

FLEX CEUs



## Torticollis



# Do obstetric risk factors truly influence the etiopathogenesis of congenital muscular torticollis?

## Abstract

**Background** Congenital muscular torticollis (CMT) is seen in childhood and presents within months after birth. The etiology remains unknown; however, medical textbooks suggest trauma at birth as a main reason. The aim of this study was to systematically describe obstetric and perinatal outcomes in a population of children with a confirmed congenital muscular torticollis diagnosis.

**Materials and methods** Children with a validated diagnosis of congenital muscular torticollis born at Aarhus University Hospital from 2000 to 2014 were included in the study. Information on perinatal, intrapartum and neonatal characteristics were obtained from databases and from medical records, and systematically described.

**Results** In this study, there were no differences in birth characteristics in children with left- and right-sided torticollis, between boys and girls or between the conservatively treated and the children who needed surgery. Most of the children with congenital muscular torticollis in this study were delivered at term without signs of birth complications or trauma. None experienced moderate or severe asphyxia.

**Conclusions** The results of the present study suggests that complicated birth or birth trauma may not be the main cause of congenital muscular torticollis and point towards intrauterine and prenatal reasons for its development.

*Level of evidence according to OCEBM levels of evidence working group 3*

**Keywords** Child · Congenital muscular torticollis · Obstetric · Perinatal · Risk factors

## Introduction

Torticollis is a clinical diagnosis where the sternocleidomastoid muscle (SCM) is shortened on the involved side, leading to a lateral tilt towards the affected muscle and contralateral rotation of the face and chin [1–3]. Several obstetric and newborn risk factors have been proposed for the development of CMT, including prolonged labor, macrosomia, breech or other irregular fetal presentations [4–6]. The theory of birth trauma proposes disruption of the SCM muscle during the birth process [7], and medical text books state that trauma at birth is associated with CMT [8–10], although the true etiology remains unknown [7]. Recent research has proposed intrauterine risk factors [7, 11, 12], but only a few larger studies [6, 13, 14] have systematically collected information in an effort to describe the etiology, and none have used systematically collected obstetric outcomes.

The aim of this study was to describe obstetric outcomes in a population of children with a confirmed diagnosis of CMT

## Materials and methods

This study was designed as an observational case study of children referred to the Department of Children's Orthopedics (DCO) at Aarhus University Hospital (AUH)

between 1 January 2000 and 31 June 2014 with a diagnosis of CMT. AUH serves a population of ~325,000 inhabitants with 4500 deliveries annually. A tertiary neonatal intensive care unit (NICU) and orthopedic facilities for children are available at AUH. In Denmark, healthcare is financed by public taxes and includes antenatal, intrapartum and post-partum care.

The inclusion criteria were; children under the age of 18 years at time of referral and treatment for CMT, with a clinically confirmed CMT diagnosis, born at AUH. The diagnosis of CMT was based on the International Classification of Diseases, 10th revision (ICD-10), defined as torticollis ICD-10 codes DM436, DQ680A, DG243, and DP158A. Further, a post hoc examination of the medical record was made to ensure fulfillment of the diagnostic criteria in all included cases.

### Orthopedic data

We performed a retrospective examination of medical records from 2000 to 2014, using torticollis diagnosis codes. The medical records were reviewed by the first author (NH) to determine the specific diagnosis of CMT.

Cases were included if the symptoms were consistent with torticollis (lateral tilt and contralateral rotation of the face and chin, restricting movement) and stated in the medical record at the time of initial evaluation. Cases were excluded if history and physical examination were inadequate to confirm a diagnosis of torticollis. The following information was required for all included patients: gender, age at time of diagnosis, affected side of the torticollis, and history of prior treatment. Children with torticollis were classified as having CMT or non-CMT.

### Obstetric data

For children born at AUH, information about the birth process was retrieved from the Aarhus Birth Cohort (ABC). The ABC contains information on all deliveries at AUH. After delivery, the attending midwife enters information on the course of delivery and newborn status in a structured birth registration form into the birth cohort database. Information about the course of pregnancy and birth includes: parity (nullipara/multipara), in vitro fertilization (IVF) pregnancy, singleton pregnancy, gestational age, fetal presentation, augmentation of labor (syntocinon<sup>®</sup>), induction of labor (prostaglandin, artificial rupture of membranes), colour of amnion fluid, delivery mode and duration of the second stage of labor. Information about the newborn includes: gender (male/female), Apgar score, umbilical cord pH, umbilical cord base excess (BSE), infant weight, infant length, infant head circumference, and transfer to the NICU.

## Results

In total 95 patients had been referred to DCO with torticollis in the study period. Of these, 17 patients were excluded because they were older than 18 years at the time of referral. Seven patients were born before the ABC was established and 32 patients were born outside AUH, leaving 39 children with torticollis fulfilling the inclusion criteria. Five had been admitted to the emergency department, but the diagnosis could not be confirmed, two patient's medical records were missing, nine children had non-CMT and 23 children had CMT (Fig. 1). Of these, 13 had left-sided torticollis and 10 had right-sided. Fourteen children were treated conservatively and nine children had one operation or more.

Table 1 presents perinatal and obstetric outcomes and shows the following.

Of the children born at AUH, 19 were borne by nulliparous women and three by multiparous women. One was assigned with unknown parity. Two pregnancies were gemelli, and one of the twin pregnancies was conceived by IVF. Six women had their birth induced, five with prostaglandin and one with artificial rupture of the membranes, and a total of ten women received syntocinon to augment labor. In total, 17 children were in vertex presentation, two in unspecified cephalic presentation and four in breech presentation. Five children were delivered by cesarean section. Of those born vaginally, five children were delivered by vacuum extraction, and two children were assisted vaginal breech births. The second stage of labor for the vaginal births was on average 32 min, ranging from 4 to 105 min.

There were 10 girls and 13 boys. Most children were born at term between 37 + 0 weeks of gestation and 42 + 0 weeks of gestation. However, three were born near-term at 34 + 4, 36 + 0 and 36 + 6 weeks of gestation. All but two children had full Apgar score after 5 min and none of the children experienced moderate or severe asphyxia or acidosis (pH < 7.10 and BSE ≥ -10 mmol/l) during birth as measured in umbilicus cord blood. Four

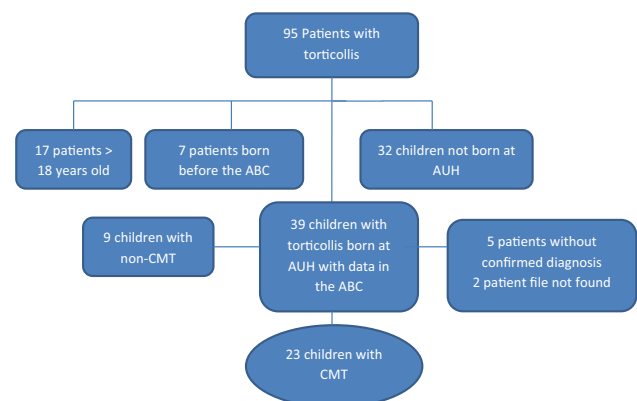


Fig. 1 Flowchart of patient recruitment

**Table 1** Perinatal and obstetric outcome in 23 children with a diagnosis of torticollis born at Aarhus University Hospital from 2000 to 2014

Pregnancy #	Gender	IVF pregnancy	Singleton	Parity	Gestational age	Fetal presentation	Augmentation <sup>®</sup> (Syntocinon <sup>®</sup> )	Induction	Amnion fluid	Delivery mode	Duration of stage 2 (min)
#1	Boy	No	Yes	Nulli	41 + 2	Vertex	Yes	No	Clear	Vaginal	38
#2	Girl	No	Yes	Nulli	39 + 5	Vertex	Yes	No	Thick green	Vaginal	62
#3	Boy	No	Yes	Nulli	40 + 1	Vertex	No	Prostaglandin	Clear	Vaginal	40
#4	Boy	No	Yes	Nulli	40 + 6	Vertex	No	No	Light green	Metal cup	4
#5	Girl	No	Yes	Nulli	40 + 0	Cephalic <sup>a</sup>	Yes	No	Clear	CS acute	-
#6	Boy	No	Yes	Nulli	40 + 2	Vertex	No	No	Green	Vaginal	54
#7	Girl	No	Yes	Nulli	40 + 2	Vertex	No	No	Clear	Vaginal	31
#8	Girl	No	Yes	Nulli	41 + 3	Vertex	Yes	No	Clear	Vaginal	19
#9	Girl	No	Yes	Nulli	40 + 0	Breech	No	Prostaglandin	Clear	Vaginal/assisted	16
#10	Boy	No	Yes	Multi	39 + 1	Breech	No	No	Clear	CS planned	-
#11	Boy	No	Yes	Nulli	41 + 0	Vertex	No	No	Clear	Vaginal	16
#12	Boy	No	Yes	Nulli	39 + 3	Vertex	No	No	Clear	Soft rubber cup	30
#13	Boy	No	Yes	Nulli	36 + 6	Vertex	No	No	Clear	Soft rubber cup	42
#14	Girl	No	No	Multi	37 + 3	Cephalic <sup>a</sup>	No	No	Clear	CS planned	-
#15	Boy	No	Yes	Nulli	40 + 0	Breech	Yes	Prostaglandin	Thick green	Vaginal/assisted	10
#16	Girl	No	Yes	Nulli	39 + 6	Vertex	Yes	Prostaglandin	Clear	Vaginal	19
#17	Girl	No	Yes	Nulli	42 + 0	Vertex	Yes	Prostaglandin	Light green	Metal cup	47
#18	Boy	Yes	No	Nulli	37 + 0	Vertex	Yes	No	Unknown	CS acute	-
#19	Boy	No	Yes	Nulli	34 + 4	Vertex	No	No	Clear	Vaginal	22
#20	Girl	No	Yes	Nulli	40 + 0	Vertex	No	No	Light green	Vaginal	10
#21	Boy	No	Yes	Multi	38 + 4	Vertex	No	No	Clear	Vaginal	13
#22	Boy	No	Yes	Missing	36 + 0	Breech	Yes	No	Clear	CS acute	-
#23	Girl	No	Yes	Nulli	39 + 6	Vertex	Yes	Ruptures of membranes	Clear	Metal cup	105

CS cesarean section

<sup>a</sup> Not specified

**Table 2** Neonatal and treatment outcomes in 23 children with a diagnosis of torticollis born at Aarhus University Hospital from 2000 to 2014

Number	Apgar Scores 1 min/5 min	Umbilical cord pH	Umbilical cord BSE	Fetal weight (g)	Fetal length (cm)	Fetal head circumference (cm)	NICU	Side of torticollis	Treatment
#1	9/10	a 7.29	-5.7	3990	55	37	No	Left	Conservative
#2	6/8	v 7.19	-7.9	3280	52	33	Yes	Right	Operated × 3
#3	10/10	a 7.22	-3	3640	52	38	No	Right	Conservative
#4	8/9	a 7.12	-5	3680	54	37	No	Left	Conservative
#5	10/10	Missing	Missing	3910	53	35	No	Left	Operated × 3
#6	10/10	v 7.31	-2	3400	52	33	No	Left	Conservative
#7	10/10	a 7.28	-8	3270	53	35	No	Right	Conservative
#8	9/10	a 7.27	-5	3160	51	34	No	Left	Conservative
#9	6/10	a 7.40	-4.6	3350	55	36	No	Right	Operated × 1
#10	10/10	v 7.38	-1	3590	51	36	Yes	Right	Operated × 2
#11	10/10	v 7.30	Missing	3850	52	32	No	Left	Conservative
#12	10/10	v 7.43	-5	2620	48	34	No	Left	Conservative
#13	10/10	a 7.27	-8	3240	50	35	No	Right	Operated × 1
#14	10/10	a 7.31	-1	2610	47	32	No	Left	Conservative
#15	9/10	v 7.36	Missing	2680	48	Missing	No	Left	Conservative
#16	10/10	a 7.35	-2	2700	49	32	No	Right	Operated × 2
#17	7/10	a 7.18	-6	3630	54	34	No	Right	Conservative
#18	10/10	Missing	Missing	3515	51	36	No	Right	Conservative
#19	10/10	v 7.21	-3	2260	54	34	No	Left	Conservative
#20	9/10	v 7.19	-5.5	3560	50	34	No	Left	Operated × 1
#21	10/10	7.41	-1	2850	41	35	No	Left	Conservative
#22	8/10	7.11	Missing	2330	49	33	Yes	Left	Operated × 3
#23	5/10	v 7.22	-10	3830	51	36	Yes	Right	Operated × 1

a arterial, v venous, NICU neonatal intensive care unit

children were admitted to the neonatal ward; one due to thick meconium-stained amnion fluid and respiratory distress together with an affected Apgar score (6/1, 8/5), and two children after emergency cesarean section, due to asymmetric head shape and low birth weight, and the last child was referred for antibiotic treatment because of prolonged rupture of membranes.

The median birth weight was 3259 g, ranging from 2260 to 3990 g. The median length was 49.2 cm, ranging from 41 to 55 cm and the median head circumference was 34 cm for the 23 children (one child's head circumference was not measured). Table 2 presents neonatal and treatment outcomes in the 23 children with a diagnosis of CMT born at AUH.

## Discussion

In this observational case study we systematically reviewed the obstetric outcomes in a population of children with a confirmed diagnosis of CMT and found that there were no

differences in birth characteristics in children with left- and right-sided CMT, between boys and girls or between the conservatively treated and the children who needed surgery. The children were primarily born by nulliparous women. Most were delivered without any trauma, seven experienced an assisted delivery, either by vacuum extraction or assisted breech birth, and with a mean second stage of labor of 32 min. Complicated birth, as measured by Apgar score, umbilical cord pH, and umbilical cord base excess, indicated that none of the children suffered moderate or severe asphyxia. Three initially had low Apgar score but all children had normal scores after 10 min. Most of the children with CMT in this study were delivered at term without signs of birth complications or trauma and none of the children could be classified as macrosomia.

Comparing our data with the existing literature we found two studies suggesting that the side of the torticollis is related to CMT either by intrauterine positioning [15] (head positioning in utero can selectively injure the SCM muscle) or due to delivering of the first shoulder [16].

Information about first delivered shoulder, the final fetal position being either left occipital or right occipital, was not available in the ABC cohort. Moreover, ultrasound is only done as routine in Denmark at around gestational weeks 12 and 19 and could therefore not provide further information about the specific fetal position during pregnancy.

No previous studies with information about parity, augmentation, or induction of labor are available. A case-control study [7] examined gestational age and birth weight for CMT patients, but not in relation to complicated birth or developing CMT. Several have studied fetal presentation and delivery mode related to CMT [7, 11, 12, 15–19]. To our knowledge no former studies have examined the duration of second stage of labor, Apgar score, umbilical cord pH and base excess, infant head circumference and transfer to the neonatal ward as indicators of complicated birth.

In our data, we found a lower prevalence of breech presentation in children with CMT, compared to earlier studies [17]. Half of the children in breech presentation were delivered vaginally and the other half by cesarean section. In a former case control study with 178 patients, Lee et al. [7] compared vaginal births with cesarean sections and found no difference in the clinical severity of CMT according to the mode of delivery, suggesting that prenatal factors most likely cause CMT due to the reduced risk of birth trauma in cesarean sections. This is in accordance with two case reports [12, 15], questioning the traumatic vaginal breech delivery theory as being the dominant pathophysiology behind CMT.

Other studies questioned trauma and difficult birth, and instead pointed towards sequelae from intrauterine and prenatal factors as the main cause of CMT. Stellwagen et al. [11] found an association between torticollis and the fetus being in the same intrauterine position for more than 6 weeks before delivery and Davids et al. [16] used magnetic resonance imaging (MRI) to observe the SCM muscle in infants and found signals similar to those in compartment syndrome.

In contrast, Hollier et al. [19] found a high frequency of complications during pregnancy and delivery in their small retrospective study of 11 patients, and Ho et al. [18] found higher rates of assisted breech births, instrumental deliveries and cesarean sections, which led them to conclude that birth trauma appears to be the main etiological factor in CMT. Suzuki et al. [17] suggested that stretching of the SCM muscle during delivery may be a direct cause of CMT. In our population only a few cases experienced moderate birth trauma: mainly those delivered with vacuum extraction. In general, most of the studies [17–19] had

only examined fetal presentation and delivery mode, lacking more specific information from obstetric and neonatal medical records.

There seems to be a tendency towards intrauterine and prenatal cause, but the possibility of a perinatal trauma to the SCM muscles cannot be excluded. In our study, most of the children with CMT were born after uncomplicated deliveries, contradictory to the most common theories described in medical textbooks.

However, our study has some limitations. Primarily it only included 23 cases of CMT. One reason for this is that 90–95% of CMT resolves within a year by manual stretching and therefore the majority of these children are never referred to an orthopedic facility. It is therefore expected that children included in this study represent the more severe cases. Our study size was further limited by including only children born at AUH, as this was the only hospital where we were able to retrieve validated obstetric data. However, we believe the study sample to be representative.

We were unable to retrieve family history of CMT in the patient records. A potential genetic association may accumulate cases of CMT within families.

Finally, this study was a retrospective observational case study with prospective collected obstetric information. Retrospective studies are useful for studying diseases with low incidence. A large prospective cohort study with evaluation of fetal positioning during pregnancy with systematic examination of the SCM in both the perinatal and the neonatal period using ultrasound or MRI, together with collection of obstetric information may provide further information of CMT etiology.

The results of the present study contribute to existing knowledge by pointing mainly towards intrauterine and prenatal reasons for developing CMT, and indicate that complicated birth and trauma may not be the main cause of CMT, even though this is stated in pediatric orthopedic textbooks.

**Conflict of interest** The authors declare that they have no conflict of interest.

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# Spinal manual therapy in infants, children and adolescents: A systematic review and meta-analysis on treatment indication, technique and outcomes

## Abstract

### Background

Studies on effectiveness and safety of specific spinal manual therapy (SMT) techniques in children, which distinguish between age groups, are lacking.

### Objective

To conduct a systematic review of the evidence for effectiveness and harms of specific SMT techniques for infants, children and adolescents.

### Methods

PubMed, Index to Chiropractic Literature, Embase, CINAHL and Cochrane Library were searched up to December 2017. Controlled studies, describing primary SMT treatment in infants (<1 year) and children/adolescents (1–18 years), were included to determine effectiveness. Controlled and observational studies and case reports were included to examine harms. One author screened titles and abstracts and two authors independently screened the full text of potentially eligible studies for inclusion. Two authors assessed risk of bias of included studies and quality of the body of evidence using the GRADE methodology. Data were described according to PRISMA guidelines and CONSORT and TIDieR checklists. If appropriate, random-effects meta-analysis was performed.

### Results

Of the 1,236 identified studies, 26 studies were eligible. Infants and children/adolescents were treated for various (non-)musculoskeletal indications, hypothesized to be related to spinal joint dysfunction. Studies examining the same population, indication and treatment comparison were scarce. Due to very low quality evidence, it is uncertain whether gentle,



**Competing interests:** The authors have declared that no competing interests exist.

low-velocity mobilizations reduce complaints in infants with colic or torticollis, and whether high-velocity, low-amplitude manipulations reduce complaints in children/adolescents with autism, asthma, nocturnal enuresis, headache or idiopathic scoliosis. Five case reports described severe harms after HVLA manipulations in four infants and one child. Mild, transient harms were reported after gentle spinal mobilizations in infants and children, and could be interpreted as side effect of treatment.

## Conclusions

Based on GRADE methodology, we found the evidence was of very low quality; this prevented us from drawing conclusions about the effectiveness of specific SMT techniques in infants, children and adolescents. Outcomes in the included studies were mostly parent or patient-reported; studies did not report on intermediate outcomes to assess the effectiveness of SMT techniques in relation to the hypothesized spinal dysfunction. Severe harms were relatively scarce, poorly described and likely to be associated with underlying missed pathology. Gentle, low-velocity spinal mobilizations seem to be a safe treatment technique in infants, children and adolescents. We encourage future research to describe effectiveness and safety of specific SMT techniques instead of SMT as a general treatment approach.

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## Introduction

Is manual therapy effective in reducing or resolving complaints or symptoms in infants, children or adolescents? Is it a safe therapeutic approach? Which specific manipulative techniques are performed? In the field of pediatric care, these questions raise interest of healthcare professionals, parents and other stakeholders. Worldwide, manual therapy is performed in infants (<1 year), children (1–11 years) and adolescents (12–18 years), by various healthcare professionals with different therapeutic backgrounds.[1, 2] They use different conceptual frameworks regarding the relationship between symptoms and underlying spinal dysfunction. Manipulative therapeutic techniques differ between professionals and health conditions, and between infants and children/adolescents.[3–7] Distinctions in techniques are made between high-velocity, low-amplitude (HVLA) manipulations[8] and low-velocity mobilizations which can be performed to the full spine or to specific spinal segments. Moreover, treatment indications vary extensively. Infants and children are frequently treated for musculoskeletal conditions, such as movement related complaints,[9] or non-musculoskeletal conditions, including colic, otitis media and asthma.[1, 4, 10] Adolescents are mainly treated for musculoskeletal conditions, such as scoliosis and headache.[1, 2, 4, 10] Non-musculoskeletal conditions as treatment indication in children differs from manipulative treatment approaches in adults, which are mainly focused on musculoskeletal conditions, such as headache, neck pain and low back pain.[11–16]

Pediatric manual therapy and its safety has provoked debates and ethical challenges.[17–19] Although several literature reviews summarize the evidence of manual therapy in children with various indications,[2, 4, 5] systematic reviews describing effectiveness of specific manual therapeutic treatment techniques, specified by treatment indication and age group, are lacking, especially in the field of spinal manual therapy (SMT).[14] Hypotheses regarding underlying spinal dysfunction that could be related to complaints in children differ between professionals,

and the therapeutic approaches used within SMT overlap. This overlap impedes the interpretation of effects and harms of SMT. In addition, research concludes on SMT as a general treatment approach instead of on the used techniques. A clear overview of the current state of the evidence is therefore needed to assess the value of specific SMT techniques in different age groups.[20, 21] This systematic review and meta-analysis of the literature provides a broad overview of the evidence regarding the effectiveness and harms of specific SMT techniques in infants, children and adolescents, related to specified treatment indication.

## Methods

We report the results of our systematic review in accordance with the PRISMA guidelines.[22] Prior to the study, the review protocol was registered at PROSPERO (CRD42017056031).

### Literature search strategy

The following electronic databases were searched up to 20 December 2017: PubMed, Index to Chiropractic Literature, Embase, CINAHL and Cochrane Library. The scientific literature was systematically searched, combining key words related to “manual therapy” and key words related to “children”. The search strategy for PubMed is shown in Fig 1. The searches in other databases were consistent with this strategy. Reference checking of included articles was used to identify potential studies that were missed with the initial search strategy (n = 1).

### Definitions

To date, there is no international consensus on the specific definition of manual therapy in pediatrics. Overall, three different therapeutic approaches can be recognized. First, chiropractic manual therapy, which uses high-velocity spinal manipulation or instrumented adjustments using minimal forces (e.g. using an Activator).[1, 23, 24] It aims to influence the nervous system, visceral functions and/or soft tissue tensions to correct segmental joint dysfunction.[18, 25, 26] Besides spinal manipulative therapy, chiropractic manual therapy incorporates additional therapies, such as soft tissue massage, nutritional counseling and exercise.[27] Second, osteopathic manual therapy, which follows a similar line of reasoning, but also intends to maintain or restore the flow of body fluids and to support homeostasis of the body.[26, 28] Third, spinal manual therapy (SMT), which relies on segmental, single spinal joint low-force oscillating mobilizations and HVLA manipulations,[8] focuses on the biomechanical aspect of spinal dysfunction by eliciting neurological, physiological and/or muscular changes.[29]

SMT techniques are integrated in all these treatment approaches, but conclusions on effectiveness and safety are mainly given on treatment approach instead of treatment technique. Hence, in this systematic review we focused on specific treatment techniques instead of SMT as a general treatment approach.

In our systematic review, manual therapeutic interventions in which treatment techniques were primarily performed on the full spine or on specific spinal segments, by any healthcare professional, were indicated as SMT. We made a distinction between two main SMT techniques: manipulation and mobilization. Manipulation was described as a HVLA or low-velocity thrust, resulting in a mechanical response of articular surface separation and a cracking sound, which is also defined as cavitation in the affected joint.[8] Mobilization was described as low-velocity, low-amplitude oscillating spinal joint play, without a thrust and without cavitation. Infants were defined as those aged between 0 to 12 months; children were defined being between 1 and 11 years; adolescents as being between 12 and 18 years. Treatment indications were categorized as musculoskeletal or non-musculoskeletal conditions. Hypothesized

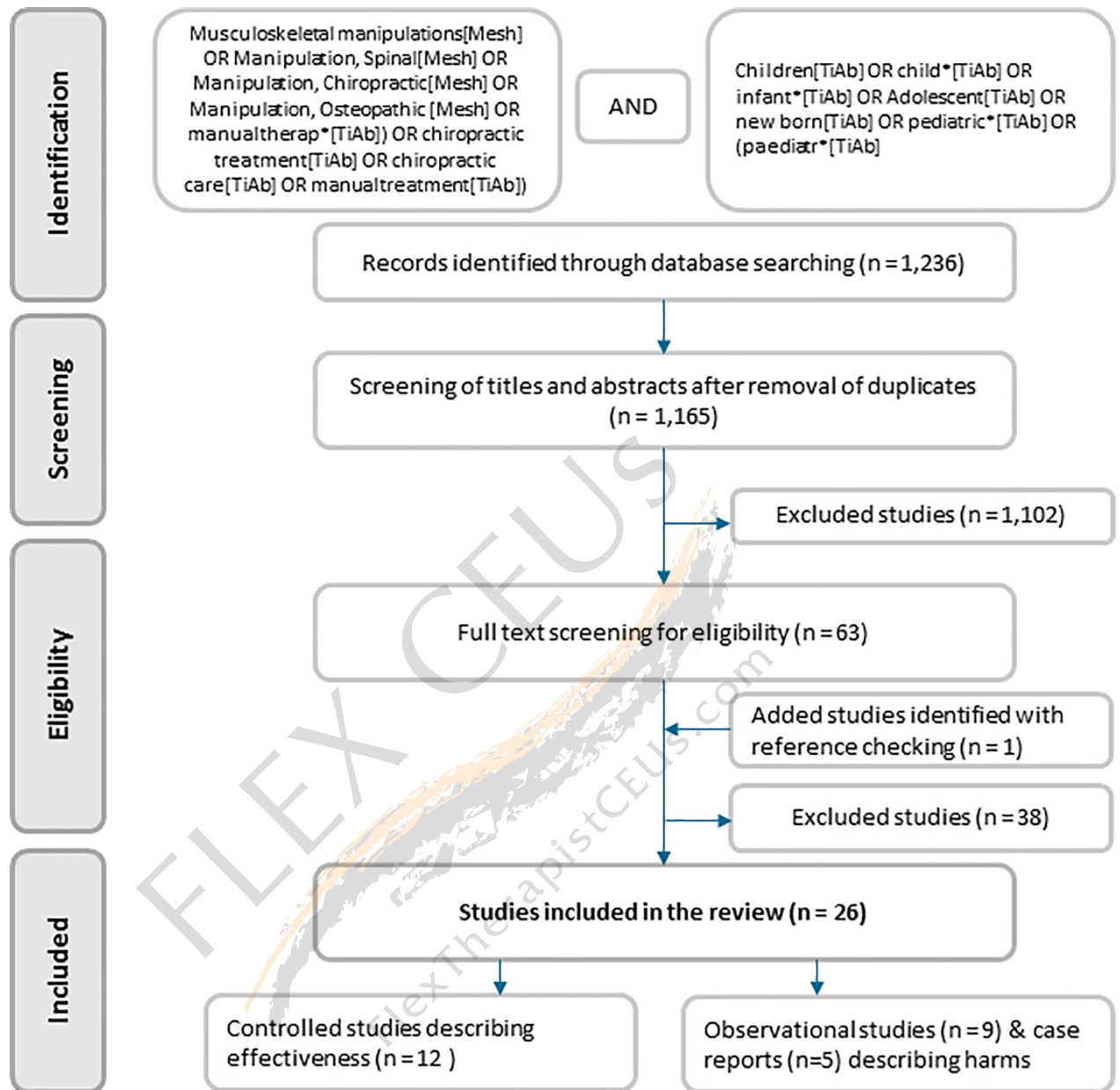


Fig 1. Flowchart search strategy.

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dysfunction could be postulated to have had a primarily biomechanical, neuroreflectory or physiological origin in the spine or could be described as dysfunction of the whole body, such as disturbed flow of body fluids, myofascial, visceral or parietal bone problems. Treatment outcomes were defined as patient- or parent-reported outcomes, such as symptoms (e.g. asymmetry), behavior (e.g. crying), perceived effect, and quality of life and/or as intermediate outcomes, which were related to therapist-reported impairment or function, such as asymmetry, spinal mobility, spinal dysfunction, or performance. Harms were also interpreted as a treatment outcome and were classified as; mild (transient side effect, lasting <24 hours), moderate (requiring medical and/or general practitioner treatment) and severe (requiring hospital treatment or adverse event; life threatening situation or death).[30]

## **Selection procedure and criteria for eligibility**

The initial search was performed by the primary author (FD). All studies were collected using EndNote, an online library system, which enabled us to remove duplicates. Screening of titles and abstracts was performed by one author (FD) using predefined eligibility criteria (S1 Table). Controlled studies were included to investigate effectiveness and harms. Observational studies and case reports were included to investigate harms.[31, 32] Subsequently, two authors (FD, TH) independently reviewed the full text of potentially relevant articles for eligibility. Discrepancies were discussed with all authors until consensus was reached, and eligible studies were included for an in-depth review.

## **Assessment of risk of bias of individual studies**

The assessment of risk of bias was done independently by two authors. Risk of bias of controlled studies was assessed using the Cochrane Risk of Bias tool, focusing on selection-, performance-, detection-, attrition- and reporting bias[33] by FD and JBS. Observational studies were assessed with the Item Bank for Assessing Risk of Bias and Confounding for Observational Studies of Interventions or Exposures (RTI Item Bank)[34] by FD and TH, focusing on selection-, performance-, detection-, attrition- and reporting bias, and confounding. Risk of bias of case reports was assessed using the JBI Critical Appraisal Checklist for Case Reports [35] by FD and JBS.

## **Data extraction and analysis**

Data extraction was performed by FD using a Summary of Findings table, and thereafter checked by TH in a random sample of 8 studies. Outcomes of effectiveness and harms were described separately. The CONSORT checklist[36] in conjunction with the TIDieR checklist [37] were used to describe the extracted data from controlled studies focusing on study population, treatment indication, hypothesized dysfunction, specific SMT treatment technique and outcomes. If appropriate, study outcomes were pooled. For random effects meta-analysis, outcomes of controlled studies were transformed to standardized mean differences between baseline and follow-up according to Cochrane recommendations.[33] Meta-analysis was performed when two or more studies described a similar intervention and comparable control treatment, and used a similar study population regarding condition and age. If appropriate, intervention groups ( $\geq 2$  groups) were combined into a single group according to the Cochrane Handbook. Statistical heterogeneity of the intervention effect was assessed using the  $I^2$  statistic ( $>50\%$  indicates high heterogeneity).[33] All analyses were conducted using Stata Software, version 12.0 (Stata Inc., College Station, Texas). If studies were not similar, meta-analysis was not considered appropriate, and findings were narratively reported. Data extraction to describe harms detailed treatment indication, specific SMT treatment technique and the reported harm.

## **Assessment of quality of body of evidence**

Quality of the body of evidence related to effectiveness was assessed using the Grading Recommendations Assessment, Development and Evaluation (GRADE) criteria.[38, 39] Each outcome was assessed in the previously specified age group and treatment indication using five criteria: 1) risk of bias,[40] 2) inconsistency,[41] 3) indirectness,[42] 4) imprecision[43] and 5) publication bias.[44] The assessment using GRADE was based on data from the assessment of risk of bias and the data extraction process. The completion of the GRADE tables was done by FD. The quality of the body of evidence was assigned as high, moderate, low or very low

## Box 1. GRADE levels describing the quality of the body of evidence (39)

### GRADE levels

**High:** Research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.

**Moderate:** Research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.

**Low:** Research provides some indication of the likely effect. The likelihood that the effect will be substantially different is high.

**Very low:** Research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

(Box 1) and described according to Cochrane recommendations.[45] Randomized controlled studies were considered high quality evidence and were downgraded by one level for serious concerns and by two levels for very serious concerns.[31, 46] Non-randomized controlled studies were automatically downgraded for limitations in the study design. They were further downgraded for any concerns in the five grading criteria. If the number of studies per specific age group, intervention and outcome was limited, inconsistency could not be graded and was interpreted as 'unknown'.[47] For each comparison and outcome measure, a GRADE table was completed. Because of the varying designs of studies that solely described harms of SMT, GRADE was not used; instead, results were reported narratively.

## Results

Electronic database searching identified 1,236 articles. After removing duplicates, 1,165 records were screened on title and abstract. A total of 1,102 records were excluded because of ineligible intervention, study design or study population. For the remaining 63 articles, eligibility was assessed based on full-text; 38 were excluded because of study population (n = 5), study design (n = 17), outcomes (n = 8) or the intervention could not be described as SMT (n = 8) (S2 Table); reference checking added one study (Fig 1). In total 26 studies were included; 12 controlled trials, of which 10 were randomized controlled trials,[48–59] 9 observational studies[60–68], and 5 case reports.[69–73]

Methodological limitations of controlled studies were related to unclear allocation concealment, partial or no blinding of participants and personnel, and incomplete outcome reporting. Limitations of observational studies were related to performance, detection and attrition bias, and selective outcome reporting. Limitations of case reports were lack of detail or unclear description of the intervention or treatment procedure. Outcomes of the quality assessments are presented in S3 and S4 Tables.

## Effectiveness

Study characteristics on treatment indication, hypothesized dysfunction, treatment technique and outcomes of the included 12 controlled studies are shown in Table 1. In the studies involving infants (n = 5), interventions consisted of low-force, gentle, light fingertip spinal mobilizations. In studies involving children/adolescents (n = 7), HVLA thrust spinal manipulations

**Table 1. Treatment indication, hypothesized dysfunction, treatment technique, outcome measures and outcomes of controlled studies (n = 12) on effectiveness of SMT in infants, children and adolescents.**

Studies involving infants									
Treatment indication	Authors	Study population (age)	Hypothesized dysfunction	Intervention (IV)	Outcome measures	Comparator (C)	Outcomes	Risk of bias*	GRADE**
Colic (N-MSK)	Olafsdottir et al., 2001 [49]	86 infants (3–9 weeks)	Spinal joint dysfunction	Spinal mobilizations using light fingertip pressure, performed by a chiropractor	Crying hours/day after 8 days	No treatment (infants were just held)	Both groups decreased crying hours/day (IV: -2 (SD:2.1), C: -2.3 (SD: 2.2)). No significant difference between groups (p:0.37).	Moderate	Very low quality of evidence
Colic (N-MSK)	Miller et al., 2012 [50]	104 infants (<8 weeks)	Not described	Spinal low-force mobilizations (1 blinded group (IV), 1 not-blinded group (IV-nb)), performed by a chiropractor	Crying hours/day after 10 days	No treatment (infants were not touched)	Both groups decreased crying hours/day (IV: -2.4 (SD:2.5), IV-nb: -2.8 (SD:2.2), C: -1.0 (SD:1.6)). Significant (p<0.05) decrease (-1.4) in IV group compared to no treatment.	Moderate	
Colic (N-MSK)	Browning & Miller, 2008 [48]	43 infants (<8 weeks)	Not described	Spinal low-force mobilizations, performed by a chiropractor	Crying hours/day after 14 days	Occipito-sacral decompression	Both groups decreased crying hours/day (IV: -2.1 (SD:2.2), C: -2.0 (SD:1.4)). No significant difference between groups (p:0.85).	Moderate	
Colic (N-MSK)	Wiberg et al., 1999 [51]	50 infants (2–10 weeks)	Spinal joint dysfunction	Spinal mobilizations using light fingertip pressure, performed by a chiropractor	Crying hours/day after 14 days	Dimethicone medication	Both groups decreased crying hours/day (IV: -2.4 (SD:0.4), C: -1.0 (SD:0.6)). Significant decrease of crying hours (-1.7 hours/day) in IV group compared to medication (p = 0.04).	High	Very low quality of evidence
Torticollis (MSK)	Haugen et al., 2010 [52]	32 infants (3–6 months)	Upper cervical dysfunction	Spinal low-force mobilizations by a manual therapist and pediatric physical therapy	Change in torticollis after 8 weeks	Pediatric physical therapy	In both groups torticollis positively changed (IV: 80% improvement, C: 81.3%). No significant difference between groups (p:0.85).	Moderate	Very low quality of evidence
Studies involving children and/or adolescents									
Treatment indication	Authors	Study population (age)	Hypothesized dysfunction	Intervention (IV)	Outcome measures	Comparator (C)	Outcomes	Risk of bias*	GRADE**

(Continued)

Table 1. (Continued)

Asthma (N-MSK)	Balon et al., 1998 [53]	91 children (7–16 years)	Spinal joint dysfunction	Spinal HVLA manipulations, performed by a chiropractor	Peakflow (FEV <sub>1</sub> ), symptoms, medication use and quality of life after 16 weeks	Low-velocity, low-amplitude push in gluteal and scapulae region	Both groups showed small increases in peakflow (IV: 103.6% (SD:13.7), C: 104.3% (SD:13.3)), improvement in symptoms and quality of life and decrease in medication use. No significant differences between groups (p:0.82).	High	Very low quality of evidence
Asthma (N-MSK)	Bronfort et al., 2001 [54]	36 children (6–17 years)	Spinal joint dysfunction	Spinal HVLA manipulations, performed by a chiropractor, and standard medical treatment	Peakflow (FEV <sub>1</sub> ), medication use and quality of life after 12 weeks	Light gentle spinal pressure, without a thrust, standard medical treatment	Little insignificant increase in peakflow and quality of life and decrease in medication use in intervention group. Control group outcomes not reported. Groups could not be compared.	NA	
Autism (N-MSK)	Khorsid et al., 2006 [56]	14 children (age not specified)	Not described	Upper cervical manipulations, using the Atlas Orthogonal, performed by a chiropractor	Autism related symptoms after 3 months	Diversified technique SMT on the full spine	Both groups decreased in symptoms (IV: -32%, C:-19%). No significant difference between groups (p-value not reported).	High	Very low quality of evidence
Headache (MSK)	Borusiak et al., 2009 [55]	56 children (7–15 years)	Cervical joint dysfunction	Cervical HVLA manipulation, performed by a manual therapist	Headache duration (hours) and intensity (VAS scale) after 2 months	Light touch of spinal segments	Both groups decreased in symptoms (duration IV:-7.5, C:-6.6; intensity IV:-0.3, C:0.1). No significant differences between groups (p>0.05).	Moderate	Very low quality of evidence
Nocturnal enuresis (N-MSK)	Reed et al., 1994 [57]	46 children (5–13 years)	Spinal joint dysfunction	HVLA manipulations, performed by a chiropractor	Frequency of bed wetting after 12 weeks	Instrumented adjustment using an Activator on the thoracic area	Intervention group decreased in frequency (IV:-1.2% (SD:2.2), C:+17.9% (SD:46.1%). No significant difference between groups (p:0.07).	Moderate	Very low quality of evidence
Idiopathic scoliosis (MSK)	Swierkosz & Nowak, 2015 [58]	35 adolescents (15–18 years)	Spinal joint dysfunction	Lower lumbar segmental mobilizations and traction, performed by a physical therapist	Back pain and quality of life after 3 weeks	No treatment	Pain decreased and physical health related quality of life increased (p<0.001) within IV group. No between group comparisons were reported.	NA	Very low quality of evidence

(Continued)

**Table 1.** (Continued)

Grip strengthening (MSK)	Botelho & Andrade, 2012 [59]	18 judo athletes	Stimulate nerve innervations	Cervical HVLA manipulations, performed by a chiropractor	Grip strength	SMT using the head piece drop mechanism	Significantly better grip strength ( $p < 0.05$ ) in IV (+13.7% mean left/right hand) compared to C (+5%) ( $p: 0.0025$ ).	Moderate	Very low quality of evidence
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IV: Intervention group, C: Control group, MSK: musculoskeletal, N-MSK: non-musculoskeletal, SMT: spinal manual therapy, HVLA: high-velocity, low-amplitude, FEV<sub>1</sub>: forced expiratory volume at the end of the first second of expiration

\* Risk of bias table is shown in Table A in [S3 Table](#)

\*\* Detailed information about the GRADE assessment (GRADE tables) are presented in [S4 Table](#)

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were most frequently used ( $n = 6$ ). Control interventions consisted of no treatment ( $n = 3$ ), sham treatment ( $n = 4$ ) or other treatments ( $n = 5$ ), such as physical therapy, medication and manual therapy using the drop mechanism ([Table 1](#)).

**Effectiveness of SMT techniques in infants.** The review included five studies evaluating SMT techniques in infants. Four studies included infants with colic [48–51] and one study infants with torticollis.[52] Outcomes are presented in [Table 1](#).

#### Infants with colic

Two studies compared SMT to no treatment.[49, 50] Miller et al. compared a blinded treatment group ( $n = 35$ ), non-blinded treatment group ( $n = 33$ ) and a non-treatment group ( $n = 34$ ) and found that crying hours significantly decreased ( $p < 0.05$ ) with 1.5 hours/day after 10 days between blinded treatment and non-treatment.[50] Olafsdottir et al. showed no significant differences between the SMT ( $n = 46$ ) and control group ( $n = 34$ ) in decrease of crying hours/day (-2 and -2.3, respectively) after 8 days.[49] Before meta-analysis, the two intervention groups of Miller et al. were combined into one single intervention group. Analysis of the overall pooled effect of SMT versus no treatment on crying hours/day was -0.33 (95% CI: -0.12 to 0.59;  $I^2$ : 89.1%,  $p: 0.484$ ). Two studies compared SMT to other treatments.[48, 51] Browning & Miller found a decrease in crying hours/day of 2.1 hours after SMT ( $n = 22$ ) and 2.0 hours after occipitosacral decompression ( $n = 21$ ) 14 days post-treatment. Groups differed not significantly.[48] Wiberg et al. compared SMT ( $n = 25$ ) to daily dimethicone medication ( $n = 25$ ) and found a significant decrease in crying hours/day in favor of the SMT group (-2.4 vs. -1.0,  $p = 0.04$ ).[51] No meta-analysis could be performed, due to incomparability of the control treatments. Because of very low quality evidence (serious risk of bias, very serious inconsistency, serious indirectness, serious imprecision) we are uncertain whether SMT consisting of spinal mobilizations reduces crying hours/day in infants with colic.

#### Infants with torticollis

Haugen et al. compared pediatric physical therapy combined with SMT ( $n = 16$ ) to pediatric physical therapy alone ( $n = 16$ ) on change in torticollis and cervical mobility, and found no significant differences (SMT improved 80%, pediatric physical therapy alone improved 81.3%).[52] Because of very low quality evidence (unknown inconsistency, very serious imprecision) we are uncertain about the effect of SMT consisting of spinal mobilizations on change of torticollis and increased cervical mobility in infants.

**Effectiveness of SMT techniques in children/adolescents.** Seven studies investigated the effectiveness of SMT in children and/or adolescents ([Table 1](#)).[53–59]

#### Children/adolescents with asthma

Two studies compared SMT to sham treatment on lung function and asthma related symptoms in children.[53, 54] Balon et al. compared spinal HVLA manipulation ( $n = 38$ ) to sham



treatment with low-velocity, low-amplitude push in the gluteal and scapulae region (n = 42). After 16 weeks, lung function (+103.6% after SMT vs. +104.3% after sham treatment), quality of life and reduction in medication were not significantly different between groups.[53] Bronfort et al. compared HVLA spinal manipulations (n = 24) to light gentle manual pressure (sham treatment) to the spine (n = 12), and found no significant difference between groups in lung function, quality of life and medication use.[54] No meta-analysis could be performed, because Bronfort et al. only reported data of outcomes of the intervention group. We contacted the author, but did not get a response. Because of very low quality evidence (serious risk of bias, serious inconsistency, very serious imprecision) we are uncertain whether SMT consisting of HVLA manipulations improves lung function in children/adolescents with asthma.

#### **Children/adolescents with autism**

Khorshid et al. compared upper cervical SMT (n = 7) to full spine diversified care (n = 7) on autism related symptoms. No significant differences between groups were found (32% improvement after SMT, 19% after diversified care).[56] Because of very low quality evidence (serious risk of bias, unknown inconsistency, very serious imprecision) there is uncertainty about the effect of SMT consisting of upper cervical manipulations on reducing autism related symptoms in children/adolescents with autism.

#### **Children/adolescents with headache**

Borusiak et al. compared cervical HVLA manipulation (n = 28) to light touch of spinal segments as sham treatment (n = 28) on headache related symptoms (e.g. days with headache, duration, intensity) and showed no significant differences after 2 months.[55] Outcomes of HVLA manipulation versus sham treatment were; days with headache -9.7% vs. -9.4%, duration (hours) -7.5% vs. -6.6%, intensity (VAS scale) -0.3 vs. 0.1. Because of very low quality evidence (unknown inconsistency, very serious imprecision) we are uncertain about the effect of cervical SMT with HVLA manipulations on reducing headache related symptoms in children/adolescents with headache.

#### **Children/adolescents with nocturnal enuresis**

Reed et al. compared HVLA adjustments (n = 31) to sham treatment using an Activator at a non-tension area in the thoracic spine (n = 15). There were no significant differences between groups after 12 weeks in the frequency of bed-wetting (-1.2% after HVLA adjustments, +17.9% after Activator).[57] Because of very low quality evidence (serious risk of bias, unknown inconsistency, very serious imprecision) we are uncertain whether SMT consisting of HVLA manipulations reduces the frequency of bed-wetting in children with nocturnal enuresis.

#### **Children/adolescents with idiopathic scoliosis**

Swierkosz & Nowak compared segmental spinal mobilizations and traction at level L5-S1 (n = 21) to no treatment (n = 11) on back pain and quality of life. Post-treatment outcomes were only reported for the SMT group. Hence, between group comparison were not described.[58] Because of very low quality evidence (serious risk of bias, unknown inconsistency, very serious imprecision) there is uncertainty about the effect of segmental spinal mobilizations on reducing back pain and increasing quality of life in adolescents with idiopathic scoliosis.

#### **Healthy adolescent judo athletes**

Botelho & Andrade compared cervical HVLA manipulations (n = 9) to adjustments using the head piece drop mechanism (n = 9) on grip strength immediately after treatment. After cervical HVLA manipulations adolescents showed significantly ( $p:0.0025$ ) better grip strength in both hands (mean increase 13.7%) compared to the control group (+5%).[59] Because of very low quality evidence (unknown inconsistency, serious risk of bias, very serious imprecision) we are uncertain whether cervical HVLA SMT increases transient grip strength in healthy adolescents.

## Harms

Nine observational studies[60–64, 66–68, 74], five case reports[69–73], and four controlled studies[50, 53, 55, 59] reported on harms. Patient characteristics, treatment indication, treatment technique and related harms are shown in Table 2.

All observational studies and case reports showed methodological shortcomings and moderate-to-high risk of bias, suggesting a negative impact on the quality of evidence (see S3 Table). Studies lacked details about the performed treatment and information on the background, education/training and experience of professionals were often not provided.

**Infants.** Three case reports described adverse events in infants after cervical HVLA manipulations including death[71, 72] and temporary paralysis.[70] In all case reports, these adverse events could not be demonstrated to be a direct effect of cervical HVLA manipulations, rather, they were suspected to be related to missed underlying pathology. No studies reporting on harms after full spine HVLA manipulations were found.

One case report described a severe harm of rib fractures after mobilizations of the full spine using an Activator device in an infant. Physical abuse was suspected but could not be proved. [73] Two observational studies, including a total of 894 infants showed mild harms in terms of transient physiological responses and side effects, such as bradycardia and flush (n = 384), after short, gentle thrust cervical mobilizations.[66, 74] Three studies (n = 412) reported no harms occurred after spinal mobilizations; a retrospective case series (n = 114) reported no harms occurred after cervical mobilizations[68] and an observational study (n = 104) and a controlled study (n = 194) reported that no harms occurred after full spine mobilizations in infants.[50, 62]

**Children/adolescents.** Three studies described harms after cervical HVLA manipulation in children/adolescents. One case report described a severe harm of muscle weakness.[69]

Table 2. Studies on harms of spinal manual therapy: Patients, treatment indication and treatment technique.

Study population	Treatment indication	Clinical history	Reported harm	Treatment technique	Study design	Author	Risk of bias
<b>Cervical spinal manipulation in infants</b>							
4 month old boy	Congenital torticollis	A few hours after manipulation, the infant was difficult to arouse, was limp, pale and moaning. Infant's mother went back to the chiropractor, who manipulated the neck again. Thereafter the infant moaned and grunted continuously. Three hours after the second cervical manipulation, the infant was hospitalized, had a seizure and was comatose. He suffered from paralysis of both legs and the right arm. MRI showed a spinal cord tumor, which was immediately removed. After surgery, motor and sensory function regained to T4-level. 18 months postoperatively, the child had full use of his arms, sensory function at T9-level and some spontaneous but nonfunctional motion of the right leg.	Temporary quadriplegia	Cervical spinal manipulation towards flexion- extension and axial (un)loading, performed by a chiropractor	Case report	Shafir & Kaufman, 1996 [70]	Moderate

(Continued)

Table 2. (Continued)

Study population	Treatment indication	Clinical history	Reported harm	Treatment technique	Study design	Author	Risk of bias
3 month old girl	Minimal motor restlessness	After manipulations, the infant cried heavily and developed fecal incontinence and breathed loudly. After 10 minutes infant's lips turned blue, muscles were weak and there was no response on touching. Infant's father started CPR until ambulance took over. After 1 hour, infant had her own heart rhythm again. After hospital exam no abnormalities were found on x-ray and CT. MRI showed abnormalities in the pons and mesencephalon confirming vertebrobasilar ischemia, specifically in the spinal cord. 12 hours after manipulation treatment, infant had no spontaneous breathing, brainstem reflexes and tendon reflexes. Hospital treatment was stopped and infant died within minutes. Autopsy showed infarcts in spleen and heart due to oxygen deficiency and multi organ failure.	Death	Manipulations of the (cervical) spine towards forced full spine flexion, performed by a cranio-sacral therapist	Case report	Holla et al., 2009 [71]	High
3 month old girl	Torticollis and muscular hypotonic	Ten minutes after treatment, the infant looked pale and had blue lips, cold legs, blue/black skin and breathing difficulties. Infant was hospitalized because of asystole. CPR was started and the heart was defibrillated for 25 minutes. The infant suffered from bleeding into the vertebral arteries at C1 resulting in caudal brainstem ischemia and subarachnoid hemorrhage. Authors state that underlying cardiovascular and neurological issues before starting the treatment could not be ruled out.	Death	Cervical spinal manipulation towards forced rotation according to the Vojta method, performed by a physical therapist	Case report	Jacobi et al., 2001 [72]	Low
<b>Cervical spinal manipulation in children/adolescents</b>							
6 year old boy	Sinus infection	The day after manipulation, child experienced complaints of tingling and numbness in the left arm and developed gradual weakness of the left arm during the week. Two weeks after manipulation MRI showed a bilateral lesion in the ventral horns of the spinal cord from C3 –C7. A vascular compromise of vertebral arteries resulting in anterior cordischemia was proposed.	Muscle weakness in the arm	Cervical spinal manipulation, performed by a chiropractor	Case report	Deputy, 2004 [69]	Moderate

(Continued)

Table 2. (Continued)

Study population	Treatment indication	Clinical history	Reported harm	Treatment technique	Study design	Author	Risk of bias
Cohort of 52 children	Headache	Children were randomized to SMT or sham treatment. Evaluation of side effects was performed immediately after treatment and after the 2-month follow-up period.	Mild harms: dizziness (n = 11), hot skin (n = 26)	Cervical HVLA manipulation, performed by a manual therapist	RCT	Borusiak et al., 2009 [55]	Moderate
Cohort of 18 adolescent judo athletes	Grip strength improvement	Adolescents were randomized to SMT or sham treatment. Side effects were evaluated during and after treatment.	Mild harms: neck pain (n = 1), headache (n = 1)	Cervical manipulation consistent with the Diversified technique, performed by a chiropractor	RCT	Botelho & Andrade, 2012 [59]	Moderate
<b>Full spine manipulation in infants</b>							
No studies							
<b>Full spine manipulation in children/adolescents</b>							
Cohort of 171 children	Nocturnal enuresis	Children were treated and outcomes were monitored and reported by their parents.	Mild harms (pain, headache, stiffness, n = 2)	Chiropractic adjustments on the area of dysfunction, performed by chiropractors	Prospective cohort	LeBoeuf et al., 1991 [64]	Moderate
Cohort of 54 pediatric patients	Low back pain	Abstraction from records of included consecutive pediatric patients.	No harms	Lumbar spinal manipulation, performed by chiropractors	Prospective cohort	Hayden et al., 2003 [63]	Moderate
Cohort of 577 cases of children (0–18 years)	Various conditions	A survey was used to describe pediatric chiropractic practice, including safety. 21 chiropractors reported on 577 cases in which children (0–18 years) received SMT, in a total of 5,438 visits. Parents reported on 239 children after treatment. Chiropractors and patients or parents documented treatment-associated changes, such as aggravations (worsening or complaints), complications or improvements.	Mild harms: stiffness, soreness (n = 3)	Various techniques, e.g. diversified-, Gonstaed-, Thompson- and cranial technique, performed by chiropractors	Cross-sectional study	Alcantara et al., 2009 [60]	Moderate
Cohort of 781 cases of pediatric patients (<3 years)	Various conditions	Pediatric case files were checked to identify any adverse effects after chiropractic care.	Mild harms: crying (n = 4), restlessness, not feeding well, head tilt.	Various techniques, e.g. full spine manipulation, cervical manipulation, occipital-sacral decompression, performed by chiropractors	Retropective review	Miller & Benfield, 2008 [67]	Moderate
Cohort of 91 children	Asthma	Children were randomized to SMT or sham treatment. Side effects were evaluated using completed diaries.	No harms	Spinal HVLA manipulation, performed by a chiropractor	RCT	Balon et al., 1998 [53]	High
<b>Cervical mobilizations in infants</b>							
Cohort of 695 infants	Upper cervical dysfunction and asymmetry	Heart rate, blood pressure, breathing frequency, oxygen saturation and peripheral temperature before, during and after the application of a high cervical impulse were compared. In 47% a change in heart rate was noticed. In 40%, heart rate almost immediately decreased (range 15–83%). In infants younger than three months the decrease was statistically significantly larger than older infants. The decrease in heart rate was often combined with vegetative responses, like flush.	Bradycardia (n = 279)	Short gentle thrust in suboccipital region (50 Newton), performed by a manual therapist	Observational study	Koch et al., 2002 [66]	Moderate

(Continued)

Table 2. (Continued)

Study population	Treatment indication	Clinical history	Reported harm	Treatment technique	Study design	Author	Risk of bias
Cohort of 199 infants	Muscle tension disorders of mouth or pharynx or asymmetry of skull, neck, trunk or hip	Responses after an upper cervical impulse were investigated. Physiological responses were shown in 53%; flush (49%), short spells of apnea (22%), hyperextension of the back and/or neck (13%) and sweating (8%). The short spells of apnea lasted less than 10 seconds and breathing pattern was immediately restored by blowing into the child's face. The authors stated that these responses were normal physiological responses and cannot be interpreted as adverse reaction or harm.	Physiological responses (n = 105)	Short gentle thrust (50 Newton) in suboccipital region, performed by a manual therapist	Observational study	Koch et al., 1998 [74]	Moderate
Cohort of 114 cases of infants (<12 weeks)	Sub-optimal breast-feeding	Data abstraction out of case series to describe circumstances, clinical features, role and treatment outcomes.	No harms	Low force spinal mobilization, performed by chiropractors	Retro-spective case series	Miller et al., 2009 [68]	Moderate
<b>Cervical mobilizations in children/adolescents</b>							
No studies							
<b>Full spine mobilizations in infants</b>							
21-day-old girl	Colic and fussiness	After manipulation infant immediately cried and fell asleep. Infant remained fussy and the mother felt a crackling sensation of the back. X-ray showed acute fractures of the 7 <sup>th</sup> and 8 <sup>th</sup> posterior left ribs. No additional fractures were found. Infant went for follow-up to the child abuse center. Results of bone laboratory tests were normal. The center concluded that child abuse could not be definitively ruled out, but chiropractic manipulation was seen as a plausible explanation for the fractures.	Rib fractures	Spinal fingertip pressure and adjustments using a 'spring-activated device', performed by a chiropractor	Case report	Wilson et al., 2012 [73]	High
Cohort of 194 infants	Various conditions	Data were extracted from mother's completed questionnaires about infant characteristics, symptoms and perceived effect.	No harms	Low-force mobilizations of spinal joints in the area of dysfunction, performed by chiropractors	Cross-sectional survey	Nicolas-Schmid et al., 2016 [62]	High
Cohort of 104 infants (<4 weeks)	Colic	Infants were randomized to SMT and no treatment. Parents reported on adverse events during the treatment period.	No harms	Low-force spinal mobilization (2 Newton), performed by a chiropractor	RCT	Miller et al., 2012 [50]	Moderate
<b>Full spine mobilizations in children/adolescents</b>							
No studies							
<b>Unspecified treatment techniques</b>							

(Continued)

Table 2. (Continued)

Study population	Treatment indication	Clinical history	Reported harm	Treatment technique	Study design	Author	Risk of bias
956 chiropractors reported on treatment of children (0–18 years)	Various conditions	A survey was used to investigate characteristics of pediatric chiropractic practice, including side effects.	Unspecified mild and moderate harms (n = 557)	Treatment techniques were not specified. Treatments were performed by chiropractors	Cross-sectional survey	Marchand et al., 2012 [61]	Moderate

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Two controlled studies reported mild, transient harms in terms of side effects: one study (n = 52) reported dizziness (n = 11) and hot skin (n = 26),[55] one study (n = 18) reported neck pain (n = 1) and headache (n = 1).[59] Five studies reported harms after HVLA manipulations performed on the full spine. In three of these studies (n = 1529) a small number of mild harms (n = 9) was reported;[60, 64, 67] the other two studies (n = 145) reported no harms.[53, 63] No studies were found reporting on harms after cervical or full spine mobilizations. One study (n = 956) reported side effects or reactions in children after chiropractic treatment (n = 557), but both side effects or reactions and treatment techniques were not specified.[61] Hence, conclusions on treatment technique cannot be given.

## Discussion

This review provides a unique overview of the evidence investigating the effectiveness and safety of specific SMT techniques specified per treatment indication and age group, instead of concluding on SMT as a general treatment approach. We found limited evidence for all age groups and treatment indications; overall the body of evidence is of very low quality due to moderate-to-high risk of bias, imprecise estimates, and lack of demonstrated consistency across studies. The effectiveness of gentle, low-velocity spinal mobilizations in infants with colic or torticollis remains uncertain. The effectiveness of HVLA spinal manipulations to manage asthma, nocturnal enuresis, headache, idiopathic scoliosis, and to improve grip strength in children and/or adolescents, also remains uncertain. We found that the number of reports of severe harms as direct side effects of SMT techniques were scarce and may be underreported. Where reported, harms differed between treatment techniques and between age groups. Gentle, low-velocity mobilization techniques appear to be a safe treatment technique in infants and children and/or adolescents. Cervical and full spine HVLA manipulations, however, might be associated with severe harms, although underlying pathology was suspected in the cases reported on.

### Effectiveness of SMT techniques

The very low quality of the body of evidence prevented us from drawing clinically meaningful conclusions on effectiveness of specific SMT techniques for specified treatment indications. These findings are consistent with previous reviews investigating the effectiveness of pediatric manual therapy as a general treatment approach.[1, 2, 4, 13] Specifically, the systematic review of Bronfort et al. (2010) also concluded that effectiveness of SMT in children is uncertain.[13] However, Bronfort et al. summarized the evidence regarding general manual treatment performed in both adults and children, and included various interventions, such as spinal and extremity joint manipulation or mobilization, craniosacral and osteopathic therapies and massage. In contrast to our systematic review, Bronfort et al. did not distinguish between SMT techniques in their analysis. Even though in our systematic review five additional (randomized) controlled studies were included, available literature was re-examined using the state-of-

the-art GRADE methodology, and harms were examined in relation to specific treatment techniques, our conclusion about the lack of evidence remains largely the same as previous research. Our review sets itself apart from previously performed research by focusing on specific SMT treatment techniques, instead of making conclusions about SMT as a general therapeutic approach.

A large number of the included studies in our review showed shortcomings. We highlight these shortcomings here in an attempt to emphasize the need of high quality future research and reporting. First, authors reported a hypothesized relation between the child's (non-)musculoskeletal condition and a particular spinal dysfunction.[49, 51–55, 57, 58] However, intermediate outcomes to assess or indicate this potential dysfunction, such as range of motion, were often neglected and only scarcely described. All studies assessed parent- or patient-reported outcomes to indicate perceived treatment effect, while only four out of twelve controlled studies additionally assessed functional outcomes to evaluate spinal dysfunction, such as change in torticollis,[52] lung function[53, 54] and grip strength.[59] Therefore, currently, no conclusions on the effect of specific SMT techniques on spinal dysfunction in these patients can be drawn. In future research it is important to include these intermediate outcomes in addition to patient-reported outcomes. Second, we would like to highlight that for adequate interpretation it is of great importance that studies provide a detailed description of the SMT technique performed. Important information regarding the specific treatment technique was often omitted from publications. As a consequence, it is challenging (or even impossible) for researchers and, maybe more importantly, healthcare professionals to interpret study findings and draw scientifically substantiated conclusions about effective treatment techniques. As such, this will hamper translation of study findings to clinical practice. Third, in the majority of the included controlled studies, decrease in complaints/symptoms and improvement in function over time was seen in both the intervention and control group. This may suggest a potentially favorable natural course for the indications under study. However, the majority of studies did not describe or consider this phenomenon. They focused on changes due to the intervention and only emphasized differences over time within the intervention group, instead of between group differences. Apart from a potential favorable natural course, the observed decrease in complaints/symptoms or improvement in function in the sham or control group may have occurred by other treatment effect, including placebo effect. To manage this, and to gain a better understanding of the course of complaints/symptoms over the longer time, effectiveness of SMT treatment techniques and potential harms of treatment, we recommend a change in study designs and a shift in the focus of research. We underline the importance of RCT designs using three-group-comparisons where a non-treatment group should be included. Moreover, we recommend research to focus on examining outcomes of specific SMT techniques and describing effectiveness in relation to these techniques, instead of making conclusions on SMT as a general treatment approach.

### **Harms of SMT techniques**

Worldwide, manual therapy is regularly performed in children of all ages. Previous reports indicate that 5 to 40% of patients receiving manual therapy are younger than 18 years old.[3, 9, 10, 27, 75–78] In view of this, severe harms such as death, paralysis and rib fractures after HVLA manipulations[69–72] or spinal instrumented-adjustments[73] are rare. Authors often concluded that underlying preexisting pathology was found and potentially related to the occurrence of these severe harms, and HVLA manipulations were not the direct cause of harm.[70, 72] Mild, transient harms, such as stiffness, soreness or headache, were reported in two controlled trials[55, 59], and five larger observational studies,[60, 61, 64, 67, 74] but may

be underreported. Due to the lack of reported information on the specific treatment technique, specific symptoms and indications, and professional background of the health care professional, and because of the unknown total prevalence of pediatric SMT performed worldwide, conclusions about the prevalence of harms cannot be made and harms may be underreported. Taking these limitations into account, conclusions about the risk of harm and safety of SMT techniques are hard to draw. As such, we would encourage researchers to include detailed descriptions of specific performed techniques and details about the education and clinical experience of performing therapists. Moreover, to improve transparency and quantification of harms, we acknowledge the importance of continuous review of harms, as previously indicated by Vohra et al. and Humphreys et al.[79, 80] Observational cohorts with a longer follow up period could provide a more realistic estimation on risk of harm of a specific intervention in comparison to non-placebo controlled trials, in which strict inclusion criteria could limit the representation of a realistic study population.[32] Furthermore, databases and registries of performed treatments in infants and children could facilitate the reporting and review of harms. Such resources provide a mechanism to continuously monitor treatment outcomes and harms, and could be more reliable for reporting on harms as they do not aim to collect data for research in only a specific period and population.[32]

### **Strengths and limitations**

Our systematic review has a number of strengths. Our review sets itself apart from previous research by focusing on the effectiveness and harms of specific SMT treatment techniques, instead of concluding about SMT as a general therapeutic approach. A further strength is that we examined the evidence for infants separately from children and/or adolescents, providing a more nuanced overview of the effectiveness and safety of SMT techniques in children of different ages. In addition, we assessed the quality of the body of evidence using GRADE.

A limitation is that meta-analysis could only be performed for one comparison and on one outcome due to low consistency across studies. Sparse data meant that the quality of evidence for any given comparison of treatments and treatment outcome was very low. Finally, many studies were excluded from the review because they did not report on harms. Importantly, this does not necessarily indicate absence of harms and may underestimate the occurrence of harms.

### **Conclusion**

Due to very low quality of the evidence, the effectiveness of gentle, low-velocity mobilizations in infants and HVLA manipulations in children and/or adolescents is uncertain. Assessments of intermediate outcomes are lacking in current pediatric SMT research. Therefore, the relationship between specific treatment and its effect on the hypothesized spinal dysfunction remains unclear. Gentle, low-velocity spinal mobilizations seem to be a safe treatment technique. Although scarcely reported, HVLA manipulations in infants and young children could lead to severe harms. Severe harms were likely to be associated with unexamined or missed underlying medical pathology. Nevertheless, there is a need for high quality research to increase certainty about effectiveness and safety of specific SMT techniques in infants, children and adolescents. We encourage conduction of controlled studies that focus on the effectiveness of specific SMT techniques on spinal dysfunction, instead of concluding about SMT as a general treatment approach. Large observational studies could be conducted to monitor the course of complaints/symptoms in children and to gain a greater understanding of potential harms.



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# Longitudinal follow-up of muscle echotexture in infants with congenital muscular torticollis

## Abstract

Unilateral fibrous contracture of the sternocleidomastoid (SCM) muscle is the major pathophysiology in infants with congenital muscular torticollis (CMT). Physical examination is not always sufficient to detect minimal muscle fibrosis in involved SCM muscles.

A prospective study for SCM muscle fibrosis in CMT infants by quantifying echotexture and muscle thickness during the course of treatment is highlighted in the study.

Convenience samples of 21 female and 29 male infants with CMT, who were 1 to 12 months old, underwent physiotherapy for at least 3 months and were followed for  $4.7 \pm 0.4$  months. All infants had at least 2 clinical assessments and ultrasonographic examinations for bilateral SCM muscles during follow-up. The  $K$  value, derived from the difference in echo intensities between the involved and uninvolved SCM muscles on longitudinal sonograms, was used to represent the severity of muscle fibrosis. Bilateral SCM muscle thickness and ratio of involved to uninvolved muscle thickness (Ratio I/U) were obtained simultaneously. Clinical outcome was also recorded.

No subjects underwent surgical intervention during follow-up. The  $K$  value decreased from  $6.85 \pm 0.58$  to  $1.30 \pm 0.36$  at the end of follow-up ( $P < 0.001$ ), which reflected the decrease of muscle fibrosis. The Ratio I/U decreased from  $1.11 \pm 0.04$  to  $0.97 \pm 0.02$  during treatment, which was possibly related to the increased uninvolved SCM muscle thickness.

In conclusion, echotexture is an efficient indicator for reflecting a wide degree of muscle fibrosis in infants with CMT and is informative during the treatment course.

**Abbreviations:** BL = body length, BW = body weight, CMT = congenital muscular torticollis, dB = decibel, DMD = Duchenne muscular dystrophy, EI = echo intensity, MEI = mean echo intensity, Ratio I/U = ratio of involved to uninvolved muscle thickness, ROI = region of interest, SCM = sternocleidomastoid, US = ultrasonography.

**Keywords:** fibrosis, infant, torticollis, ultrasonography

## 1. Introduction

Infants with congenital muscular torticollis (CMT) feature unilateral fibrous contracture of the sternocleidomastoid (SCM) muscle with a characteristic head tilt, limited neck rotation, or a palpable mass.<sup>[1]</sup> Physical examination is not always sufficient in diagnosing CMT in infants with minimal clinical presentations, and image workup is sometimes required for determining the treatment strategy.<sup>[1,2]</sup> Because of lack of related cohort studies, randomized controlled trials, or meta-analyses, imaging has been suggested as level II evidence for infants with CMT, but clinical practice guidelines still recommend that physical therapists obtain all image interpretations before informing prognosis.<sup>[2]</sup> Compression sonoelastography<sup>[3,4]</sup> and color Duplex images<sup>[5]</sup> have been used to help describe the degree of SCM muscle fibrosis. However, lacking constant loading force and quantification of blood flow in target muscles, these new technologies represent less objective analyses for SCM muscle fibrosis.

Ultrasonography (US) can be used for quantifying the degree of muscle fibrosis,<sup>[6]</sup> defining the size and location of muscle masses,<sup>[1]</sup> and guiding the clinical approach and treatment duration in CMT.<sup>[1,7]</sup> This imaging type has been widely advocated because of the ability to identify different patterns of SCM muscle fibrosis.<sup>[1,2,7,8]</sup> Most infants showed a pseudotumor (type I fibrosis) or diffuse fibrosis mixed with normal muscle and thickening of involved muscles (type II fibrosis).<sup>[1]</sup>

The muscle fibrosis pattern was altered during follow-up, and a certain of them turned into total fibrosis (type III fibrosis) or fibrous bands (type IV fibrosis), with surgical intervention indicated.<sup>[1,7]</sup> A duplicate blinded examination of different examiners has been done to assess the interobserver variation for the above US classifications and  $\kappa$  value was 1.00 in the interrater agreement.<sup>[9]</sup> Although there is high concordance in the US classification, we still believe that only digitalized sonograms can totally eradicate not only inter- but also intraobserver errors.

US can accurately measure SCM muscle thickness in CMT infants, and revealed a significant reduction in ratio of involved to uninvolved SCM muscle thickness (Ratio I/U) after adequate rehabilitation.<sup>[10]</sup> Findings in muscle thickness measurement may reflect clinical improvement but cannot directly reflect the progress of muscle fibrosis during follow-up. Therefore computer-assisted analysis has been developed to quantify the muscle echo intensity (EI) to directly associate the muscle sonogram findings with the severity of muscle fibrosis.<sup>[6,11]</sup>

Echotextures on sonograms are the result of reflected waves from interfaces between materials of different acoustic impedance and reflect different muscle pathologies.<sup>[1,6,12]</sup> The skeletal muscle consists of grouped muscle fibers separated by fibroadipose septa.<sup>[13]</sup> This tissue arrangement results in inhomogeneous and speckled muscle sonograms.<sup>[14]</sup> Strong correlations were observed between percentage of intramuscular fat seen on magnetic resonance imaging and muscle EI.<sup>[15]</sup> Quantification of muscle EI has also been found objective and reproducible and is used in screening dystrophic and inflammatory myopathies.<sup>[15]</sup> Animal studies showed muscle EI highly correlated with the extent of fibrosis in affected muscles<sup>[6,16]</sup> and US characterization was found useful in estimating muscle fibrosis.<sup>[6]</sup> However, the application of muscle EI in clinical surveys of nondystrophic muscle disorders is still limited.

We wished to quantify the therapeutic effect of physiotherapy directly through the tissue characterization of involved muscles instead of indirectly through the clinical evaluation. The *K* value, derived from the difference in mean echo intensity (*MEI*) between the involved and uninvolved muscle in every examination under the same ultrasound setting, reflects the severity of fibrosis in affected muscles.<sup>[6]</sup> The present work aimed to document echotexture in CMT infants by the *K* value and thickness of bilateral SCM muscles derived from US during the treatment course. Findings concerning echotexture and muscle thickness alterations during follow-up may provide additional insights into the progression of SCM muscle fibrosis with physiotherapy.

## 2. Methods

### 2.1. Participants

The institutional review board of a tertiary care hospital approved the study protocol (100-4436B) and the clinical trial registry number is NCT02889705. CMT infants whose parents gave signed informed consent were prospectively enrolled. Infants with neurological, cervical spine abnormalities, or developmental dysplastic hip problems were excluded. The presenting clinical features, including head tilt in the upright position, facial asymmetry, limited passive range of motion in neck rotation, palpable neck mass, and results of US were carefully evaluated and documented at every visit. Age, gender distribution, body weight (BW), body length (BL), characteristics of the affected muscle side, follow-up duration, visit times, and interval between 2 visits were also recorded. Physiotherapy involving passive stretching of the involved muscle, positioning, and massage can diminish the development of scoliosis and facial asymmetry for CMT infants.<sup>[1,7,17]</sup> All infants received the above physiotherapy 2 to 4 times a week for at least 3 months and were regularly followed at our rehabilitation clinic. Those who still had prominent clinical presentations after physiotherapy for 6 months or were older than 1 year would undergo surgery. Presenting clinical features that subsided with physiotherapy were determined by the clinician.

### 2.2. Procedures

The study was a prospective, experimental pre-post design with 1 participant group. Figure 1 illustrates the selection of infants and follow-up.

### 2.3. Quantification of US findings

An experienced sonographer performed US examinations with the infant in the supine position and the head rotated contralaterally to the examination side. A 5 to 12 MHz linear-array ultrasound transducer (Philips iU22, Philips Healthcare, Andover, MA) was used to obtain longitudinal and transverse views of bilateral SCM muscles. The ultrasound system settings, including gain (86%), monitor dynamic range (70 dB), and depth (2 cm), were kept constant throughout the study.

All infants underwent at least 2 US measurements and 35 of them had  $\geq 3$  examinations (6 had  $\geq 4$  examinations, and 1 of the 6 had 7 examinations). Sonograms for involved and uninvolved muscles were compared. The maximum anterior-posterior diameter, defined as muscle thickness, was measured from the

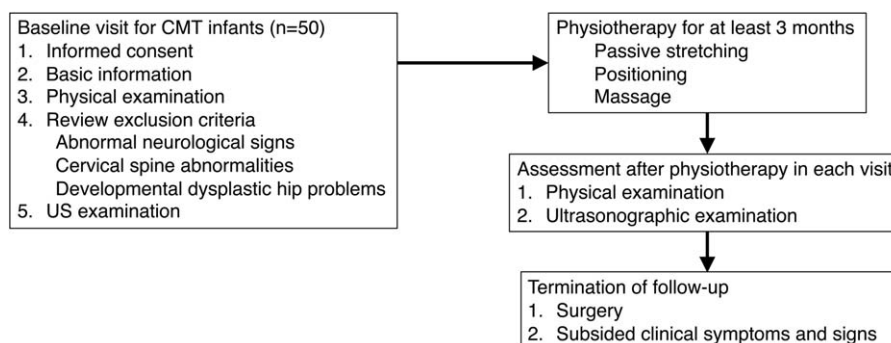
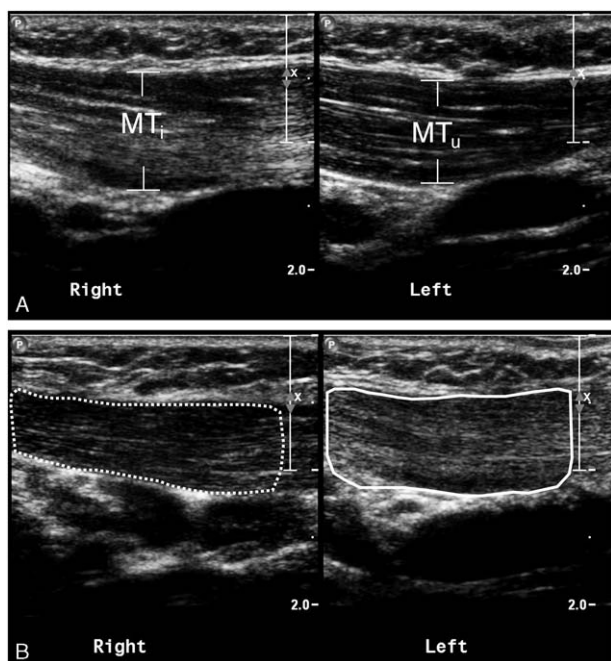


Figure 1. Flowchart of infant selection, intervention, and follow-up.



**Figure 2.** US of bilateral SCM muscles in infants with CMT. (A) Longitudinal sonograms of maximum anterior–posterior diameters of the involved ( $MT_i$ ) and uninjured ( $MT_u$ ) SCM muscles. Ratio  $I/U$  was calculated as  $MT_i/MT_u$ . (B) Longitudinal sonograms of the  $MEI$  of every pixel in the ROI in the uninjured (dotted line) and involved (solid line) muscles. The  $K$  value was calculated by  $MEI_{uninvolved} - MEI_{involved}$ .

longitudinal view, then the Ratio  $I/U$  was derived (Fig. 2A). The muscle EI was determined by computer-assisted gray-scale analysis and calculated using MATLAB 2006b (The MathWorks, Natick, MA). The  $MEI$  of every pixel in the region of interest (ROI) and the  $K$  value used to compare sonograms between infants or between times for the same infant were estimated by the following equations (Fig. 2B)<sup>[6]</sup>:

$$MEI = \frac{\sum_{x=1}^r \sum_{y=1}^c I(x, y)}{r \times c} \quad (1)$$

$$K = MEI_{involved} - MEI_{uninvolved} \quad (2)$$

where  $r$  and  $c$  represent the pixel counts for the height and width of the ROI on the sonogram, respectively. A decrease in  $K$  value indicates reduced muscle fibrosis.<sup>[6]</sup>

#### 2.4. Statistical analysis

All data are presented as mean  $\pm$  standard error of mean. Because only 1 infant underwent US more than 4 times, the 5th to 7th measurements for this infant were incorporated into the 4th measurement for statistical analysis. Initial US images in 10 different subjects were analyzed as the above procedure in the same program on the same International Business Machines Corporation-compatible personal computer by 2 different operators. Each obtained image was analyzed 10 times and the coefficient of variance ranged from 3% to 5% in each examination. The analyzed values of each image between different operators were similar. A generalized estimating equation was used to compare different US measurements of muscle thickness (involved and uninjured SCM muscles) and the

$K$  value during follow-up. Student  $t$  test was used to compare the thickness between bilateral SCM muscles. Pearson correlation was used to analyze the relationship between US measurements, especially the initial examination, and clinical information.  $P < 0.05$  was considered statistically significant.

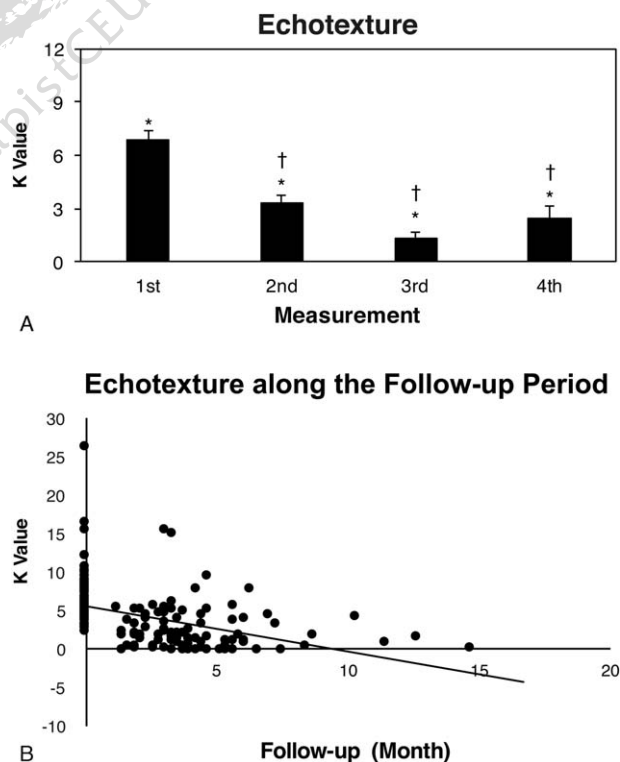
### 3. Results

#### 3.1. Clinical information

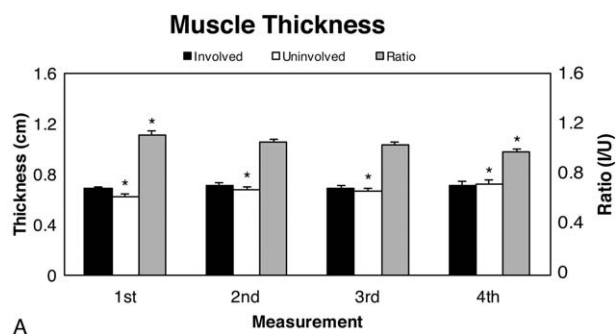
We prospectively recruited 50 infants for the study (21 females and 29 males) with the mean age of  $4.3 \pm 0.3$  months (range 1–12). Among them, 23 infants had left and 27 had right SCM muscle involvement. Their initial mean BW and BL of all subjects was  $7.0 \pm 0.2$  kg and  $63.4 \pm 0.9$  cm, respectively, and was about 10 kg and about 80 cm at the end of follow-up. The mean follow-up period and interval were  $4.7 \pm 0.4$  months (range 1.4–14.7) and  $2.5 \pm 0.2$  months (range 0.7–12.6), respectively. All included infants had facial asymmetry and limited neck rotation to the lesion side. Four had a palpable neck mass (right/left: 3/1). The clinical symptoms and signs subsided after physiotherapy of different durations. Therefore, no CMT infants had surgical intervention at the end of follow-up.

#### 3.2. Ultrasonographic measurement of echotexture

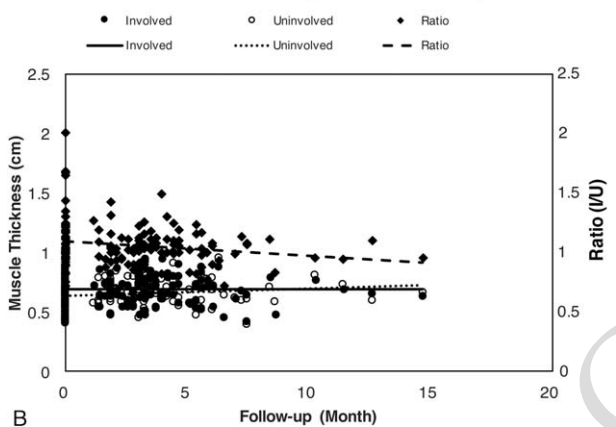
Each CMT infant underwent US examination for a mean of  $2.9 \pm 1.2$  times (range: 2–7) during follow-up. The initial mean  $K$  value for all CMT infants was  $6.85 \pm 0.58$  (range 2.22–26.23) and decreased to  $1.30 \pm 0.36$  (range 0–7.72) during follow-up ( $P < 0.001$ ) (Fig. 3A). The high 4th measurement for 6 CMT infants



**Figure 3.** Measurements of (A)  $K$  value and (B) scatter diagrams for  $K$  value during follow-up. (A) \* $P$  values between the 1st and 2nd, 3rd, and 4th measurements (all  $P < 0.001$ ). † $P$  values between the 2nd and 3rd ( $P < 0.001$ ) and 4th measurements ( $P = 0.015$ ). (B) The  $K$  value of involved SCM muscles shows a negative-slope linear regression trend line (solid line).



**Muscle Thickness along the Follow-up Period**



**Figure 4.** Measurement of (A) muscle thickness and (B) scatter diagrams for muscle thickness during follow-up. (A) Difference in involved muscle thickness (black bar) between each measurement was not significant. \**P* values for the uninvolved muscles (white bar) between the 1st and 2nd ( $P=0.004$ ), 3rd ( $P=0.039$ ), and 4th measurements ( $P=0.026$ ). \**P* value for Ratio I/U between the 1st and 4th measurement ( $P=0.006$ ). (B) Linear regression trend lines for uninvolved (dotted line) and involved (solid line) SCM muscle thickness, and for Ratio I/U (dashed line) during follow-up.

was possibly related to the severe SCM muscle fibrosis as reflected in the high mean initial *K* value of  $11.3 \pm 3.1$  (range 6.06–26.23) for these infants. One infant, showing severe fibrosis by a high initial *K* value of 12.1, underwent US examination of 7 times and had a high *K* value at the 5th measurement (Supplementary Fig. 1, <http://links.lww.com/MD/B563>).

We found a linear regression trend line with a negative slope of  $-0.02$  for *K* value during follow-up (Fig. 3B). This finding represented decreased echotexture difference between involved and uninvolved SCM muscles during follow-up.

### 3.3. Ultrasonographic measurement of muscle thickness

Involved and uninvolved SCM muscle thickness ranged from 0.6 to 0.8 cm during follow-up. The differences between involved and uninvolved SCM muscle thickness at each US measurement were not significant. The differences in involved SCM muscle thickness during follow-up also were not significant. However, we observed significant differences in uninvolved SCM muscles between measurements 1 ( $0.62 \pm 0.02$  cm) and 2 ( $0.68 \pm 0.02$  cm,  $P=0.004$ ), 3 ( $0.67 \pm 0.02$  cm,  $P=0.039$ ), and 4 ( $0.69 \pm 0.07$  cm,  $P=0.026$ ). The initial mean Ratio I/U was  $1.11 \pm 0.04$  (range: 0.78–1.48). This ratio decreased progressively during follow-up to the  $0.97 \pm 0.02$  (range: 0.83–1.10), with a significant difference between the 1st and 4th measurement ( $P=0.006$ ) (Fig. 4A).

**Table 1**

**Correlation between ultrasonographic measurement and clinical information.**

	<i>K</i> value	Initial <i>K</i> value	Uninvol. m.	Ratio I/U
F/U duration	$P < 0.001$ $r = -0.437$	$P = 0.013$ $r = 0.349$	NS	NS
Age	$P < 0.001$ $r = -0.457$	NS	NS	NS
BW	$P = 0.001$ $r = -0.316$	NS	NS	NS
BL	$P < 0.001$ $r = -0.477$	NS	NS	NS
US exam. no.	NS	$P = 0.002$ $r = 0.432$	NS	NS
Invol. m.	$P = 0.009$ $r = 0.215$	$P = 0.045$ $r = 0.284$	$P = 0.012$ $r = 0.208$	$P < 0.001$ $r = -0.359$
Ratio I/U	$P = 0.004$ $r = 0.238$	NS	NS	NS

BL=body length, BW=body weight, F/U=follow-up, Invol. m.=involved SCM muscle thickness, NS=nonsignificant, Ratio I/U=ratio of involved to uninvolved muscle thickness, uninvol. m.=uninvolved SCM muscle thickness, US exam. no.=number of ultrasonographic examination.

A mildly increased trend of uninvolved and nearly no change in involved SCM muscle thickness occurred during follow-up (Fig. 4B). We also observed a linear regression trend line for Ratio I/U during follow-up, with a negative slope of  $-0.0004$ . This observation was possibly related to the increase in uninvolved SCM muscle thickness over time.

### 3.4. Correlation between the ultrasonographic measurement and clinical information

The *K* value, reflecting the degree of muscle fibrosis, was negatively and fairly correlated with age, follow-up duration, and number of US examinations. *K* value was negatively and weakly correlated with BW and BL, which suggested the effects of growth and development on muscle fibrosis. *K* value was positively and weakly correlated with involved SCM muscle thickness and Ratio I/U. The initial *K* value was positively correlated with follow-up duration, number of US examination, and involved muscle thickness. Fibrotic SCM muscle thickness was fairly correlated with normal SCM muscle thickness and Ratio I/U. Uninvolved SCM muscle thickness was poorly correlated with number of US examinations and negatively with Ratio I/U. Detailed information is listed in Table 1.

## 4. Discussion

US examination is helpful in daily practice because it is noninvasive and reflects underlying pathological changes without the need for muscle biopsy and patient cooperation. In a typical muscle fibrosis image, the normal muscle architecture is disrupted by infiltrated collagen fibers, which cause increased reflection of the ultrasound beam and results in increased muscle EI.<sup>[1,6,12,16,18]</sup> Varied US system settings during each examination and operators with different experience are responsible for the high intra- and interobserver errors during US interpretation based on muscle EI.<sup>[18,19]</sup> Therefore, the *K* value was developed to decrease study error and increase experimental reliability.<sup>[6]</sup> The initial *K* values of all our infants with CMT varied from 2.22 to 26.23, which represented a wide degree of fibrosis in affected SCM muscles rather than only 2 different types of fibrosis. After receiving regular physiotherapy, our CMT infants showed a



significant decrease in  $K$  values during follow-up on serial sonograms of affected SCM muscles (Fig. 3A). The decrease in  $K$  value indicates that the MEI for involved muscle approaches that for uninvolved muscle, for overall decreased muscle fibrosis.<sup>[6]</sup>

Muscle biopsy specimens from patients with neuromuscular disease show common histopathologic findings of atrophied muscle fibers and increased perimysial fibrosis.<sup>[20]</sup> Muscle EI has been clinically used to quantify severity of muscle fibrosis in patients with Duchenne muscular dystrophy (DMD),<sup>[21]</sup> inflammatory myopathy,<sup>[12]</sup> metabolic myopathy,<sup>[22]</sup> and lumbar radiculopathy.<sup>[23]</sup> The muscle EI of serial muscle images was used in the follow-up of boys 4 to 12 years old with DMD and was inversely related to ambulatory status, functional grading, muscle strength, and motor ability.<sup>[21]</sup> A study used the Heckmatt scale to follow the spasticity of involved gastrocnemius muscles in stroke patients before and after botulinum toxin-A injection.<sup>[24]</sup> The EI is difficult to differentiate in different muscle pathologies, but it seemed a good candidate for reflecting the clinical status during the course of treatment from the above reports.

Besides the muscle fibrosis, growth and development may affect muscle components.<sup>[25,26]</sup> The uninvolved muscle thickness increased along the follow-up period representing muscle growth effects in the study. Thickness changes of involved muscles, reflecting the complex of decreased fibrosis after physiotherapy and increased normal muscle component with growth, were not distinctive. Selective activation of protein kinase B caused by the release of insulin growth factor-1 from muscle fibers during passive stretch promotes myosatellite cell proliferation and induces skeletal muscle hypertrophy.<sup>[27,28]</sup> Stretch-induced antifibrotic effects, as much as the well-known antifibrotic agent decorin, has also been reported in injured gastrocnemius muscles of rats.<sup>[29]</sup> Therefore, both normal growth and development and physiotherapy may affect the improvement of SCM muscle fibrosis as reflected in the change in  $K$  value during follow-up. The  $K$  value is useful for continuously observing severity of SCM muscle fibrosis and may be a competent indicator in mirroring the progression of muscle fibrosis during treatment.

With pure imaging, sonograms can tell us only the change in fibrosis type or sustained decrease in muscle fibrosis in the involved SCM muscle during the treatment course for CMT infants. However, the image presentation lacks a digitized indicator to show the amelioration of fibrosis in CMT infants after physiotherapy, which can be demonstrated by the  $K$  value (Supplementary Fig. 1, <http://links.lww.com/MD/B563>). In contrast, changes in sequential measurements of the involved SCM muscle thickness and differences between bilateral SCM muscles during the treatment course were not significant. We found an increasing trend of uninvolved muscle thickness during follow-up, with a significant increase at about 3 months ( $2.9 \pm 0.2$  months) (Fig. 4A). Uninvolved SCM muscle thickness in all infants slowly increased with follow-up duration (Fig. 4B). Ratio I/U tended to decrease during treatment, with no decrease in involved SCM muscle thickness during follow-up (Fig. 4B). The significant negative correlation between uninvolved muscle thickness and Ratio I/U was largely due to the increase in uninvolved SCM muscle thickness.

As compared with changes in muscle thickness and thickness ratio during treatment, the improvement in echotexture was noticeable. Nevertheless, our results showed that involved SCM muscle thickness was not related to treatment period. Both these findings suggest that the  $K$  value is a better candidate than muscle thickness in describing the therapeutic effect on affected SCM

muscles during physiotherapy. From our observations, infants with high initial  $K$  value, implying severe fibrosis, will receive a long treatment course and frequent US examinations. More frequent US examinations and longer physiotherapy course may be required for infants with greater degree of SCM muscle fibrosis.

#### 4.1. Study limitations

US is a valuable workup tool for following the clinical status of CMT infants but cannot elucidate the pathogenesis of the muscle fibrosis. Echotexture analysis and thickness measurement of involved SCM muscles are end-clinical presentations of CMT infants. Study design only correlated the  $K$  value with the existence of clinical symptoms of head tilting, facial asymmetry, and neck range of motion, instead of the severity of clinical presentation. We will stress on this field in the near future. Muscle histopathological results were not available, because no subjects in the study underwent surgical intervention. Therefore, it is hard to differentiate the effects of maturation, therapy, or growth on involved muscle in the study.

#### 5. Conclusions

In addition to decreasing fibrosis, both growth and development and stretch-induced muscle hypertrophy affect the muscle architecture in affected SCM muscles in infants with CMT. The muscle EI reflects muscle tissue characterization and is correlated with muscle fibrosis in different disease entities.<sup>[12,21–23]</sup> The  $K$  value, derived from the difference between the involved and uninvolved muscle MEI, can aid in following the progression of muscle fibrosis in CMT infants during treatment. Quantification of muscle fibrosis is a digitized and sensitive indicator reflecting a wide degree of SCM muscle fibrosis in CMT and can be of great help in clinical practice.

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