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Title:

Brain, cognition and language development in spinal muscular atrophy (SMA) type 1: a scoping review

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Abstract:

AIM To summarize the current knowledge on brain involvement in SMA type 1, focusing on brain pathology, cognition, and speech/language development ~~in SMA 1~~.

METHOD A scoping review was performed ~~according to the~~ (Joanna Briggs Institute methodology). ~~PubMed/MEDLINE, Scopus, Embase, PsycINFO, Web of Science~~ Five databases and references from relevant articles were searched up to December 2019. ~~References from relevant articles were searched to include additional papers not previously identified.~~ Articles were screened based on titles and abstracts. Full-text papers published in peer-reviewed journals in the English language were selected.

RESULTS Nineteen articles met eligibility criteria. ~~Eleven~~ Eight case series/reports on brain pathology showed ~~brain~~ abnormalities in few SMA 0/1 cases, supported by findings in 3 post-mortem examinations in mice. Four studies (3 case-control,1 cross-sectional) ~~papers~~ on cognition reported contradictory results, with impaired cognitive performances in recent small SMA 1 groups~~cohorts~~. Four studies (3 cross-sectional,1 observational) ~~articles~~ on speech/language showed untreated SMA 1 patients ~~indicated~~ rarely achiev~~ement of~~ functional and intelligible speech ~~in untreated SMA 1 patients~~, with data limited to parent reports~~ or~~ non-formal evaluations.

INTERPRETATIONS Brain involvement is ~~pathology, cognition, speech/language development are~~ an under-investigated aspect~~s~~ of SMA 1 requiring further exploration in. ~~Future~~ longitudinal studies ~~on brain neuroimaging, cognition, speech/language development are required~~. ~~Data obtained will help to plan~~ A deeper knowledge of brain involvement would improve the interpretation of clinical phenotypes and the personalisation~~ed~~ of rehabilitation programs ~~thus~~ supporting patients' autonomies and quality of life. ~~The results will also help to define additional~~ Additionally, it may help to define further outcome measures ~~to~~ testing the efficacy of current and new developing drugs on th~~i~~~~se~~ domain~~s~~.

Shortened form of the title:

Brain, cognition and language in SMA 1

What this paper adds:

- Brain involvement is under-investigated in SMA 1, considering both anatomical and functional data;
- Neuropathological data suggest ~~A~~ progressive brain involvement in severe forms of SMA; ~~forms is described but data are sparse~~
- Impaired cognitive performances are reported in small SMA 1 groups~~cohorts~~; ~~are reported~~
- Data on language in SMA 1 are limited to parent reports and non-formal assessments;
- Longitudinal and well-designed studies on ~~standardised~~ brain pathology, cognition~~ve~~ and language ~~assessments~~ in SMA 1 are strongly needed.~~required~~

INTRODUCTION

Rationale

Spinal muscular atrophy (SMA) encompasses a group of neuromuscular disorders characterized by degeneration of alpha motor neurons in the spinal cord with progressive muscle atrophy, weakness and paralysis [1]. The most common form of SMA is due to a defect in the survival motor neuron 1 (*SMN1*) gene located on chromosome 5q11.2-q13.3 [2] resulting in insufficient SMN protein levels. However, humans have at least one copy of the highly homologous *SMN2* gene producing a low amount of functional full length (FL) SMN protein, which is sufficient to allow survival in the absence of FL SMN from the *SMN1* gene [2, 3]. The incidence is 1 in 7-10,000 live births and the carrier frequency is approximately 1 in 50 [4]. The disease presents a wide range of phenotypes that are classified into five clinical groups (type 0 to 4) depending on age of onset and maximum motor milestone achieved, with type 0 and 1 being the most severe ones. SMA type 0 is an extremely severe prenatal/congenital form, with reduced foetal movements, congenital contractures and early respiratory failure. SMA type 1, also called Werdnig Hoffman disease, presents shortly after birth and before six months of age with inability to achieve independent sitting and limited life expectancy (high mortality rate by 2 years of age). This form is further classified into three subgroups according to the age of symptoms onset: within the first two weeks of life (type 1a), by 3 months of age (type 1b), and between 3 and 6 months of age (type 1c). Overall, SMA 1 accounts for 60% of all patients and is the most common genetic cause of death in infants. ~~As a result, p~~Published literature on SMA 1 has mainly focused on survival and respiratory, bulbar and motor function [5, 6, 7], while less attention has been paid to other features of the disease~~comorbidities~~, including brain involvement. ~~, cognitive and speech/language impairment. However, in addition to the severe gross-motor impairment and muscle weakness, it has been reported that~~ However, clinical practice shows that some SMA 1 patients may show cognitive impairment and the majority of untreated SMA 1 children never achieve functional verbal skills [8].

Over the last few years, the natural history of the disease – and in particular of the type 1 form – has radically changed thanks to the availability of new pharmacological treatments. Nusinersen (Spinraza®), the first SMN modulating treatment targeting the RNA splicing of the *SMN2* gene, showed to prolong survival and improve motor function in clinical trials [9, 10, 11, 12] and was approved by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) in 2016 and 2017, respectively. Onasemnogene abeparvovec-xioi (Zolgensma®), the first gene replacement therapy for this disease, has also shown positive results in clinical trials in SMA type 1 patients [13, 14, 15], and was approved by the FDA in 2019 and more recently by EMA. Other drugs are at a very advanced stage of clinical development, including ~~(e.g.~~ the orally administered *SMN2* splicing modifier risdiplam [16] ~~(which has also been~~recently approved by FDA~~)~~, and represent promising additional pharmacological options for SMA.

With the increasing number of long-term SMA 1 survivors worldwide, it has become obvious that treated children show new phenotypes, presenting changes not only in respiratory, bulbar and motor function, but also in other areas of functioning, including cognition and speech and language development. A better understanding of the characteristics and extent of brain involvement in SMA 1 would be crucial for a deeper comprehension of the clinical features of the disease and for personalised patient management.

~~In the pre-treatment era, the limited knowledge of brain involvement in SMA 1 lied in the difficulty of assessing cerebral functions and other cognitive abilities in so severely affected patients. Severe muscle weakness as well as respiratory and bulbar dysfunction significantly limit the interactions with the environment. Augmentative and alternative communication and the use of eye tracking devices have been recommended in patients with SMA, but there are some limitations in the use of a non-physiological way of communication to study cognitive and verbal skills in comparison with typically developing peers. Furthermore, although the expression of the SMN protein throughout the central nervous system (CNS) is known since the late '90s, neuropathological studies in SMA type 1 are sparse. The study of brain involvement through autopsies on very young babies was probably slowed down by ethical considerations, given the apparent secondary interest of the topic in such a devastating neuromuscular disorder. Neuroimaging studies in this population are very limited as well.~~

~~Overall, a comprehensive understanding of brain involvement in SMA type 1 is currently lacking, and represents one of the most relevant aspects requiring further investigation.~~

Objectives

Firstly, with this scoping review we aim to explore and summarize the current knowledge on brain involvement in SMA type 1, analysing the domains of brain pathology, cognition and speech/language development~~, in SMA type 1~~ through an extensive search of the published literature. The aim is to identify the available evidence regarding a primary brain involvement in the disease.

Secondly, by providing up-to-date information on structural and functional brain involvement in SMA type 1, we aim to pave the way for future research focusing on these domains. We believe that understanding the nature and degree of brain involvement in this disease may help to better characterize the new emerging phenotypes of treated patients~~ with SMA type 1.~~ This, in turn, would shed light on aspects that are still unclear, including the impact of new pharmacological treatments on cognitive and speech/language functions and the role of recovered motor abilities on brain development. ~~In future, t~~These aspects may become increasingly important in the future ~~will increasingly have to be taken into account~~ when choosing between different drugs and planning personalized rehabilitation programs~~. This is~~ particularly ~~important~~ in children with SMA 1, who may present with a developmental disorder in addition to the neuromuscular disease.

~~**INCLUSION CRITERIA**~~

~~The inclusion criteria used to select the articles for the review are based on the Population, Concept and Context (PCC) elements reported below.~~

~~Population. We included studies addressed to the 5q11.2-q13.3 SMA, excluding all other forms of SMA. Afterwards, only papers on 5q SMA type 1 have been analysed, according to the aim of the review. The only exception is the brain pathology domain, where we discuss also the findings from other 5q SMA subtypes (0 and 2). The reason is that the biological mechanisms underlying brain pathology might be considered similar in all forms of 5q SMA, although with different degrees of severity.~~

~~Concept. We selected studies analysing the following concepts: "brain pathology": we included pathological and imaging studies on both humans and animal models; "cognition and speech/language development": we included studies testing cognitive functions as well as receptive and expressive communication skills with any tests for the paediatric population (both validated and non-validated in large paediatric cohorts).~~

~~Context. No cultural, geographical, race or gender-specific limits were considered for our review, the reason being the equal presentation of the disease in the above mentioned categories.~~

METHODS

The Joanna Briggs Institute (JBI) methodology for scoping reviews described in the online JBI Reviewer's Manual [17] was employed to conduct the review. Results are presented following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [18].

No a priori protocol was registered. Further information on the process can be obtained from the corresponding author on request.

Inclusion criteria

The inclusion criteria used to select the articles for the review are based on the Population, Concept and Context (PCC) elements reported below.

Population. We included articles addressed to the 5q11.2-q13.3 SMA, excluding all other forms of SMA. Afterwards, only papers on 5q SMA type 1 have been analysed, according to the aim of the review. The only exception is the brain pathology domain, where we discuss also the findings from other 5q SMA subtypes (0 and 2). The reason is that the biological mechanisms underlying brain pathology might be considered similar in all forms of 5q SMA, although with different degrees of severity [19, 20, 21].

Concept. We selected articles analysing the following concepts: "brain pathology", we included pathological and imaging studies on both humans and animal models; "cognition" and "speech/language development", we included studies testing cognitive functions as well as receptive and expressive communication skills with any tests for the paediatric population (both validated and non-validated in large paediatric cohorts).

Context. No cultural, geographical, race or gender-specific limits were considered for our review, the reason being the equal presentation of the disease in the above mentioned categories.

Search strategy

The review covers data available up to December 2019. Selected key words were combined to create search strategies, adjusted for each screened database. Articles were searched in the following databases: PubMed/MEDLINE (1950–2019), Scopus (1996–2019), Embase (1980-2019), PsycINFO (1806-2019), Web of Science (1990–2019). Search terms included: "spinal muscular atrophy", "brain", "magnetic resonance imaging", "central nervous system", "cognition", "intellectual disability", "speech", "language", "communication", "augmentative alternative communication", "attention", "executive functions", "working memory", "neuropsychology". Table SI (online supporting information) shows the search process used to retrieve the final articles discussed in the review. Search strategies and search terms are reported for PubMed/MEDLINE, Scopus, Embase and PsycINFO. References from relevant articles were searched for inclusion of additional papers not previously identified through the systematic search.

Study screening and selection

Articles were initially screened based on titles and abstracts according to the PCC elements previously described (data on central nervous system~~CNS~~ morphology and functions in SMA 1). Duplicates were removed. Only full-text papers published in peer-reviewed journals and in the English language were selected. The articles were examined by two authors (RM and CB), and eligibility for inclusion was performed independently; in case of discordant opinion between the reviewers, the eligibility of the article~~study~~ was discussed until consensus was reached.

Level of evidence and ~~Q~~qualitative analysis of eligible articles

The strength of evidence for each article was assessed according to the Levels of Evidence developed by the Joanna Briggs Institute (JBI) [22].

In addition, ~~T~~the methodological quality of papers focusing on cognitive and speech/language development was assessed following amended criteria from Cross and Hare [23] reported by Pearson et al. [24]. ~~Studies~~ The

articles were rated from 0 to 2 on six areas: control group; sample size; recruitment; syndrome diagnosis; methodology; and appropriate statistics / comparisons. Table SII (online supporting information) shows the scoring criteria used to assess the methodological quality of eligible articles. A total score was obtained for each article, with papers scoring in the upper tertile of possible scores (9+) deemed to be of reasonable methodological quality. The qualitative assessment was performed by two authors (RM and CB) independently; in case of discordant opinion between the reviewers, the scoring was discussed until consensus was reached.

Extraction and presentation of results

All data relevant to inform the scoping review objectives and questions were extracted and summarised in tables 1, 2, 3 and 4 (tables 3 and 4 also report the quality assessment of articles focusing on cognitive and speech/language development). Results were grouped according to the domains explored: brain neuropathology, brain neuroimaging, cognition, and speech/language development.

RESULTS

Search results

A total of 19 articles were included in the review after study screening and selection: 11 focusing on brain pathology, 4 on cognition and 4 on speech/language development as shown in Figure 1. All but one of these ~~studies~~ papers ~~only~~ included untreated SMA 1 cases.

Brain pathology

We identified ~~E~~eleven different articles~~studies~~ on brain involvement in SMA; ~~were identified. S~~seven ~~studies are~~on neuropathological examinations~~reports~~ (3 out of 7 performed in mouse models), and 4 on ~~studies are descriptions of~~ neuroimaging findings in patients with SMA.

Neuropathological studies – patients

Specific neuropathological abnormalities have been reported in several central nervous system (CNS) areas other than lower motor neurons from autoptic examinations~~studies~~ performed in patients with both the type 0 [25] and the type 1 [26, 27] forms of the disease. ~~Reports~~Articles published before 1980 were already summarised ~~in the report~~ by Towfighi et al. [26] and they were not counted individually as part of the results of this review. The involved CNS structures included brainstem nuclei, pigmented nuclei, thalami, basal ganglia, frontal and temporal cortices, hippocampi, and cerebellum. On top of that, few papers~~reports~~ documented different degrees of involvement according to disease severity. ~~A study analysing b~~Brain samples from patients with different subtypes of SMA 1 [27] ~~reported~~showed milder findings in patients ~~presenting~~ with the less severe forms of SMA 1 (1b and 1c) compared to patients with the most severe form of the disease (type 1a). These neuropathological findings were considered primarily related to the underlying condition by the authors. In addition, ~~a~~ neuropathological examinations~~study~~ on patients with a clinically and genetically confirmed diagnosis of SMA type 2 [28] ~~reported~~showed no neuronal changes in the areas previously described as affected in patients with SMA type 0/1 (e.g. brainstem nuclei, pigmented nuclei, thalami, basal ganglia, hippocampi, cerebellum). Changes in areas such as the precentral gyrus and the large myelinated fibres in the spinal-pyramidal tract were reported instead. The overall level of evidence regarding the presence of neuropathological abnormalities in humans was 4.b according to the JBI criteria [22].

Neuropathological studies – mouse models

Changes in brain morphology were reported in a severely affected SMA mouse model [29]. Size reduction was observed in areas normally associated with higher SMN protein levels in the healthy postnatal brain – especially the hippocampus – with more modest morphological reductions in the primary motor cortex. According to the authors, these data show~~ed~~ for the first time that high levels of SMN protein are ~~were~~ required for normal brain development in vivo and, as a result, reduced expression of SMN protein cause~~s d~~ abnormal brain development, particularly affecting regions such as the hippocampus. Neuropathological abnormalities in the developing telencephalon and in the motor cortex were also reported in other two SMA mouse model studies [30, 31]. The overall level of evidence regarding the presence of neuropathological abnormalities in mouse models was 5.c according to the JBI criteria [22].

~~Further d~~Details of each article ~~on the neuropathological changes observed and main areas involved~~ are reported in table 1.

Neuroimaging studies

Alterations of several CNS areas other than alpha motor neurons in the spinal cord have been demonstrated by both brain computed tomography (CT) [32] and brain magnetic resonance imaging (MRI) [33, 34, 35] studies. The largest case series ~~study, which is also the less recent one,~~ reported results of CT scans performed in 8 children with a clinical diagnosis of SMA type 1 [32]. Images showed generalised cerebral cortical atrophy in all but one patient~~,~~ who presented mild abnormalities in the white matter of both frontal lobes~~. In this study,~~ (the authors could not exclude chronic hypoxic-ischemic brain injury as a cause for the described

abnormalities). All subsequent neuroimaging case series/report~~studies~~ presented ~~used~~ brain MRIs performed in patients with both SMA type 1 [33] and type 0 [34, 35] with no~~out~~ documented history of hypoxic-ischemic events. A first case report ~~The study in~~ of a patient with SMA type 1 [33] showed~~identified~~ thalamic abnormalities in the anterolateral portions. Very recently, marked progressive CNS alterations have been ~~were~~ documented in a longitudinal neuroimaging case series ~~study~~ in 3 patients with SMA type 0 [34]. Predominant brain MRI findings at the first scan were supratentorial atrophy of subcortical predominance, tapered corpus callosum, and widening of sulcus and ventricles; imaging follow-up showed a marked progression of the supratentorial brain atrophy in all patients, characterized by severe reduction of white matter (3/3), ~~and~~ severe hippocampal atrophy (2/3), and relative sparing of the cerebellum. Symmetrical signal abnormalities were detected in the putamen and thalamus (lateral and pulvinar) in two patients, with additional atrophy of caudate in the third case. Marked ventricular dilatation was also detected in the third patient. ~~After that,~~ Finally, a progressive atrophy of the cerebral cortex, subcortical white matter, thalami, basal ganglia, brainstem and cerebellum accompanied by epilepsy has been ~~was~~ reported at follow-up MRI scans in a very severely affected patient with SMA type 0 [35]. The overall level of evidence regarding the presence of neuroimaging abnormalities was 4.b according to the JBI criteria [22]. Details of each article~~study~~ are reported in table 2.

Cognition

According to the review inclusion criteria, only 4 papers on cognitive performances in type 1 SMA patients were found, and the available data seem contradictory.

The comparison of a group of SMA patients (type 1 and 2, age 8 - 13 years) to Duchenne muscular dystrophy (DMD) patients and healthy children in verbal and non-verbal intelligence (Wechsler Intelligence Scale for Children – WISC-Revised), language (Batterie d'Evaluation du Langage; Test de vocabulaire actif e passif; North Syntax screening test) and reading (le pipe et le rat; single-word lists reading) showed lower performances in the DMD group (verbal intelligence quotient, language and reading) than in SMA patients [36]. Overall, the SMA group ~~i~~was described to have similar performances to healthy subjects, but a direct statistical comparison has not been made between these two groups in the study. Another study of cognitive skills in 96 children with SMA (18 with type 1, age 6 - 18 years), assessed through the Raven coloured and standard progressive matrices (CPM / SPM), the Kaufman assessment battery for children (K-ABC) and the WISC, showed very similar results between the SMA and control groups (non-affected siblings and healthy peers~~children~~), with no differences between the types of SMA [37]. It should be noted that patients classified as type 1 in both of these studies were probably not representative of this form of disease, as only some of them were unable to sit and the age was higher than expected by natural history. Furthermore, the adolescent patients described in the second study seemed to perform better than healthy controls on verbal IQ subscale of Weschler tests and Raven SPM, suggesting that the environmentally mediated aspects of intelligence were higher in patients with SMA compared to controls. The authors speculated that this was a compensatory effect for the restrictions resulting from physical disability.

On the other hand, the description of the functional status of 83 SMA patients (22 type 1) through the WeeFIM (an interview-based questionnaire for caregivers) showed that the overall performance of children with SMA was below normal, with the worst performance in type 1 patients, who required help or assistance in most of the cognitive functioning domains and particularly in expression, social interaction and problem solving [38]. Furthermore, even the most recent study on cognition [39] confirmed a poorer performance in SMA patients than in controls. It was specifically addressed to SMA type 1 patients (age 3 - 9 years), compared to sex- and age-matched healthy controls. Cognitive assessment was completed with pair-matching tasks, consisting of verbal request to match objects, figures and colours, letters (upper and lower cases), numbers (arabic and words), by using an eye tracker device. SMA patients performed worse than controls in correct answer rate and time performance in all tasks.

The overall level of evidence regarding cognitive impairment was 4.b according to the JBI criteria [22]. ~~-~~Details of ~~these studies~~ each article are reported in table 3.

Speech and language development

Four articles were found on speech and language development in patients withof SMA type 1.~~, all published in the last few years.~~

Two ~~articles~~cross-sectional studies provided information on patients' communication abilities based on researchers-developed questionnaires completed by parents/carers (a postal questionnaire [40] and an online survey via email invitation [41], respectively). Both surveys focused on questions related to the communication methods used by the child, including electronic and non-electronic communication devices. In the first study, the authors observed that the five communication methods most frequently used were signs (e.g. eye movements indicating 'yes' or 'no', 50%), eye fixation (47%) electronic communication devices (47%), vocalizing (30%), and non-electronic communication devices (22%). No communication methods were used by 19.4%. The acquisition of the ability to communicate without using devices, such as through eye fixation, vocalization, or use of signs was delayed compared to typically developing peers. In this population~~cohort~~, children showed the ability to communicate using electronic devices from the age of 3 years and non-electronic devices from the age of 4 years. This is ~~was~~ the first study providing insight on the communication skills of children with SMA type 1 according to age and use of devices. In the second study, variability in the communication methods used was reported, including speech (59%), gesture (69%), speech-generating device (38%), and no-tech picture or symbol board/book (16%). Three parents reported that all four methods were used by their children (9%). In patients able to speak, speech deficits were reported and were related to clarity, independence and intelligibility. Among ~~parents who reported their~~ children with no ~~having no~~ functional natural speech, 22% used gesture only. Results also illustrated parental perception of greater receptive than expressive language abilities. The benefit of implementing speech-generating devices in terms of communication effectiveness and quality of life was highlighted, although several obstacles to their acquisition and implementation were reported.

~~The t~~Two further ~~other~~ studies ~~on speech/language development in SMA 1~~ provided information on patients' communication abilities based on clinicians' observations. In one study [8], the authors reported functional abilities and other clinical findings – including speech – in a cohort of 122 untreated children with SMA type 1. In their cross-sectional analysis only 28% had acquired comprehensible speech, defined as the ability to produce at least short sentences that could be understood by the examiner and not just by the carers. These were mainly type 1c patients who are at the milder end of the spectrum. The last study [14] is the only one providing information on treated SMA 1 patients, and in particular on health outcomes – including the acquisition of the ability to speak – in 12 SMA 1 children treated with ~~the~~ gene replacement therapy. It ~~Results~~ showed an increase to 92% of patients able to speak by the end of the two years follow-up period.

~~Further d~~The overall level of evidence regarding speech/language impairment was 4.b in all but one study (level 3.e) according to the JBI criteria [22]. Details of each article ~~study~~ are reported in table 4.

DISCUSSION

This review suggests that a comprehensive understanding of brain involvement in SMA type 1 is still lacking. One of the reasons of this limited knowledge is the difficulty of assessing cerebral functions and other cognitive abilities in so severely affected patients. Severe muscle weakness as well as respiratory and bulbar dysfunction significantly limit the interactions with the environment. Augmentative and alternative communication and the use of eye tracking devices have been recommended in patients with SMA, but there are some limitations in the use of a non-physiological way of communication to study cognitive and verbal skills in comparison with typically developing peers.

Furthermore, although the expression of the SMN protein throughout the central nervous system (CNS) is known since the late '90s [19, 20], neuropathological studies in SMA type 1 are sparse. The study of brain involvement through autopsies on very young babies was probably slowed down by ethical considerations, given the apparent secondary interest of the topic in such a devastating neuromuscular disorder [42, 43]. Neuroimaging studies in this population are very limited as well.

~~This scoping review showed that~~ Available data show that brain structures can be primarily affected in the severe forms of SMA. This was originally documented before the identification of the *SMN1* gene, based on neuropathological findings at post-mortem examinations [26]. Subsequent studies in patients with a genetically confirmed diagnosis of 5q SMA clearly demonstrated brain involvement ~~, as shown in neuropathological [25, 27, 28, and neuroimaging [33, 34, 35] studies~~, especially in the most severe forms (type 1a or 0). Several structures, including thalami, basal ganglia, temporal and frontal cortices, hippocampi and cerebellum have been reported to be variably affected. Interestingly, a marked progression of initial brain abnormalities has been documented by follow-up brain scanning [34, 35]. This is something ~~that should~~ to be considered and further investigated, especially now that treated patients are surviving longer. Experimental evidence from mouse models – although very limited [29, 30, 31] – further supports a possible primary brain involvement in SMA 1 patients. Of note, neuropathological alterations in other nervous system areas such as the primary spinal sensory neurons of dorsal root ganglia were reported as well, both in human [25, 26, 27] and in mouse model [44, 45] studies. Although the study of the peripheral nervous system is beyond the scope of this review, it should be noted that sensory inputs may play a role in the overall brain functioning of these patients~~ and probably should be better understood.~~

The clinical correlates of these findings in terms of cognitive and other neuropsychological functions including speech and language are still largely unclear, and no study has investigated the correlation between neuropathology/neuroimaging reports and cognitive and neuropsychological functioning. As already mentioned, this was mainly due to the clinical severity of the disease and the high mortality rate by 2 years of age of untreated SMA 1 patients, who were often not able to provide verbal or gestural responses during the assessments. Most of the studies focusing on the intellectual abilities in SMA were initially performed in less severely affected patients (SMA types 2 and 3), who could be more easily assessed using the available validated tests and assessments. These studies showed that patients with SMA types 2 and 3 obtained normal to higher than normal intelligence quotient and speech/language abilities scores compared to their peers [46]. Average vocabulary scores and above the average early grammar scores [46, 47] as well as significantly higher level of lexical and semantic development [48], and rich spatial language abilities were reported, despite SMA 2 children, by definition, never experience locomotion abilities [49].

More recent studies [38, 39] specifically investigating cognitive abilities in SMA 1 patients, also using adapted assessments [39], showed that they have poorer performances compared to their peers, particularly in the attention and executive function domains. Speech and language development is also affected, with published data showing that functional and intelligible speech is rarely achieved in untreated SMA 1 children [12, 40, 41].

Considering that the limited interaction with the environment due to poor expressive communication skills has been shown to further impact on cognitive development in a number of neurodevelopmental disorders [50], alternative and augmentative ways to communicate are recommended since early in life.

The advances in the multidisciplinary care, and the recent clinical implementation of SMN modulating treatments have contributed to prolonging event-free survival and improving motor function in treated patients. However, it is still unclear whether other areas of functioning, including cognitive development and the achievement of effective speech and language abilities, which can significantly impact on independence and quality of life, may equally benefit from treatments. In fact, there are no published studies directly addressed to cognition and language in treated SMA 1 children. The report from Al-Zaidy et al. [14] is the only one providing information on the effect of a treatment (gene replacement therapy) on one of the domains considered in our review (speech/language), simply reporting that the vast majority of patients were "able to speak" two years after receiving the treatment. Additionally, the role of bulbar function in the development of articulate speech abilities is also unclear. Whether SMA 1 children treated with the new SMN modulating treatments will recover bulbar function and will improve speech, having the possibility to experience and develop their pre-verbal and verbal social and communication skills as typically developing children do, or whether residual structural and/or functional brain pathology will affect achievement of mature language abilities will need to be clarified.

This scoping review provides very preliminary information on this regard, and the included articles~~studies~~ present some limitations. One of the main limitation is the methodological quality of papers focusing on cognitive and speech/language development, with most articles presenting scores below the threshold for a reasonable methodological quality [8, 14, 36, 38, 40, 41]. This is due to the lack of control groups, the very limited sample sizes and the lack of appropriate statistical data analyses. Other weaknesses are the lack of validated and/or standardised measures, with the necessary use of information reported by parents/carers or by clinicians, and the difficulties of assessing severely disabled children with alternative methods (e.g. eye tracker) and of comparing these results with the control groups.

Longitudinal multicentric studies with standardised assessments of cognitive and speech/language abilities are required in children with SMA type 1. The use of adapted methodology ~~assessment strategies~~ to perform these assessments should be considered. ~~taken into account.~~ Moreover, longitudinal neuroimaging studies performed alongside the clinical assessments would provide additional valuable information on the new emerging clinical phenotypes in this population, especially in patients at the most severe end of the spectrum.

Data collected from these studies would also provide a significant contribution to the growing evidence that SMA may be a multi-system disorder [51]. SMN protein is ubiquitously expressed throughout the body and is involved in a number of physiologic mechanisms, including the assembly of spliceosomal small nuclear ribonucleoproteins [52], critical to RNA splicing of multiple genes. One of the most intriguing features in the pathogenesis of SMA is the selective vulnerability of motor neurons. However, several studies have shown that various cell types other than motor neurons can be affected in SMA [53], particularly in the most severe early-onset forms. There may be differential thresholds between different cell types, with spinal motor neurons being the most sensitive to a reduction in SMN protein expression [19]. Several gene modifiers have been demonstrated to impact disease severity in SMA, with the number of copies of the *SMN2* gene playing a major role. Patients with only 1 copy of the *SMN2* gene and the lowest levels of SMN protein compatible with survival, have shown the highest degree of brain involvement, as well as of other organs dysfunction. Additionally, SMN protein levels have been shown to decrease during development not only in the spinal cord but also in the brain, with a substantial decline between foetal and postnatal stages, reaching very low levels after 3 months of age [54]. This emphasizes the crucial role of the SMN protein during the early stages of brain development, and further supports the need of longitudinal standardised assessments of cerebral structures and functions in children with SMA type 1.

CONCLUSIONS

In conclusion, brain pathology, cognition and speech/language development are under-investigated aspects of SMA type 1. In literature there is some limited evidence of potentially progressive brain involvement in the severe forms of the disease. Impaired cognitive performances are reported in recent small SMA 1 cohorts, while data on speech/language development in SMA 1 are limited to parent-reported information or non-formal evaluations. Future longitudinal studies focusing on standardised assessments of cognitive and speech/language development in SMA type 1 are required, as well as longitudinal neuroimaging evaluations performed alongside. Data obtained would contribute to a better knowledge on new emerging phenotypes in treated SMA 1 patients, and guide more accurate, personalised rehabilitation programs thus supporting patients' emerging abilities, autonomies and quality of life. The information gathered will also help to define additional outcome measures to test the efficacy of current and new developing drugs for SMA.

FUNDINGS

No funding was received.

SUPPORTING INFORMATION

The following additional material can be found online.

Table SI. Search strategy

Table SII. Qualitative analysis: scoring criteria

FIGURE LEGENDS

Figure 1. Study screening and selection flow chart

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TABLES

Table 1. Neuropathological studies in SMA patients and mouse models

Authors	Study design	Sample (size, SMA type, age range)	Assessment	Results	Level of evidence [22]
Towfighi et al. (1985) [26]	case series	n=4 SMA type 1 9 days – 8.5 months	autopsy examination	neuronal ballooning, chromatolysis, degeneration and neuronophagia in ventral thalamic nuclei, primary spinal sensory neurons	4.b
Devriendt et al. (1996) [25]	case report	n=1 SMA type 0 25 days	autopsy examination	severe neurodegenerative changes including ballooned neurons and neuronophagia in brainstem nuclei, thalami, cerebellum, dorsal root ganglia	4.b
Araki et al. (2003) [28]	case series	n=2 SMA type 2 5 years and 37 years	autopsy examination	reduction in the number of the Betz cells in the precentral gyrus and reduction of the large myelinated fibres in the spinal-pyramidal tract	4.b
Harding et al. (2015) [27]	case series	n=5 SMA type 1 18 days – 10 years	autopsy examination	neuronal degeneration with ballooning and chromatolysis in cerebral cortex, hippocampus, basal ganglia, thalami, brainstem, pigmented nuclei, cerebellum, dorsal root ganglia	4.b
Wishart et al. (2010) [29]	bench research (mouse model)	Smn-/-;SMN2 mice	post-mortem examination	decreased cell density, reduced cell proliferation and impaired neurogenesis in primary motor cortex, hippocampus	5.c
Liu et al. (2010) [30]	bench research (mouse model)	Smn-/-;SMN2 mouse embryos	post-mortem examination	dramatic increase in cell death in the developing telencephalon at both the dorsal and ventral sides around the lateral ventricle	5.c
d'Errico et al. (2013) [31]	bench research (mouse model)	Smn-/-;SMN2+/+;SMNΔ7+/+ mice	post-mortem examination	selective decrease in the number of large layer V pyramidal neurons in the motor cortex	5.c

Table 2. Neuroimaging studies in SMA patients

Authors	Study design	Sample (size, SMA type, age range)	Assessment	Results	Level of evidence [22]
Yohannan et al. (1991) [32]	case series	n=8 SMA type 1 21 days – 15 months	baseline brain CT [a]	generalised cerebral cortical atrophy, low attenuated non-enhancing areas in the white matter of both frontal lobes	4.b
Ito et al. (2003) [33]	case report	n=1 SMA type 1 6 years	baseline brain MRI [b]	high signal intensity lesions in the anterolateral portions of the bilateral thalami	4.b
Mendonça et al. (2019) [34]	case series	n=3 SMA type 0 First assessment: by 2 months Follow-up assessment: at 11 months, 1 year and 3 years, respectively	longitudinal brain MRI [b]	First assessment: supratentorial atrophy of subcortical predominance, tapered corpus callosum and widening of sulcus and ventricles Follow-up assessment: severe reduction of the white matter (3/3), severe hippocampal atrophy (2/3); symmetrical signal abnormalities in the putamen and thalamus - lateral and pulvinar -(2/3), with additional atrophy of caudate (1/3); marked ventricular dilatation (1/3)	4.b
Maeda et al. (2019) [35]	case report	n=1 SMA type 0 First assessment: neonatal Second assessment: 7 months Third assessment: 2 years	longitudinal brain MRI [b]	First assessment: no findings suggestive of hypoxic ischemic encephalopathy Second assessment: atrophy of the cerebral cortex, subcortical white matter, thalamus and basal ganglia Third assessment: additional reduction of volumes of cervical cord, brainstem and cerebellum	4.b

[a] Computed Tomography; [b] Magnetic Resonance Imaging

Table 3. Studies exploring cognitive function in SMA 1

Authors	Study design	Sample (size, SMA type, age range [a])	Assessment	Results	Level of evidence [22]	Quality score [23,24]
Billard et al. (1998) [36]	case-control study	n=11, SMA type 1 and 2, 8y 3m – 13y 6m n=21, DMD [b], 8y 6m – 13y 6m n=42, healthy controls, 6y 3m – 14y 0m	WISC-R [c] subtests; Batterie d'Evaluation du Langage, Test de vocabulaire actif e passif, North Syntax screening test; reading and processing tests: le pipe et le rat, single-word lists reading	verbal IQ [d], verbal memory, language and reading deficits in DMD patients compared to SMA and control group	4.b	6/12
Von Gontard et al. (2001) [37]	case-control study	n=96, SMA (18 type 1), 6y 0m – 18y 11m n=45, non-affected siblings, age-matched n=59, healthy controls, age-matched	Raven coloured and standard progressive matrices (CPM / SPM), subtests of the Kaufman assessment battery for children (K-ABC) and of the WISC	similar results in SMA and control groups, no differences according to SMA type; environmentally mediated aspects of intelligence higher in adolescents with SMA	4.b	9/12
Chung et al. (2004) [38]	cross-sectional study	n=83, SMA (22 type 1), age not specified no control group	interview-based questionnaire for caregivers: Functional Independence Measure for Children (WeeFIM) – Chinese version	overall performance of children with SMA below normal, with the worst performances in type 1 patients	4.b	6/12
Polido et al. (2017) [39]	case-control study	n=12, SMA type 1, 6.0 y ± 2.3 y n=12, healthy controls, age-matched	4 pair-matching tasks (assessed with an eye tracking device): task 1= matching objects, animals and fruits; task 2= matching figures and colours; task 3= matching letters; task 4= matching numbers	poorer performances in SMA patients compared to controls in terms of correct answer rate and time of performance in all tasks	4.b	9/12

[a] age: y=years, m=months; [b] DMD=Duchenne Muscular Dystrophy; [c] WISC-R=Wechsler Intelligence Scale for Children – Revised; [d] IQ=Intelligence Quotient;

Table 4. Studies exploring speech and language in SMA 1

Authors	Study design	Sample (size, SMA type, age range)	Assessment	Results	Level of evidence [22]	Quality score [23,24]
Hoshi et al. (2017) [40]	cross-sectional study	n=36 SMA type 1 11 months – 15 years	postal questionnaire for parents/carers on language development milestones classified into three main items: communication skills using devices, communication skills with no devices, communication methods used at the time of the assessment	the ability to communicate with no devices (eye fixation, vocalization, signs) is delayed in SMA 1 compared to typically developing children, but it is acquired earlier than the ability to communicate using electronic or non-electronic devices	4.b	4/12
Pane et al. (2018) [8]	cross-sectional study	n=122 SMA type 1 3 months – 266 months	clinical observation of the "*ability to produce at least short sentences that could be understood by the examiner and not just by the carers*" (reported as: yes/no)	34/122 (28%) had acquired comprehensible speech	4.b	7/12
Ball et al. (2019) [41]	cross-sectional study	n=32 SMA type 1 6 months – 30 years	researchers-developed online survey for parents/carers on interaction characteristics associated with: communication using natural speech; communication methods used; issues with speech-generating devices	speech deficits related to clarity, independence, intelligibility; methods used: speech (n=19), gesture (n=22), speech-generating device (n=12), no-tech picture or symbol board/book (n=5), all methods (n=3); several obstacles to the acquisition and implementation of speech-generating devices	4.b	4/12
Al-Zaidy et al. (2019) [14]	observational study	n=12 SMA type 1 0.9 months – 7.9 months at baseline no control group	clinical observation of the "*ability to speak*" at baseline and 2 years after (reported as: yes/no)	11/12 (92%) were able to speak by the end of the 2y follow-up period	3.e	4/12

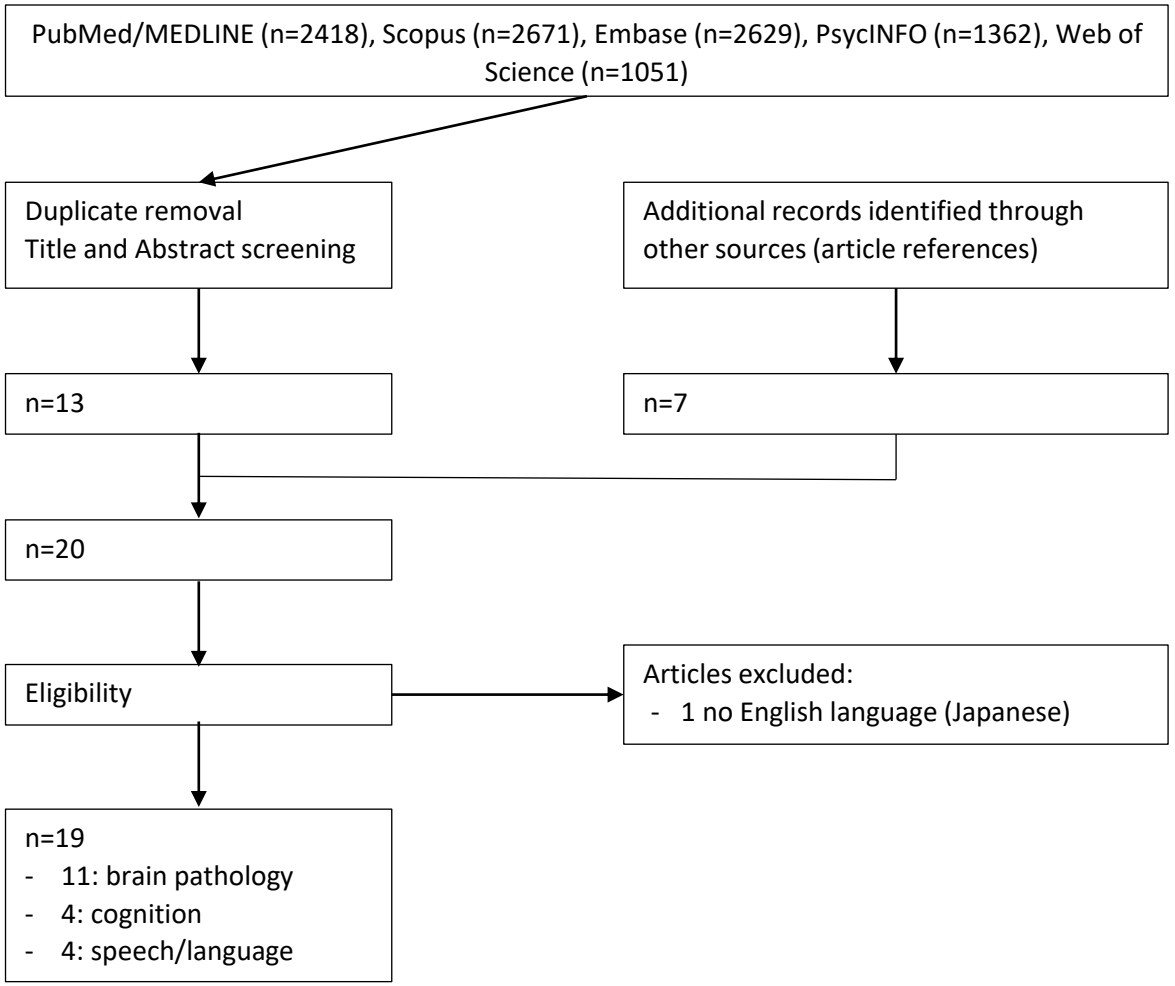
PubMed/MEDLINE (n=2418), Scopus (n=2671), Embase (n=2629), PsycINFO (n=1362), Web of Science (n=1051)
Duplicate removal
Title and Abstract screening
Additional records identified through other sources (article references)
n=13
n=7
n=20
Eligibility
Articles excluded:
- 1 no English language (Japanese)
n=19
- 11: brain pathology
- 4: cognition
- 4: speech/language

Table SI. Search strategy (PubMed/MEDLINE, Scopus, Embase, PsycINFO)

Search	*Query*	*Items*
Pubmed/MEDLINE		
1	(spinal muscular atrophy) OR ("Muscular Atrophy, Spinal"[Mesh])	8292
2	(brain) OR ("Brain"[Mesh])	1914639
3	(magnetic resonance imaging) OR ("Magnetic Resonance Imaging"[Mesh])	533582
4	(central nervous system) OR ("Central Nervous System"[Mesh])	1444329
5	(cognition) OR ("Cognition"[Mesh])	273074
6	(intellectual disability) OR ("Intellectual Disability"[Mesh])	101327
7	(speech) OR ("Speech"[Mesh])	22539
8	(language) OR ("Language"[Mesh])	326561
9	(communication) OR ("Communication"[Mesh])	543205
10	(augmentative alternative communication) OR ("Communication Aids for Disabled"[Mesh])	3022
11	(attention) OR ("Attention"[Mesh])	450670
12	(executive functions) OR ("Executive Functions"[Mesh])	32427
13	(working memory) OR ("Working Memory"[Mesh])	50992
14	(neuropsychology) OR ("Neuropsychology"[Mesh])	21390
15	1 AND 2	977
16	1 AND 3	502
17	1 AND 4	1291
18	1 AND 5	45
19	1 AND 6	107
20	1 AND 7	40
21	1 AND 8	46
22	1 AND 9	77
23	1 AND 10	3
24	1 AND 11	85
25	1 AND 12	6
26	1 AND 13	5

27	1 AND 14	4
28	15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27	2418

Scopus		
1	Spinal muscular atrophy AND brain	1196
2	Spinal muscular atrophy AND magnetic resonance imaging	811
3	Spinal muscular atrophy AND central nervous system	724
4	Spinal muscular atrophy AND cognition	74
5	Spinal muscular atrophy AND intellectual disability	27
6	Spinal muscular atrophy AND speech	76
7	Spinal muscular atrophy AND language	48
8	Spinal muscular atrophy AND communication	111
9	Spinal muscular atrophy AND augmentative alternative communication	4
10	Spinal muscular atrophy AND attention	150
11	Spinal muscular atrophy AND executive functions	9
12	Spinal muscular atrophy AND working memory	7
13	Spinal muscular atrophy AND neuropsychology	7
14	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	2671

Embase		
1	Spinal muscular atrophy AND brain	1073
2	Spinal muscular atrophy AND magnetic resonance imaging	441
3	Spinal muscular atrophy AND central nervous system	468
4	Spinal muscular atrophy AND cognition	60
5	Spinal muscular atrophy AND intellectual disability	25
6	Spinal muscular atrophy AND speech	62
7	Spinal muscular atrophy AND language	48
8	Spinal muscular atrophy AND communication	106
9	Spinal muscular atrophy AND augmentative alternative communication	0
10	Spinal muscular atrophy AND attention	1320

11	Spinal muscular atrophy AND executive functions	195
12	Spinal muscular atrophy AND working memory	104
13	Spinal muscular atrophy AND neuropsychology	240
14	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	2629

PsycINFO		
1	Spinal muscular atrophy AND brain	1198
2	Spinal muscular atrophy AND magnetic resonance imaging	168
3	Spinal muscular atrophy AND central nervous system	351
4	Spinal muscular atrophy AND cognition	152
5	Spinal muscular atrophy AND intellectual disability	78
6	Spinal muscular atrophy AND speech	71
7	Spinal muscular atrophy AND language	130
8	Spinal muscular atrophy AND communication	153
9	Spinal muscular atrophy AND augmentative alternative communication	1
10	Spinal muscular atrophy AND attention	16
11	Spinal muscular atrophy AND executive functions	3
12	Spinal muscular atrophy AND working memory	2
13	Spinal muscular atrophy AND neuropsychology	109
14	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	1362

Table SII. Qualitative analysis: scoring criteria amended from Cross and Hare and reported by Pearson et al.

1. Control group. Papers will score: 0 no control group, 1 comparisons between non-genetically distinct groups or utilise standardised assessment tools, 2 genetically distinct control group.

2. Sample size. Papers will score: 0 fewer than 15 participants, 1 15+, 2 30+.

3. Recruitment. Papers will score: 0 participants selected by clinician(s), 1 participants recruited either through charity or medical clinic, and 2 multiple methods, multiple clinics or multiple charities are used for recruitment.

4. Syndrome diagnosis. Papers will score: 0 syndrome diagnosis based on self-report, 1 diagnosis based on physical features or sibling diagnosis, 2 diagnosis based on appropriate genetic/ enzyme testing.

5. Methodology. Papers will score: 0 no validated measures are used, 1 use validated and/or standardised assessment tools, 2 validated and/or standardised measures are used alongside new measures, observations or other methodology.

6. Appropriate statistics/ comparisons. A paper will score: 0 data not analysed, 1 descriptive statistics are used, 2 appropriate comparative/correlative statistics are reported.

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3, 4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	supporting information
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	5
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	5, 6, tables
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	6

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7, 8, 9
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	7, 8, 9
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	tables 1, 2, 3, 4
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	10, 11
Limitations	20	Discuss the limitations of the scoping review process.	11
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	12
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	12

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.