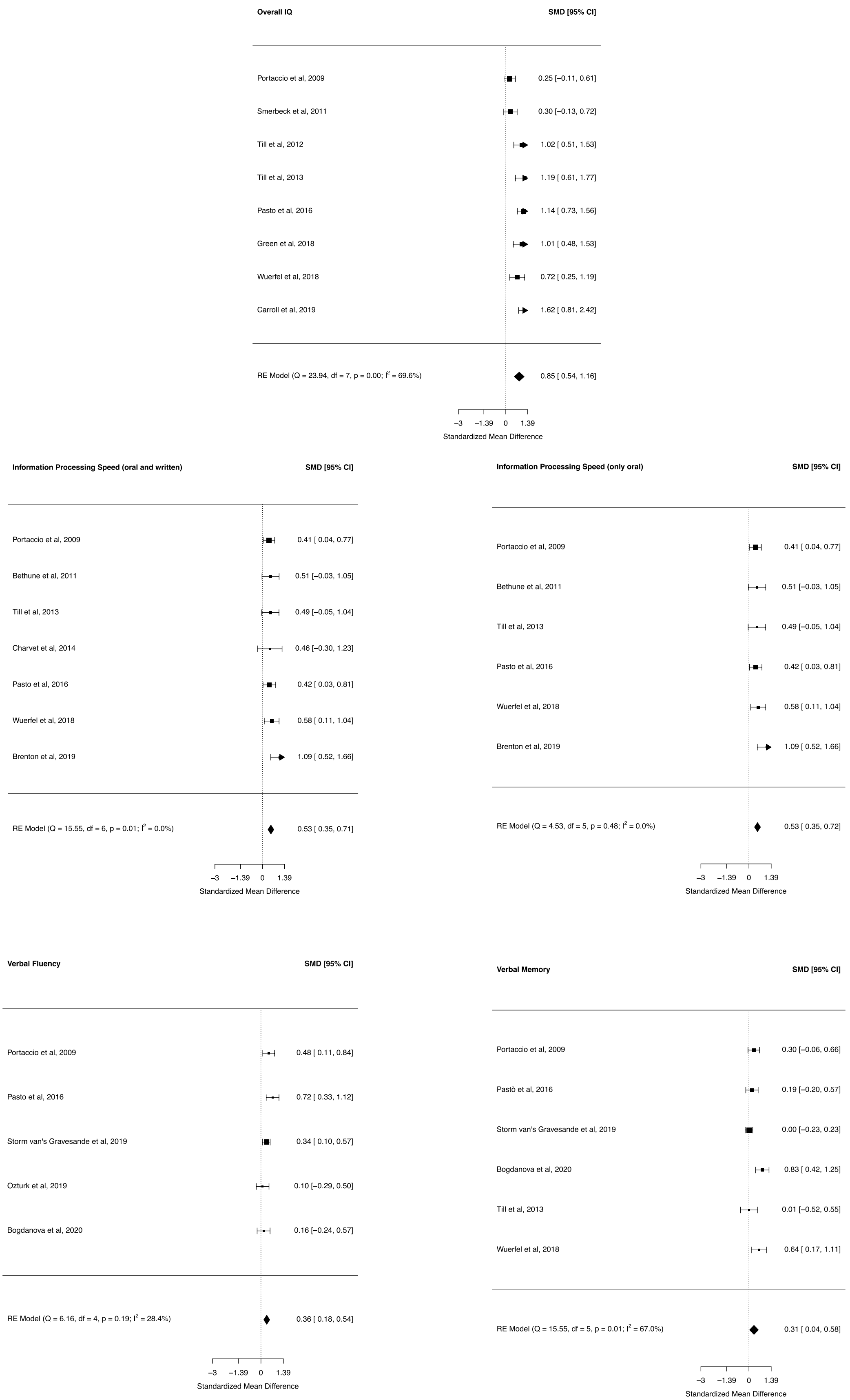


Fig. 3 Forest plots indicating effect-sizes for each cognitive category

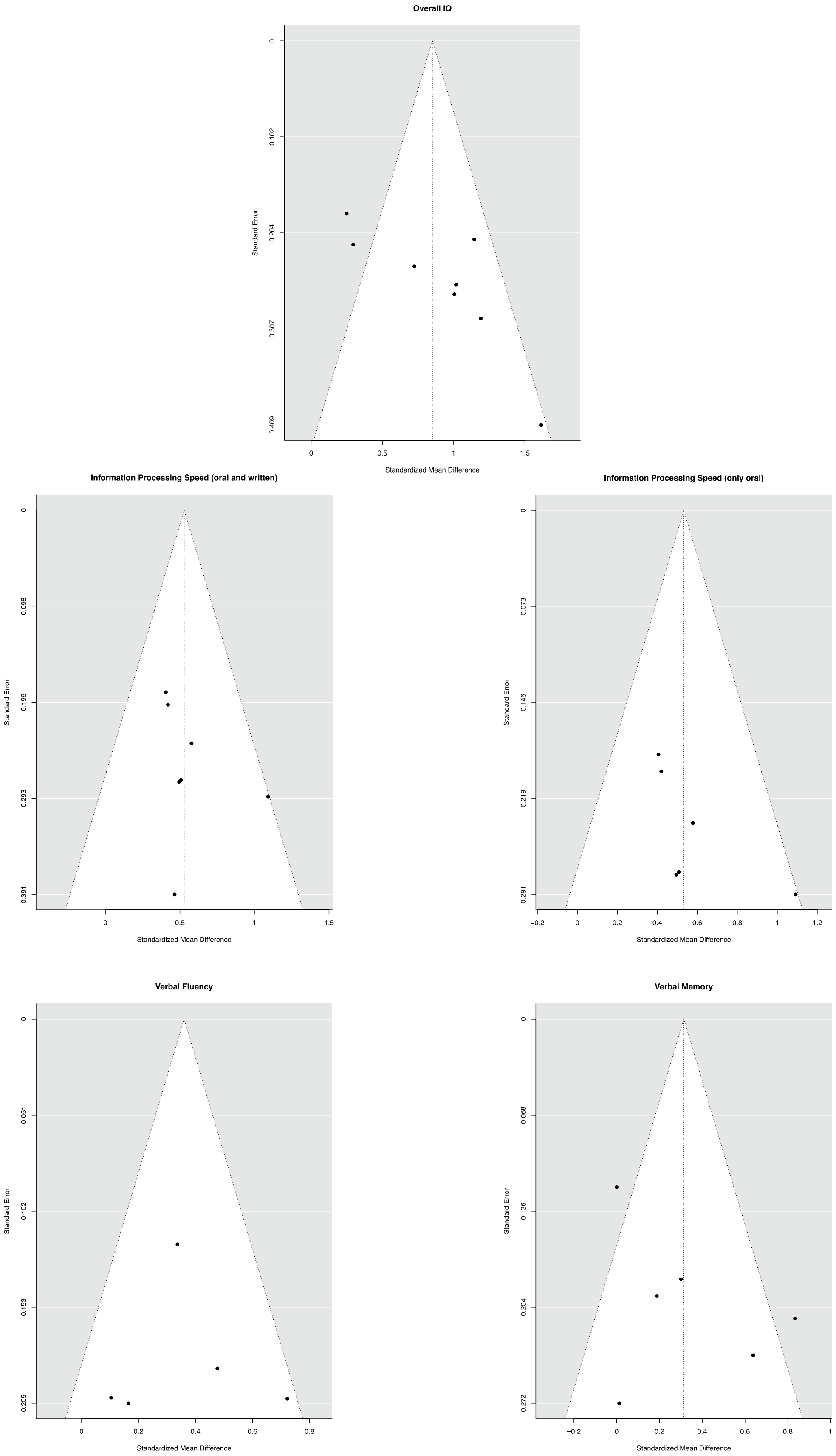


Fig. 4 Funnel-plots of Hedges' g effect-sizes for all cognitive categories

Table 2 Effect-sizes for overall neuropsychological scores for each included study

Study	Year	Test	Hedges'g	95%-CI	N	p-value
Overall IQ						
Portaccio et al.	2009	WISC-R	0.25	[−0.11, 0.61]	119	0.18
Smerbeck et al.	2011	WASI-II	0.3	[−0.13, 0.72]	86	0.05
Till et al.	2012	WASI-II	1.02	[0.51, 1.53]	77	0.07
Till et al.	2013	WASI-II	1.19	[0.61, 1.77]	54	0.09
Pasto et al.	2016	WISC-R	1.14	[0.73, 1.56]	105	0.04
Green et al.	2018	WASI-II	1.01	[0.48, 1.53]	62	0.07
Wuerfel et al.	2018	WISC	0.72	[0.25, 1.19]	74	0.06
Carroll et al.	2019	WISC-IV or WAIS-IV	1.62	0.81, 2.42]	36	0.17
Information processing speed						
Portaccio et al.	2009	SDMT oral	0.41	[0.04, 0.77]	119	0.03
Bethune et al.	2011	SDMT oral	0.51	[−0.03, 1.05	55	0.08
Till et al.	2013	SDMT oral	0.49	[−0.05, 1.04]	54	0.08
Charvet et al.	2014	SDMT (randomly oral or written forms)	0.46	[−0.30, 1.23]	47	0.15
Pasto et al.	2016	SDMT oral	0.42	[0.03, 0.81]	105	0.14
Wuerfel et al.	2018	SDMT written	0.84	[0.36, 1.31]	74	0.06
		SDMT oral	0.58	[0.11, 1.04]	74	0.01
Brenton et al.	2019	SDMT oral	1.09	[0.38, 0.75]	60	0
Verbal fluency						
Portaccio et al.	2009	SVFT	0.48	[0.11, 0.84]	119	0.01
Pasto et al.	2016	SVFT	0.72	[0.33, 1.12]	105	0.04
Storm van's Gravesande et al.	2019	Music verbal fluency	0.34	[0.10, 0.57]	316	0.01
Ozturk et al.	2019	KAS-Animal (Verbal Fluency in Turkish adaptation)	0.1	[−0.29, 0.50]	99	0.04
Bogdanova et al.	2020	D-KEFS VF (category fluency)	0.16	[−0.24, 0.57]	103	0.04
Verbal memory						
Portaccio et al.	2009	SRT – D	0.03	[-0.06, 0.66]	119	0.01
Till et al.	2013	TOMAL-2 WSR	0.01	[-0.52, 0.55]	54	0.17
Pastò et al.	2016	SRT – D	0.19	[-0.20, 0.57]	105	0.04
Wuerfel et al.	2018	VLMT	0.64	[0.17, 1.11]	74	0.06
Storm van's Gravesande et al.	2019	MUSIC word list A delayed	0	[-0.23, 0.23]	316	0.01
Bogdanova et al.	2020	RAVLT A7 Delayed Recall	0.83	[0.42, 1.25]	103	0.05

n number of participants, *95%-CI* 95% confidence interval, *WISC-R* The Wechsler Intelligence Scales for Children, *WASI FSIQ-4* Wechsler Abbreviated Scale of Intelligence, *Overall IQ* Overall intelligence quotient, *WISC-IV Full-scale IQ (index score)* Wechsler Intelligent Scale for Children – Fourth Edition Full-scale intelligence quotient (index score), *SDMT* Symbol Digit Modalities Test, *SVFT* Semantic Verbal Fluency Test Expressive language, *MUSIC verbal fluency* Multiple Sclerosis Inventory of Cognition verbal fluency, *KAS-Animal (Verbal Fluency in Turkish adaptation)* K, A, S (letters) -Animal (Verbal Fluency in Turkish adaptation), *D-KEFS VF (category fluency)* Delis-Kaplan Executive Function Verbal Fluency, *SRT – D* Selective Reminding Test-Delayed, *TOMAL-2 WSR* Test of Memory and Learning, 2nd ed.–Word Selective Reminding, *VLMT* Verbal Learning and Memory Test, *MUSIC word list A delayed* Multiple Sclerosis Inventory of Cognition, *RAVLT A7 Delayed Recall* Rey–Osterrieth Auditory Verbal Learning Test

Discussion

We quantify using meta-analyses cognitive abilities in children with POMS compared with healthy controls in overall IQ, information processing speed, verbal fluency, and verbal memory. We highlight three main findings: Children with POMS demonstrated significantly lower performance compared with healthy controls across all four cognitive categories, however, the strength of these effects was different. The largest effect was observed in overall IQ, the effect of information processing speed was medium, whereas the effects for verbal fluency and verbal memory were small.

Our results show the highest effect size in overall IQ. Although the average intelligence scores of children with POMS were within the average range, they were significantly lower from those of children in the control group. Intelligence is fundamental for scholastic achievement and professional success (Mancini et al., 2017). Theoretically, cognitive functions implicated in higher-order cognition (i.e., mental attention and working memory; Arsalidou

Table 3 Summary of meta-analytic results and statistical power analysis for each cognitive category

Functions	K	N	Pooled effect size Hedges'g (p-value)	95% confidence intervals		Heterogeneity statistics			Egger's t-test for publication bias0	Median statistical power
				LL	UL	Q(df)p	P	I^2		
Overall IQ	8	603	0.85; $p < 0.01$	0.54	0.16	23.94 (7)	<0.01	69.62%	$z = 2.74$, $p = 0.01$	0.88
			0.78;* $p < 0.01$	0.47	1.11	27.8(8)	< 0.01	71.33%	$z = 0.65$, $p = 0.52$	
Information processing speed (oral and written)	7	514	0.57; $p <0.01$	0.38	0.75	5.99(6)	0.42	1.0%	$z = 0.99$, $p = 0.32$	0.65
Information processing speed (only oral)	6	467	0.53;$p<0.01$	0.35	0.72	4.53(5)	0.42	0.01%	$z = 1.47$, $p=0.14$	0.55
Verbal fluency	5	742	0.36; $p < 0.01$	0.18	0.54	6.16(4)	0.19	28.40%	$z= 0.02$, $p = 0.98$	0.43
Verbal memory	6	771	0.31; $p = 0.02$	0.04	0.58	15.55 (55)	0.01	67.00%	$z = 0.85$ $p = 0.39$	0.33

*For Overall IQ we calculated two Hedges' g the initial one (top) and the one with trim and fill method that controls for publication bias

et al., 2010, 2013, 2019; Pascual-Leone & Johnson, 2021) are related to intelligence scores (Johnson et al., 2003) and are required for solving aspects of intelligence tests (e.g., logic; Bird et al., 2004). Problem-solving relies on tertiary association brain areas such as the prefrontal cortex, which undergoes protracted development (Cipolotti et al., 2020; Cole et al., 2015; Gogtay et al., 2004). Thus, neurodevelopmental interruptions associated with POMS may affect brain networks associated with higher-order functions (De Meo et al., 2017). Clinically, these findings suggest that intelligence tests may be crucial for the assessment protocol for children diagnosed with POMS. Theoretically, core cognitive indices such as working memory and processing speed may give rise to overall IQ, however, current data in the POMS literature are insufficient to empirically draw this conclusion. Specifically, our current review identifies only two articles documenting between group effects (Wuerfel et al., 2018) or lack of them (Carroll et al., 2019) for working memory and processing speed indices. Critically, we recognize that intelligence tests may be language and background biased, thus measures of executive function and core cognitive abilities may be more suitable for non-English speaking, non-Western samples. Currently, there is not sufficient literature for carrying out meta-analyses on executive functions and working memory, however, burgeoning research in this area will be important for further understanding the core cognitive capabilities of children with POMS.

Our analyses demonstrated that information processing speed was significantly slower for children with POMS compared to their typically developing peers, and the effect size was medium when considering (a) both oral and written versions, and (b) only oral version. Adults with multiple sclerosis and healthy controls show similar effects (Prakash et al., 2008). Our study confirms that this effect is observed in patients with early onset of the disease. Studies using neuroimaging techniques in combination with behavioural tests showed that success on the symbol digit modalities test in patients with multiple sclerosis is related to aberrant activation patterns in the lateral prefrontal cortex (DeLuca et al., 2008; Genova et al., 2009; Sumowski et al., 2012). Costa et al. (2017) proposed a theoretical tri-factor model of information processing speed deficit in multiple sclerosis. This deficit relies on the idea of three distinct speed factors such as 1) a sensorial speed deficit, which is related to visual/auditory system functioning; 2) a cognitive speed deficit, which is related to the speed at which one can manipulate information and plan an answer; and 3) a motor speed deficit, which is related to the time it takes for a person to respond. Comparable effect sizes when oral and combined oral and written versions were considered suggest that performance may rely primarily on the first two speed factors (Costa et al., 2017). As many cognitive tasks are timed it may be important to investigate whether accuracy on a task improves if more time is allowed for children with POMS. This knowledge will shed light on compensatory mechanisms used in problem-solving in various visual-spatial and language functions.

Verbal fluency showed a significant albeit small effect for performance differences between children with POMS and healthy groups. Past research suggests that verbal fluency is particularly vulnerable in children with POMS (Amato et al., 2010; MacAllister et al., 2005; Till et al., 2011). However, it is likely that language abilities reached earlier in development (Kwok et al., 2018) are less affected compared to overall IQ that requires complex problem-solving. This is consistent with meta-analyses on adult patients with multiple sclerosis who also show lower small effects on language function (Johnen et al., 2017; Santangelo et al., 2019). Interstudy heterogeneity was moderate, the lowest across cognitive categories we examined. This may suggest that verbal fluency is more homogeneous as a task. Further, because POMS has a small effect on verbal fluency, one may question whether this effect is driven by other cognitive requirements of the task. For instance, verbal fluency can be attributed not only to the speech functioning and language system but also to executive function components (Cermak et al., 2021). In other words, developing a specific strategy and creating a concrete search program may allow quick access to the words. Typically developing children and adults implement several mental steps in verbal fluency tasks: lexical search, initiation and control over the implementation of the task (Henry & Crawford, 2004; Jurado & Rosselli, 2007), which may be related to with classification of verbal fluency as an executive function (e.g., Baron et al., 2014). Executive functions are often expressed by the prefrontal and temporal regions of the brain (Hung et al., 2018; Perret, 1974; Santarnecchi et al., 2021). Neuroimaging studies identified that letter fluency tasks elicits activity in the frontal lobes particularly the left hemisphere, whereas semantic fluency is related to temporal lobes activity (Henry & Crawford, 2004).

Similar to verbal fluency, verbal memory showed a significant but small effect on the performance of children with POMS compared to typically developing control children. Interstudy heterogeneity in this category was higher than verbal fluency, but also considered moderate. This increase may be due to variability in the tasks included, such as delayed verbal memory and verbal learning. Lower verbal memory performance in children with POMS could be associated with a whole-brain volume decrease (Fuentes et al., 2012). However, in another meta-analysis comparing adults with and without multiple sclerosis, effect sizes for memory and learning were medium (Prakash et al., 2008). In a meta-analysis of verbal dysfunction, the adult group with multiple sclerosis performed significantly lower in the acquisition and delayed recall than the healthy control group, with acquisition measures having the largest effect sizes relative to delayed recall and recognition (Lafosse et al., 2013). Reduced processing speed and underlying subcortical white matter pathology have been linked to multiple sclerosis related memory dysfunction (Brissart et al., 2012; Dineen et al., 2009). The role of the medial temporal lobe and hippocampal development in episodic memory control is being highlighted by increasing evidence for a pure amnestic-like profile (Thornton & Raz, 1997).

Overall, our results suggest that POMS influence performance on cognitive tasks differently, with overall IQ and information processing speed showing the strongest effects, whereas verbal abilities show small effects. The composite nature (e.g., verbal, numeric and visual-spatial) of overall IQ scores and the mainly non-verbal nature of the symbol digit modalities test is consistent with Byron Rourke's white-matter hypothesis of nonverbal learning disabilities. Rourke (1987) suggested that the nonverbal learning disabilities syndrome is expressed by white-matter dysfunction. Diffusion neuroimaging research on white-matter fiber tracts, shows that pathways connecting distant and proximal parts of the brain are critically associated with cognitive processing and follow a complex trajectory that is influenced by age in typically developing children (Buyanova & Arsalidou, 2021 for review). In adults with multiple sclerosis, diffusion tensor imaging scores predict lower performance on specific cognitive domains such as working memory, sustained attention, processing speed, visual working memory as well as verbal learning and verbal recall (Dineen et al., 2009). Children with POMS also show differential diffusion tension imaging metrics in the corpus callosum, the largest white matter fiber tract connecting the two hemispheres, which also correlated with performance on tasks of visual matching and symbol digit modalities test (Bethune et al., 2011). Further research is needed to verify the exact mechanisms that give rise to relations between brain maturation and cognitive performance.

Limitations and Future Considerations

The current meta-analyses are limited by methodological choices we had to make, and considerations shared by any meta-analysis. Although we were initially interested in identifying the effects of POMS on various executive and cognitive functions (e.g., inhibition, working memory, visual-spatial abilities, and IQ sub-test scores) there were not enough studies to allow performing such meta-analyses. Any meta-analysis is prone to publication bias, which we report to be significant for overall IQ, and provide a trim and fill procedure to account for that. Different versions of the Wechsler Intelligence Scale and differences in tasks assessing other abilities may contribute to variability, which we considered by evaluating interstudy heterogeneity tests. Interstudy heterogeneity was moderate for three of the four cognitive categories and should be considered when interpreting the findings. Critically, many studies we identified did not include a control group of typically developing children (n = 14) or did not report descriptive statistics such as mean and standard deviation (n = 5), limiting the number of studies that could be included in meta-analyses. Contacting corresponding authors did not improve the number of studies in these meta-analyses. Therefore, we strongly recommend future studies with children with POMS to include matched control groups and report descriptive statistics in their original reports as it is fundamental for meta-analyses that aim to identify convergence in effects across studies.

Conclusions

Our study aggregates peer-reviewed studies that examine cognitive abilities in children with and without POMS and identifies overarching effects on intelligence tests, information processing speed, verbal fluency and verbal memory using quantitative meta-analyses. Developing a clearer cognitive profile of children diagnosed with POMS may facilitate more accurate early intervention and personalized educational activities. Our research demonstrates that children with POMS have altered performance on all cognitive functions we investigated, however, overall IQ scores showed the more robust effect size, whereas verbal abilities showed the smallest effects. These findings support the neurocognitive notion that higher-order cognitive functions required to complete intelligence tests and rely on the prefrontal cortex continue to develop across childhood and adolescence (De Meo et al., 2017; Miller & Cohen, 2001), whereas tasks that emerge earlier and are more practiced such as language relies on brain networks that are already in place, which are less affected by neurodegenerative action of multiple sclerosis. In practice, the findings can aid in the development of rehabilitation programs by incorporating knowledge from cognitive profiles into educational program design and methodology. Considerably more research is needed in understanding the effects of POMS on cognition and we also raise awareness for the need to improve reporting practices for future studies, to include tasks specifics, a control group of typically developing children, and report descriptive statistics rather than illustrations, to eventually be able to more accurately distinguish cognitive characteristics and factors that present in profiles of children affected by POMS.

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Declarations

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