Intelligence Quotient in Paediatric Sickle Cell Disease: a Systematic Review and Meta-Analysis

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Intelligence Quotient in Paediatric Sickle Cell Disease: a Systematic Review and Meta-Analysis

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Abstract

Aim: Sickle cell disease (SCD) is the commonest cause of childhood stroke world-wide. Magnetic resonance imaging (MRI) is routinely used to detect additional silent cerebral infarction (SCI), as intelligence quotient (IQ) is lower in SCI as well as stroke. This review assesses the effect of infarction on IQ, and specifically whether, compared to healthy controls, IQ differences are seen in SCD children with no apparent MRI abnormality.

Method: A systematic review was conducted to include articles with a SCD paediatric population, MRI information and Wechsler IQ. A meta-analysis of nineteen articles was performed to compare IQ in three groups: Stroke vs. SCI, SCI vs. no SCI, and no SCI vs. healthy controls.

Results: Mean differences in IQ between all three groups were significant: Stroke patients had lower IQ than SCI patients by 10 points (6 studies), SCI patients had lower IQ than no SCI patients by 6 points (17 studies), and no SCI patients had lower IQ than healthy controls by 7 points (7 studies).

Interpretation: Children with SCD and no apparent MRI abnormality have significantly lower IQ than healthy controls. In this chronic condition, other biological, socioeconomic and environmental factors must play a significant role in cognition.

What this paper adds:
-Systematic review including recent IQ studies in SCD
-Meta-analysis including previously underreported results comparing SCD and healthy children
-Critical appraisal of SCI lesion size quantification studies
-Critical appraisal of appropriate control comparison group
-Discussion of non-radiological factors associated with lowered IQ

Running foot: IQ in Sickle Cell Disease

Introduction

Sickle cell disease (SCD) is a lifelong inherited genetic disease associated with a high prevalence of stroke and cognitive dysfunction in childhood. Approximately 10% of patients will experience an overt stroke[1]; however, in the first decade of life around one third of children with SCD will accumulate at least one silent cerebral infarct (SCI; *i.e.* an abnormality seen on T2-weighted MRI in the absence of overt stroke, or neurological symptoms lasting more than 24 hours)[2]. By definition, SCI are clinically silent and therefore age at which SCI occurred and time lapse between SCI and cognitive testing are unknown. Stroke and SCI have been associated with general cognitive dysfunction, including problems with sustained attention, cognitive flexibility and working memory[3–7].

Full-scale intelligence quotient (IQ) is the most commonly reported and widely studied standardised measure of general cognitive ability in SCD. Chodokoff & Whitten (1963) published the first study investigating IQ between patients with SCD and controls – finding no differences; however from the 1980s/early 1990s there were many studies suggesting that patients have lowered global intelligence scores than matched controls, even when excluding those with history of stroke or abnormal neurological examination[8–13]. The first study that used magnetic resonance imaging (MRI) to classify patients into groups based on whether SCI are present or absent was published in 1996[14]; collaborators in the large Cooperative Study in Sickle Cell Disease (CSSCD) study in the United States linked presence of MRI abnormality and measurable global cognitive dysfunction. Since then, several studies have confirmed that children with SCI (SCI+) generally have lower IQ scores than those without evidence of SCI (SCI-)[15–20]. These findings established a potential link between presence of lesions and lesion size as a mediating factor in a child's IQ score.

The presence, nature and aetiology of any differences in IQ between children with SCD without SCI (*i.e.* normal MRI) and healthy controls have however, received less attention. These studies are necessary to elucidate differences in neurocognitive outcome that may be due to subtle aspects of the disease other than presence of SCI, such as chronic anaemia and hypoxia[21] and school absences, and to attempt to separate them from socioeconomic[22] and environmental effects.

The purpose of this article is to evaluate the relationship between IQ and MRI status in children with SCD, through systematic review and a meta-analysis of published studies. A meta-analysis in 2002[23] found an overall difference of 4.3 standard IQ score points lower in children with SCD compared to controls, with a significant effect size. This review expands to separate the patient group by radiological status as seen on MRI (*i.e.* SCI+, SCI-), with a specific aim to answer the question of whether IQ differences are seen in children with no apparent MRI abnormality compared to healthy controls.

Methods

Literature searches were conducted on PubMed using the search terms "sickle cell" paired with either "intelligence" or "IQ" from 1980-2015. To be eligible for review, the peer-reviewed article must have been a cross-sectional design, included a paediatric SCD population, used MRI to define presence of absence of SCI and/or stroke, and used a Wechsler intelligence scale measure that reported IQ (*e.g.* WPPSI, WASI, WISC, WAIS). Systematic and other reviews were excluded, although references from those articles may have identified additional original articles. Additional articles that met inclusion criterion were also drawn from the references of each original article identified.

Seventy-three publications were identified through the literature search. From the aforementioned criteria, the following articles were excluded: 5 reviews and 1 letter to the editor, 3 articles with non-paediatric SCD populations, 28 articles without MRI information, and 6 articles without Wechsler scales. Additionally, 8 articles were excluded because the authors did not report IQ values or did not clearly state scores by MRI group, 1 article was excluded because of longitudinal design, 1 article with two groups was excluded due to only having one subject in one of the groups, and 1 article was excluded because patients only included those with HbA + SB_0 thalassaemia. Nineteen articles were included in this review (see Figure 1 for flow chart). For each article, participant age and mean IQ and standard deviation were recorded for each MRI group (Table 1).

Critical appraisal

FSIQ was not the primary outcome measure of many of these articles; however, to assess quality for this review, the articles were evaluated for characteristics that may affect FSIQ; criteria included details of how the groups were identified (*i.e.* SCI identification on MRI), lesion size assessment (if applicable) and appropriateness of control group (*i.e.* sibling/community control, data from normative databases).

Statistical analysis

Each study analysed reported Wechsler full-scale IQ scaled for developmental stage with mean 100, standard deviation 15 and range 40-160. A meta-analysis was performed using the metafor[24] package in R (www.r-project.org). Three group comparisons were analysed: 1) mean difference between Stroke and SCI+ groups (n=6 studies), 2) mean difference between SCI+ and SCI- groups (17 studies), and 3) mean difference between SCI- and healthy controls (HC; n=7 studies).

The 19 studies were drawn from different countries and were assumed to each contain a sample of the SCD population. The data was assumed to be heterogeneous (*i.e.* not every study showing the same true effect size in differences in mean IQ); therefore a random-effects restricted maximum-likelihood estimator model, which estimates heterogeneity, was fitted to the data for each group comparison. Estimates and 95% confidence intervals of between-group mean differences were calculated and displayed on forest plots.

Results

Of the 19 studies included in this review, 6 included a Stroke group, 17 included a SCI+ group, and 7 included a HC group. Mean IQ ranged between 65.9 to 76.9 in the Stroke group, between 70.6 to 93.12 in the SCI+ group, between 78.9 to 103.12 in the SCI- group, and between 88 to 108.29 in the HC group (Table 1).

Critical appraisal

As presence of SCI has been shown to affect IQ, this study aimed to critically appraise how SCI are identified in these studies and how lesion size estimation was performed. Additionally, fewer studies employed a control group for comparison, and characteristics of these control groups were critiqued.

Identification and measurement of SCI

Definitions of SCI varied; most studies defined SCI as an area of abnormally increased signal intensity on T2-weighted or FLAIR sequences, without history of a focal neurological

event[14,17,19,25–28]. Some, however, defined patient groups by normal or 'abnormal' MRI, which may have included different aetiologies including lacunar infarction, leukoencephalopathy and encephalomalacia[15,18]. Other studies included MR angiography to discern major vessel watershed infarction from unilateral and bilateral high-signal lesions[16]. More recently, several US studies defined SCI as an MRI signal abnormality at least 3mm in one direction and visible on two views on FLAIR T2-weighted images[22,29,30], as used in the Silent Infarct Transfusion trial[31].

Ten of 17 studies that included an SCI group did not describe any lesion size measurement for analysis, and three studies used a qualitative measurement (*i.e.* categorizing lesions into focal/small <0.5cm, medium 0.5-1.5cm, or large >1.5cm)[3,14,26]. The remaining four studies quantified lesion size as a continuous variable, either by manual tracing of hyperintense voxels and converting to mm^3 by multiplying by slice thickness and gap[29,30], manual tracing of T2-weighted images that have been registered to Montreal Neurologic Institute (MNI) space[19], or using a semi-automatic method and multiplying segmented voxels by voxel volume[28]. The effect of lesion quantification method on results are mixed; one study did not provide any correlation result with IQ[19], two studies found volume of SCI to be a significant predictor of IQ[28,29] and one study found only patients with larger lesions had lower IQ[30].

Studies with healthy control group

Seven studies included a healthy control group. However, 'control group' consisted of different characteristics depending on the study: group of siblings recruited contemporaneously with patients[3,16,32], group of siblings as well as non-ethnically matched control subjects recruited contemporaneously with patients[19], group of community controls matched for age, gender, race and socioeconomic status recruited contemporaneously with patients[29], group of historical sibling data (not siblings of the patients recruited)[15] and group of normative data from the WISC matched for age, race and gender[33].

The use of varied control groups gave mixed results when comparing with SCD patients with normal MRI. Two studies that included siblings as a comparison group found 5-[32] and 6-point[3] IQ reductions in patients, but results were non-significant, while one study did not specifically test those groups[16]. One study found SCI- patients had significantly lower IQ than controls, when the controls consisted of siblings and non-ethnically matched subjects[19]. No differences were found between SCI- patients and a sample of community controls[29]. When using historical sibling data[15] or normative database data[33], SCI- patients scored significantly lower than the control comparison group.

Meta-analysis

The random-effects model estimated the amount of total heterogeneity ($\boldsymbol{\tau}^2$) and performed Cochran's *Q*-test for heterogeneity[34]. There was significant heterogeneity in the Stroke vs. SCI+ comparison, while non-significant heterogeneity in the SCI+ vs. SCI- and SCI- vs. HC comparisons; however, the random-effects model was used for consistency (Table 2).

Mean differences in IQ between Stroke vs SCI+, SCI+ vs SCI- and SCI- vs HC groups were all significant (Table 2, Figure 2). For the Stroke vs SCI+ analysis, the model estimated stroke groups have a mean difference of 10.31 IQ points lower than SCI+ groups (p=0.0013). For the SCI+ vs SCI- analysis, the model estimated the SCI+ groups have a mean difference of 5.83 IQ points lower than SCI- groups (p<0.0001). For the SCI- vs HC analysis, the model estimated SCI- groups have a mean difference of 6.90 IQ points lower than healthy control groups (p<0.0001).

Discussion

IQ, a representative of a child's general cognitive ability, has been widely used in the SCD literature for more than 30 years. Many studies have established a trend for decreasing IQ with MRI status using age-appropriate Wechsler scales for children; this review analysed all studies that reported IQ by MRI status, to elucidate differences between those studies that grouped SCD patients together regardless of MRI abnormality.

The results of the meta-analysis of 19 studies confirm this trend for decreased IQ: patients with history of stroke perform significantly worse than those with SCI by approximately 10 IQ points and children with SCI perform significantly worse than children without SCI (normal MRI) by approximately 6 IQ points. This meta-analysis also finds children with normal MRI perform significantly worse than healthy controls by approximately 7 IQ points. This is in contrast to some previous conclusions[28]; these findings suggest that presence of lesions, or lesion size alone, may not account for all differences in IQ in children with SCD. Other factors, whether biologic[22], socioeconomic[22] or environmental[35], are likely to play an additional role in the child's cognitive outcome.

Effect of SCI on FSIQ

Presence of SCI

SCI have been reported to occur in at least 27% of children with SCD before 6 years of life[36], and the number and size of lesions have been shown to increase over time in children with SCI who do not develop clinical stroke[37]. SCI in children with SCD are considered to be secondary to small vessel disease, mainly affecting the white matter in the frontal lobe borderzones between the anterior and middle cerebral artery territories[38], but may also result from acute events, including posterior reversible encephalopathy syndrome[39] and fall in haemoglobin[40]. Results from a previous meta-analysis published 13 years ago found that children with evidence of SCI on MRI have IQ scores approximately 4-7 points lower than children without evidence of SCI[23], which is in line with the approximate 6 point reduction found between those two groups found in this meta-analysis.

Size of SCI

Previous reports have shown presence of SCI or lesion volume as an independent predictor of FSIQ[22,28,29]. However, there may be a threshold of lesion size before IQ is affected; in one study, small infarct volume appeared to have minimal impact on global cognitive ability but larger volume was associated with lowered FSIQ scores in eight patients with SCI[30]. It is of note that these articles showed discrepancies in lesion quantification methods. Quantitative lesion measurements from T2-weighted or FLAIR images were 2D sequences with 3mm or 5mm thick slices, sometimes with 2-3mm gaps between slices; a 3D sequence with isotropic voxel sizes would have been ideal to rule out potential partial volume effects.

Neuroimaging correlates of FSIQ

Quantitative neuroimaging has shown neuroanatomical correlates of decreased IQ in children with SCD. White matter density, as determined by voxel-based morphometry, was found to correlate with verbal IQ in the left hemisphere, as well as performance IQ in the right hemisphere, but not full-scale IQ[19]. Two studies[41,42] were excluded from this review because the authors did not report FSIQ scores by MRI group; however, these authors found neuroimaging correlates of FSIQ of note. Steen and colleagues[41] found an inverse relationship between basilar artery volume and FSIQ (r=-

0.62, p<0.005), while Strouse and colleagues[42] found an inverse correlation between right-hemisphere cerebral blood flow and FSIQ (p=0.04) and performance IQ (p=0.01).

Biological determinants of FSIQ

Previous studies have shown SCD-related markers of disease severity to correlate with intelligence, which may explain differences in IQ between patients with normal MRI and healthy controls. There have been links with anaemia severity[16,18,43–45]; more specifically, haematocrit[16,43] and the interaction between age and haematocrit[26], that have also been shown in non-SCD populations[46–48]. This correlation between anaemia and IQ could be due to a direct impact on the brain (*i.e.* anaemia-induced hypoxia/ischaemia) or due to indirect influences on processes such as the body's response to anaemic hypoxia exposure[41], which leads to increased cerebral blood flow[49–51] and cerebral blood flow velocity[52,53], reduction in cerebrovascular reserve[54] and subsequent large and small vessel injury/ischaemia[55]. In a model for explanatory factors of IQ, each 1% decrease in haemoglobin oxygen saturation was found to be associated with 0.75 IQ point decrease[22]. Chronically altered cerebral circulation may lead to a cycle of long-term hypoxia[43] and cognitive dysfunction[56]. Three studies included in this review find a negative association between chronologic age and FSIQ in cross-sectional study design[18,22,26], while a longitudinal study from the CSSCD showed on average, FSIQ decreased 1.2 point per year with age[57]. Other SCD-related biomarkers previously linked to cognitive outcome include growth delays[11,58,59], possibly linked to poor nutrition[11], that may have an effect on the development and maturation of the brain[29,60], but relatively few studies have included height as a predictor of IQ in SCD, despite the importance of this measure in the general population[61].

Environmental determinants of FSIQ

SCD has been called a neurodevelopmental disorder, in which both biological and social factors impact cognitive functioning[44,62]. Like other chronic diseases, and in addition to chronic intermittent pain[63], SCD is associated with frequent hospitalisations[64,65] for a variety of complications including acute hypoxia due to chest crisis and acute anaemia (aplastic and sequestration), which have been shown to affect cognitive functioning[66]. The home environment with a child with SCD can be especially stressful for both the child[67–69] and caregiver[70]. In an academic setting, children with SCD have been shown to demonstrate deficits in reading, writing, arithmetic and spelling compared to healthy peers and siblings[8,10,12,14,17,23,71]; this limited academic achievement[72] is likely due to high proportions of illness, school absenteeism and grade retention[73]. Poverty[35]/low socioeconomic status[74,75] and lack of parent education[22] are commonly found in SCD, and have been associated with lower IQ scores[22]. Living in cities may expose already vulnerable children to pollutants known to affect risk of cerebral infarction and to unfavourably alter brain structure in adults[76]. Lead exposure may have affected children born before 1985[77], when few studies included sibling controls, and might still have a differential effect on children with a chronic condition making them vulnerable to brain damage[78]. Noise pollution from aircraft and traffic may also play a role[79].

Use of appropriate control groups

An appropriate control group should be identical to the patient study group, with the exception of the specific variable under investigation. Siblings (recruited contemporaneously with patients) constitute the most appropriate comparison group, as many environmental factors attributing to cognition (*i.e.* socioeconomic status, parental education, ethnic background) are controlled[17,80]. Normative data from standardised Wechsler scales do not constitute a fair comparison[18,80], and one can argue community controls, while perhaps matched for ethnic background and socioeconomic

status, do not share the characteristics of the home environment of a child with SCD. This review critically analysed the composition of the control comparison groups for studies investigating IQ in SCD. Of all the studies included in this review, only two studies recruited only siblings contemporaneously with SCD patients; both found lower, but non-significant IQ scores in SCI-patients[3,32]. We recommend careful consideration when interpreting results of studies with inappropriate control comparison groups.

Limitations

While the Wechsler scales are a reliable measure of general cognitive ability, some argue that they fail to relate to real-world performance[81]. Along with school difficulties, children can also be impaired in age-appropriate life tasks, such as chores and cultural activities[82]. Cognitive impairment continues into adulthood[83], and effective education and social interventions to improve academic attainment/achievement and quality of life are necessary to ensure productivity and vocational success.

It is possible some of the studies used overlapping participants in reporting IQ. Five studies included multicentre[14,17] and single-centre[15,33] data from CSSCD, and one study[25] included data from participants enrolled in both CSSCD and Stroke Prevention in Sickle Cell Anaemia (STOP) trials.

In summary, this systematic review and meta-analysis confirms a step-wise progression of declining IQ corresponding to presence of SCI and clinical stroke, but also significantly lowered IQ between children with SCD with no evidence of MRI abnormality and healthy controls. While presence of SCI affects cognitive outcome in children with SCD, it is likely that biological, socioeconomic and environmental factors play an important role in intellectual functioning.

*denotes articles included in meta-analysis

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Author(s)	Genotype	Stroke group (n)	SCI+ group (n)	SCI- group (n)	HC Group	Age (years)	Battery	Stroke FSIQ: mean (sd)	SCI+ FSIQ: mean (sd)	SCI- FSIQ: mean (sd)	HC FSIQ: mean (sd)
Armstrong *et al.* (1996)	HbSS/HbSC (n=194)	9	24	161	none	range: 6-12	WISC-R	70.8 (5)	82.8 (2.9)	90 (1.7)	-
Steen *et al.* (1998)	SCD (n=22)	-	10	12	30	patients = mean 10.5 ± 3.4, controls = mean 10.5 ± 3.0	WISC-R WISC-III	-	70.6 (12.1)	78.9 (8.9)	88 (16.1)
Watkins *et al.* (1998)	SCD (n=39)	5	4	30	15	range: 5.9-16.7	WISC-III WPPSI-R	67.6 (16.6)	79 (5.7)	86.03 (12)	92.07 (12.2)
Bernaudin *et al.* (2000)	SCD (n=173)	11	17	104	76	range: 5-15	WISC-III WPPSI-R	73.5 (14.4)	82.6 (15.7)	86.6 (17.1)	90.3 (14.3)
Brown *et al.* (2000)	HbSS/HbSC (n=63)	22	11	30	none		WISC-III	75.05 (15.53)	81.91 (14.43)	81.67 (16.68)	-
Wang *et al.* (2000)	HbSS/HbS β^0-thalassaemia (n=73)	-	14	59	none	range: 6-16	WISC-III	-	73.0 (12.1)	86.0 (15.0)	-
Wang *et al.* (2001)	HbSS (n=185)	20	43	122	none	range: 6-12	WISC-R WISC-III	76.9 (17.2)	77.2 (13.7)	84.8 (13.5)	-
Schatz *et al.* (2002)	HbSS (n=27)	-	18	9	none	SCI+ patients = mean 12.4 ± 1.9, SCI- patients = mean 11.6 ± 3.0	WASI	-	81.9 (12.4)	89.9 (7.9)	-
Steen *et al.* (2003)	HbSS (n=49)	-	16	33	none	range: 4-19.7	WISC-R WISC-III	-	78.6 (16.1)	81.1 (11)	-
Steen *et al.* (2005)	HbSS (n=54)	-	-	30	30	10.9 ± 2.9	WISC-III	-	-	79.4 (11.9)	91.37 (12.19)
Baldeweg *et al.* (2006)	HbSS/HbSC (n=36)	-	16	20	31	SCI- patients =17.1 ± 4.1, SCI+ patients= 18.2 ± 4.4, controls = 15.7 ± 3.6	WISC-III WAIS	-	82 (13)	92 (14)	101 (11)
Hogan *et al.* (2006)	SCD (n=30)	-	17	13	none	17.4 ± 4.2	WISC-III WAIS-R	-	82.5 (12.5)	87.4 (8.1)	-

Kral *et al.* (2006)	**HbSS (n=27)**	**-**	**5**	**22**	**none**		**WASI**	**-**	**90.60 (3.05)**	**87.59 (11.42)**	**-**
Schatz & Buzan (2006)	HbSS (n=28)	8	8	12	16		WISC-III	65.9 (14.8)	92.9 (12.8)	94.5 (14.2)	97.9 (11.8)
White *et al.*, (2006)	SCD (n=65)	-	16	49	none	8.0-16.9 years	WASI	-	85.8 (12.7)	90.0 (12.9)	-
Hijmans *et al.* (2011)	HbSS/HbS β-thalassaemia (n=34)	-	22	9	none	6-12 years	WISC-III WAIS-III	-	79 (14.4)	80 (9)	-
King *et al.* (2014)	HbSS/HbS β-thalassaemia (n=150)	-	107	43	none	5-15 years	WASI WPPSI-III	-	93.12 (12.5)	100.53 (13.08)	-
van der Land *et al.* (2015)	HbSS/HbS β^0-thalassaemia (n=38)	-	19	19	none	8.2-17.1 years	WISC-III/WAIS-III	-	81 (7)	89 (12)	-
Kawadler *et al.* (2015)	HbSS (n=25)	-	-	25	14	8-18 years	WASI	-	-	103.12 (11.95)	108.29 (11.69)
WISC-R=Wechsler Intelligence Scale for Children – Revised (age 6 years, 0 months – 16 years, 11 months); WISC =Wechsler Intelligence Scale for Children (age 6 years, 0 months – 16 years, 11 months); WPPSI= Wechsler Preschool and Primary Scale of Intelligence (age 2 years, 6 months – 7 years, 3 months); WASI=Wechsler Abbreviated Scale of Intelligence (age 6-89 years); WAIS= Wechsler Adult Intelligence Scale (age 16 years, 0 months – 90 years, 11 months)											

Table 1. Overview of original articles included in meta-analysis.

	Stroke vs. SCI+ group	SCI+ vs. SCI- group	SCI- vs. HC group
Number of studies	6	17	7
Random-effects model			
Estimated total heterogeneity (τ^2)	35.11	4.49	2.37
Cochran's *Q* (p)	12.32 (p=0.03)	22.96 (p=0.11)	5.85 (p=0.44)
Model estimate (95% CI)	-10.31** (-16.58 - -4.04)	-5.83*** (-7.70 - -3.95)	-6.90*** (-9.74 - -4.07)
**p<0.01, ***p<0.001			

Table 2. Results of meta-analysis.

Figure Legends

Figure 1. Systematic review flow chart.

Figure 2. Forest plots of mean differences between groups of patients categorised by MRI status. Mean differences (estimates) were significant between patients with history of stroke vs those with SCI (left panel), patients with evidence of SCI vs patients with normal MRI (no evidence of SCI; middle panel), and patients with no evidence of SCI and healthy controls (right panel).

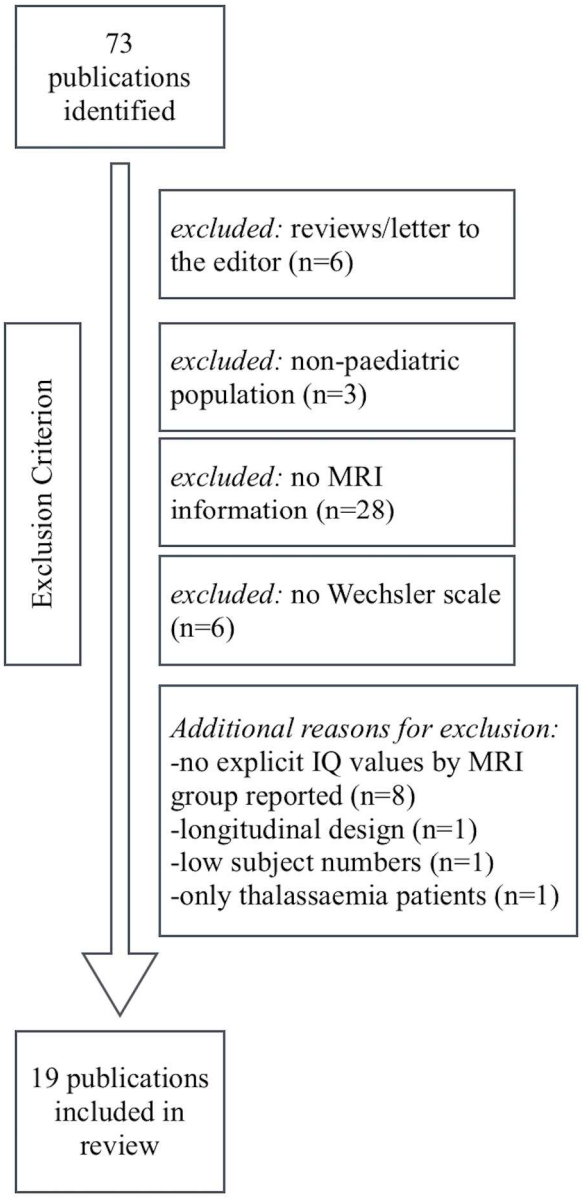

Figure 1. Systematic review flow chart.
124x253mm (300 x 300 DPI)

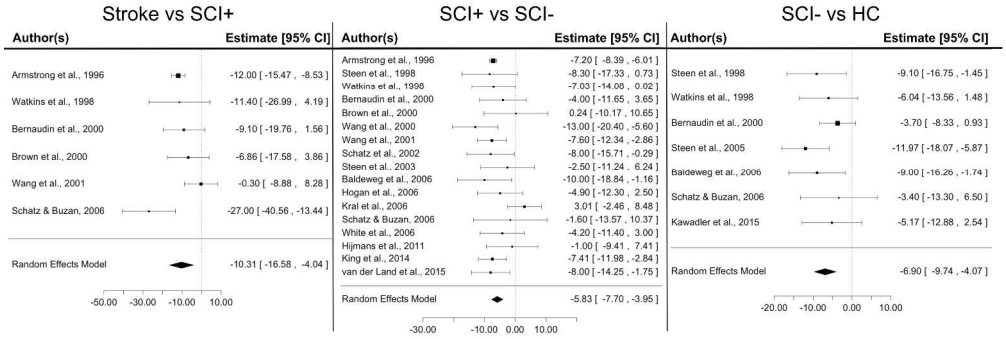

Figure 2. Forest plots of mean differences between groups of patients categorised by MRI status. Mean differences (estimates) were significant between patients with history of stroke vs those with SCI (left panel), patients with evidence of SCI vs patients with normal MRI (no evidence of SCI; middle panel), and patients with no evidence of SCI and healthy controls (right panel).

Research and Reporting Methods | 2 June 2015

The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations FREE

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Table. Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis

Section/Topic	Item # *	Checklist Item†	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	3
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	N/A
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	N/A
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	4
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: *Handling of multigroup trials;* *Selection of variance structure;* *Selection of prior distributions in Bayesian analyses; and* *Assessment of model fit.*	4
Assessment of inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	4
Risk of bias across	15	Specify any assessment of [illegible] affect the cumulative evidence (e.g., publication	8

studies		bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses if done, indicating which were prespecified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; *Alternative formulations of the treatment network; and* *Use of alternative prior distributions for Bayesian analyses (if applicable).*	4
RESULTS‡			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	N/A
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	N/A
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	5
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	8
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, researchers, and policymakers).	6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7-8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	N/A

* Boldface indicates new items to this checklist.
† Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
‡ Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.