REVIEW ARTICLE

SKELETAL MUSCLE CHANGES IN THE FIRST THREE MONTHS OF STROKE RECOVERY: A SYSTEMATIC REVIEW

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Background: Rehabilitation is important in the first months after a stroke for recovery of functional ability, but it is also challenging, since distinct recovery trajectories are seen. Therefore, studying the early changes in muscle characteristics over time (e.g. muscle strength, muscle mass and muscle volume), which are known to be associated with functional abilities, may deepen our understanding of underlying recovery mechanisms of stroke survivors.

Objective: This systematic review aims to describe the longitudinal changes in skeletal muscles, including muscle strength, muscle mass and muscle volume, during the first 3 months post-stroke.

Methods: Electronic searches were conducted in Medline, Scopus and CENTRAL. Longitudinal cohort studies or controlled interventional trials that report data about patients in the first 3 months after stroke were identified. Skeletal muscle characteristics should be measured at least twice within 3 months post-stroke by objective, quantitative assessment methods (e.g. dynamometry, ultrasound, computed tomography). Effect sizes were calculated as Hedges' g using standardized mean differences.

Results: A total of 38 studies (1,097 subjects) were found eligible. Results revealed an mean increase on the paretic side for upper and lower limb muscle strength (small to moderate effect sizes), whereas muscle thickness decreased (moderate to large effect sizes). Similar, but smaller, effects were found on the non-paretic side. There were insufficient data available to draw conclusions about lean muscle mass and muscle cross-sectional area. No studies aimed at investigating distinct trajectories of the muscle changes.

Conclusion: Muscle strength and thickness changes during the first 3 months after stroke in both the paretic and non-paretic side. Future studies should

LAY ABSTRACT

After a stroke, it is important to restore functional ability as much as possible. Studying changes in the muscles (e.g. muscle strength, muscle thickness, muscle volume) during the first months post-stroke can help to elucidate individual variations and the underlying repair mechanisms. A systematic search of the literature was performed for studies of objective quantifiable measurements of muscles at least 2 times during the first 3 months after stroke. A total of 38 studies (with in total 1,097 patients) met these criteria. Overall, an improvement in strength was measured on the paretic side for both the upper and lower limbs, but muscle thickness decreased. Similar, but smaller, effects were found on the non-paretic side. For other muscle parameters insufficient data were found to draw conclusions. Because understanding the underlying mechanism of muscle changes post-stroke can improve rehabilitation programmes, further studies should focus on why these muscle strength changes occur.

aim to understand "how" the stroke-induced muscle strength changes are achieved. Exploring existing data from longitudinal studies, by using cluster analyses, such as pattern recognition, could add to the current knowledge-base.

Stroke is one of the leading causes of acquired physical disability in the adult population (1). Rehabilitation is the most effective way to limit the amount of disability and improve patients' functionality (2). However, despite continuously improving and innovating interventions, distinct trajectories of recovery are seen. For example, two-third of patients after stroke have residual hemiparesis, resulting in chronic, long-term disability (3). This emphasizes the complex stroke recovery process and highlights the possibility of distinct underlying recovery mechanisms that support the functional ability of stroke survivors. Gaining insight into the mechanisms that contribute to the heterogeneous treatment response in stroke survivors could help us to better understand the complex recovery process and to optimize functional rehabilitation (4).

Skeletal muscle is suggested to be the main effector organ accountable for physical disability in the stroke population (5). This disability traditionally contributed to the neurological insult itself, primarily causing motor symptoms, with muscle weakness, altered muscle tone and decreased muscle control being the most common motor manifestations post-stroke (6). More recently, the functional aspects, structural adaptations and metabolic integrity of peripheral muscle tissue, which remained unrecognized until the past decades, have become an important focus in the evaluation and treatment of the stroke population (7, 8). The relevance of this changing approach is noticeable in the literature, with several reviews synthesizing the available evidence about post-stroke skeletal muscle changes (9–11).

Previous studies have shown that chronic stroke survivors (>6 months post-stroke) experience a loss in muscle mass and a decrease in muscle strength in both the paretic and non-paretic limbs (9, 10). According to research by Miller and colleagues (12), a decreased central activation can only partly explain bilateral muscle weakness, which might implicate that skeletal muscle changes after stroke can be considered as a multifactorial syndrome depending on various underlying mechanisms besides the brain lesion itself (e.g. neurodegeneration, loss of motor neurones, local muscle metabolic alterations) (8). This assumption is supported by recent research exploring changes after stroke directly at the level of the skeletal muscle (13). Muscle tissue of chronic stroke patients shows an increased intramuscular fat deposition (7) and a major shift from slow-twitch towards fast-twitch fibres in the hemiparetic muscles (14). In addition, the muscle's architecture, defined as the geometric arrangements of muscle fibres (15), appears to be altered in chronic stroke survivors with a shorter fascicle length on the paretic side. Reports about pennation angle measurements (i.e. fibre orientation) have been less consistent (16).

From a clinical point of view, these (mal-)adaptive skeletal muscle changes have an impact on the recovery process. Muscular atrophy is moderately correlated with decreased gait speed and reduced fitness levels in individuals following stroke in the chronic stage (7). Also, increased severity of gait impairments have been observed as a result of hemiparetic muscle phenotype changes (14), a decline in muscle mass and muscle strength (17). Furthermore, the muscle's architecture has a profound influence on muscle function, and therefore, structural changes might negatively affect the force-generating process and impact functional recovery (13).

Despite the growing body of evidence about the contribution of underlying skeletal muscle changes to physical disability after stroke, none of the clinical stroke guidelines address these peripheral muscle changes (18, 19). Most of the conventional physiotherapy in stroke rehabilitation includes intensive task-specific exercises aimed at improving motor performance (20). To maximize functional recovery, additional therapy strategies that address alterations of the skeletal muscle are warranted. Since most significant improvements in stroke recovery occur in the first 3 months after stroke onset (21), restorative interventions should be commenced within this critical time window, as suggested by the Stroke Roundtable Consortium (4). Unfortunately, most of the existing evidence about skeletal muscle changes have explored long-term alterations post-stroke (>6 months), leaving a paucity of knowledge regarding acute and early subacute muscle changes as an important deficiency in literature that needs to be addressed before optimal gains in neurorehabilitation can be achieved.

One way to improve our understanding of how stroke recovery is achieved in the first 3 months following stroke onset is to evaluate changes in the skeletal muscle over time. Although clinical assessment scales are an essential tool in the measurement and evaluation of motor impairments (22), they often have limitations, such as ceiling effects and a lack of sensitivity to detect small, but relevant, changes (23). Therefore, to accurately evaluate peripheral muscle changes, measurements are preferably performed by objective, quantitative assessment methods. Medical imaging techniques, such as ultrasound, medical resonance imaging (MRI) and computed tomography (CT), but also hand-held dynamometers are just a number of the widely used objective tools in research and clinical practice to address changes in function, structure and consistency of the peripheral muscles (23, 24). However, an overview of these measurements representing skeletal muscle changes early after stroke is still lacking.

Therefore, the purpose of this systematic review is to synthesize available evidence describing the time-course of peripheral muscle changes in skeletal muscles (e.g. muscle strength, muscle mass, muscle volume) measured by objective, quantitative assessment methods (e.g. dynamometry, ultrasound, CT) in the first 3 months post-stroke.

METHODS

The PRISMA guidelines were used as a general framework for transparent reporting of this systematic review. Protocol details were registered prospectively on PROSPERO (registration number: CRD42020157647).

Studies were included if they met following inclusion criteria.

Type of participants
Studies involved adult (≥18 years) stroke patients, as defined by the World Health Organization (WHO) (25), in the acute (0–7 days) and/or early subacute (> 7 days to 3 months) stages. The framework of these critical time points post-stroke was defined by the Stroke Roundtable Consortium (4).

Type of outcome
Studies evaluated changes in upper and/or lower extremity skeletal muscle characteristics (i.e. function, structure and composition) (e.g. changes in muscle strength, muscle mass, muscle fibres) measured by objective, quantitative assessment methods (e.g. dynamometer, CT, ultrasound) were included. The muscle characteristics of the subjects needed to be measured at least twice within 3 months post-stroke. Changes in muscle characteristics assessed by clinical measurements (e.g. Medical Research Council Scale, Fugl-Meyer assessment, Modified Ashworth Scale) were excluded.

Type of study design
Longitudinal cohort studies or controlled interventional trials were included. Concerning the latter, in these studies the data of the groups receiving usual care or conventional physiotherapy were considered as longitudinal data, and were included at baseline, post-intervention and follow-up. Data from the experimental groups were excluded. Clinical trial protocols, systematic reviews, narrative reviews, meta-analysis or case reports were excluded.

Type of publication
Peer-reviewed journal articles were included, conference abstracts and proceedings were excluded.

Language
Studies had to be published in English, French or Dutch.

Data sources and searches
A systematic search was undertaken in 3 electronic databases (MEDLINE, Scopus and CENTRAL) from inception until July 2019 and updated in May 2020. The search strategy was structured according to the Population, Intervention, Comparison, Outcome (PICO) method, and combined key words related to stroke and skeletal muscle characteristics. Full electronic search strategies are shown in Appendix 1. Reference lists of related systematic reviews (9, 10) and the citations of included studies were screened for missing studies.

Study selection
To identify eligible studies, titles and abstracts were screened by 2 independent reviewers (LC, NL) with the use of the web application Rayyan (26). If studies were considered relevant, full-text copies were obtained and checked for eligibility by the same independent reviewers. Disagreements between authors were resolved by consensus. If no agreement was reached, additional authors (DB, ES) were consulted.

Data extraction
A data extraction sheet was developed to collect data outcomes of interest. The data extraction sheet was pilot-tested on 3 randomly selected study trials and refined accordingly. One author (LC) collected data from the included studies.

Quality assessment
To critically evaluate the quality of the individual studies, a customized risk of bias tool was created. Key domains and judgement criteria, that had the most potential to introduce bias, were compiled from existing tools (i.e. Cochrane Collaboration's tool for randomized trials (27), the Methods Guide for Comparative Effectiveness Reviews (28) and the Newcastle-Ottawa Quality Assessment Scale for cohort studies (29)) and adapted into a specified checklist based on the research question of this systematic review. The applicable domains included sampling, confounding, performance, detection, attrition and reporting bias and were rated as "high", "low" or "unclear". An overview of the pre-specified judgement criteria is shown in Table SIV in Appendix 2. Two reviewers (LC, WVH) independently evaluated risk of bias for each study. Disagreements were discussed and settled by consensus. If no agreement was reached, an additional author (ES) was consulted.

Data synthesis and analysis

Means, standard deviations (SDs) and significance values of the paretic and non-paretic side were primarily extracted for each evaluation time-point of every outcome measure of interest.

The effect sizes were calculated as Hedges' g (g_H), a bias-adjusted estimate of standardized mean difference between 2 evaluation time-points with an additional correction for small sample sizes (30). Effect sizes were interpreted as small (≤ 0.2), moderate (0.5), or large (≥ 0.8), representing an increase (positive values) or decrease (negative values) over time. If the required data was absent or insufficiently reported, the authors were contacted individually by e-mail. When possible, researchers calculated means and SDs themselves or extracted these data from available figures in the included studies. In cases where the desired data was unobtainable, despite the aforementioned methods, a quantitative analysis via effect size calculation was not possible. Nevertheless, these studies were included in the systematic review to avoid reporting bias. For those studies, other available measures of central tendency and dispersion were extracted and reported.

RESULTS

Study selection

The database search yielded 2,843 unique records, of which a final total of 38 studies was included in this systematic review (31–68). Fig. 1 illustrates a flow diagram of the entire selection process.

Characteristics of included studies

Tables I and II list detailed information about the study characteristics.

Study design

Of the 38 included studies, 24 were longitudinal cohort studies in which muscle characteristics were measured at least twice within 3 months post-stroke (31, 33–36, 39, 41, 42, 44, 46, 48, 50, 52–55, 57, 58, 60–62, 64, 65, 67). The remaining eligible studies represent 13 randomized controlled trials (RCTs) (32, 37, 38, 40, 43, 45, 47, 49, 51, 59, 63, 66, 68) and 1 clinical controlled trial (CCT) (56). Participants in the control groups of these interventional trials were considered as longitudinal data as they received conventional physiotherapy
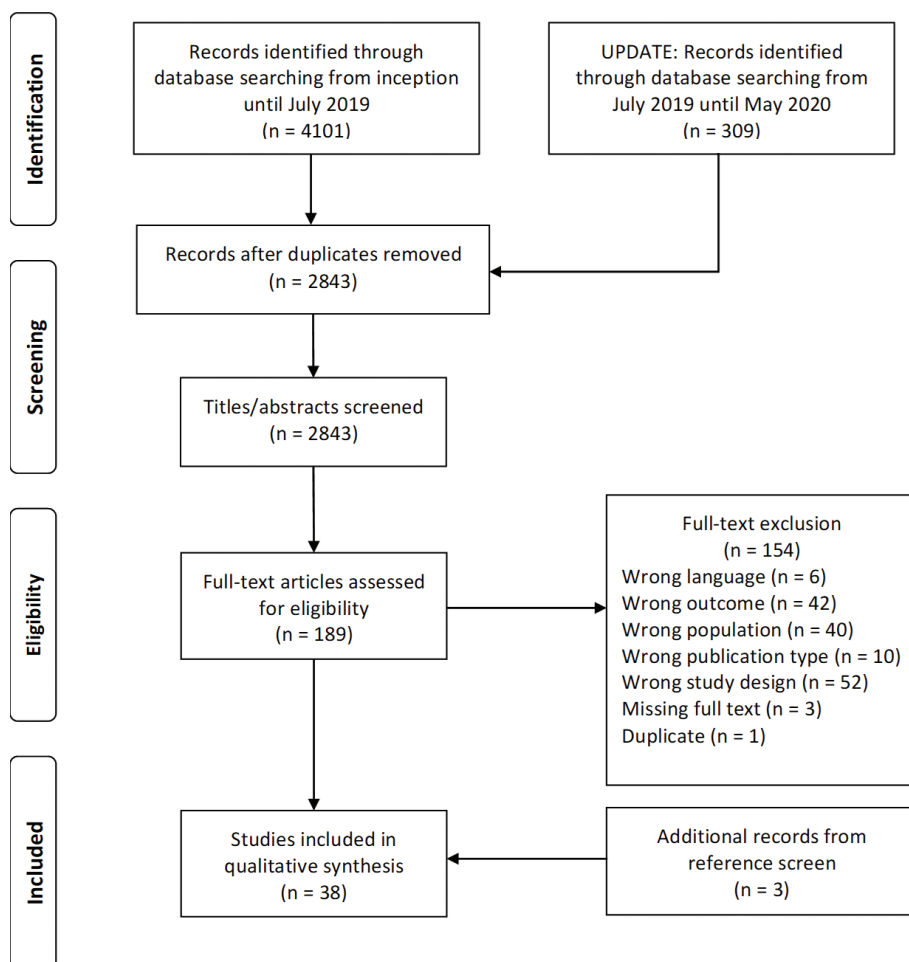
Fig. 1. Flow chart.

Table I. Muscle strength

First author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Time point	ES PS (*p*-value)	ES NPS (*p*-value)	Drop-out ratio
LOWER LIMB												
Andrews 2003 (31)	Long.	50	26M, 24F Age 61.6±12.7 y PS: 28L, 22R Type: NR Early subacute stage	Chatillon Hand-held dynamometer (N)	Hip flexors	T_0: 12d T_1: 29d	47.0 (44.1) 65.1 (44.1)	94.1 (43.3) 105.4 (46.4)	T_0 vs T_1	0.41 (<0.001*)	0.25 (<0.001*)	0%
					Knee extensors	T_0: 12d T_1: 29d	129.0 (89.9) 191.5 (91.3)	219.8 (101.5) 247.4 (93.1)	T_0 vs T_1	0.68 (<0.001*)	0.28 (<0.001*)	0%
					Ankle dorsiflexors	T_0: 12d T_1: 29d	75.6 (72.3) 102.4 (86.3)	164.7 (68.1) 185.5 (65.6)	T_0 vs T_1	0.34 (<0.001*)	0.31 (<0.001*)	0%
Bohannon 2013 (34)	Long.	55	29M, 26F Age 62.8±13.1 y PS: 32L, 23R Type: 49I, 6H Early subacute stage	Chatillon Hand-held dynamometer (N)	Hip flexors	T_0: 12d T_1: 17d	43.2 (38.1) 59.8 (38.1)	93.7 (42.2) 104.4 (47.4)	T_0 vs T_1	0.43 (≤.002*)	0.24 (≤.002*)	0%
					Knee extensors	T_0: 12d T_1: 17d	121.1 (84.4) 155.9 (89.3)	223.4 (100.0) 242.1 (94.1)	T_0 vs T_1	0.40 (≤.002*)	0.19 (≤.002*)	0%
					Ankle dorsiflexors	T_0: 12d T_1: 17d	72.5 (68.0) 99.6 (83.7)	163.7 (70.4) 181.9 (67.0)	T_0 vs T_1	0.35 (≤.002*)	0.26 (≤.002*)	0%
Carin-Levy 2006 (36)	Long.	18	11M, 7F Age 66.0±11.5 y PS: NR Type: NR Acute and early subacute stage	Isometric strain gauge (N)	Knee extensors	T_0: 7d T_1: 14d T_2: 21d T_3: 28d	*Median (IQR)* 258.4 (156.0–360.9) 284.9 (178.0–393.8) 183.9 (174.4–344.3) 213.4 (178.0–448.7)	*Median (IQR)* 270.3 (135.9–404.7)† 321.4 (178.5–406.3)† 222.5 (155.0–370.4)† 263.3 (222.1–439.2)†	T_0 vs T_1 T_1 vs T_2 T_2 vs T_3 T_0 vs T_3	NA (NS) NA (NS) NA (NS) NA (NS)	NA (NS) NA (NS) NA (NS) NA (NS)	22% 6% 0% 28% 28%
Lee 2018 (49)	RCT	18	10M, 8F Age 63.7±11.4 y PS: 10L, 9R Type: 9I, 9H Early subacute stage	Humac Norm Isokinetic dynamometer (Nm)	Knee extensors	T_0: 29d T_1: 57d	39.2 (22.9) 46.8 (25.4)	71.8 (37.0) 77.8 (36.4)	T_0 vs T_1	0.31 (0.07)	0.16 (0.22)	22%
					Knee flexors	T_0: 29d T_1: 57d	30.7 (19.7) 35.6 (26.4)	45.7 (25.6) 47.2 (24.3)	T_0 vs T_1	0.21 (0.27)	0.06 (0.56)	22%
Shapira-Vadler 2015 (62)	Long.	23	12M, 11F Age 58.0±10.5 y PS: 14L, 9R Type: 19I, 2H Early subacute stage	Hand-held dynamometer (kg/f)	Knee extensors	T_0: 20d T_1: 50d	11.6 (4.5) 13.6 (2.6)	13.2 (3.3) † 13.8 (2.9) †	T_0 vs T_1	0.55 (0.008*)	0.19 (NR)	0%
Solopova 2011 (63)	RCT	29	18M, 11F Age NR PS: 20L, 9R Type: 26I, 0H Early subacute stage	Strain gauge (Nm)	Knee extensors	T_0: 9d T_1: 23d	92.7 (59.8) 117.8 (11.1)	159.9 (51.0) 166.0 (50.1)	T_0 vs T_1	0.70 (0.01*)	0.12 (>0.05)	0%
					Knee flexors	T_0: 9d T_1: 23d	27.4 (11.9) 35.9 (18.4)	64.8 (24.3) 67.1 (29.3)	T_0 vs T_1	0.56 (0.01*)	0.08 (>0.05)	0%

Change in time

Table I (Continued). Muscle strength

First author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Change in time			Drop-out ratio
									Time point	ES PS (p-value)	ES NPS (p-value)	
UPPER LIMB												
Andrews 2003 (31)	Long.	50	26M, 24F; Age 61.6±12.7 y; PS: 28L, 22R; Type: NR; Early subacute stage	Chatillon Hand-held dynamometer (N)	Shoulder abductors	T_0: 12d / T_1: 29d	52.3 (51.4) / 67.2 (54.5)	119.1 (50.8) / 127.1 (49.3)	T_0 vs T_1	0.28 (<0.001*)	0.16 (>0.001)	0%
					Elbow flexors	T_0: 12d / T_1: 29d	61.0 (60.0) / 85.8 (64.6)	154.2 (57.0) / 159.9 (57.8)	T_0 vs T_1	0.40 (<0.001*)	0.10 (>0.001)	0%
					Elbow extensors	T_0: 12d / T_1: 29d	52.7 (52.0) / 66.6 (51.7)	120.2 (43.6) / 123.9 (44.8)	T_0 vs T_1	0.27 (<0.001*)	0.08 (>0.001)	0%
					Wrist extensors	T_0: 12d / T_1: 29d	26.3 (35.7) / 40.2 (40.6)	86.5 (37.8) / 95.1 (37.1)	T_0 vs T_1	0.36 (<0.001*)	0.23 (<0.001*)	0%
Au-Yeung 2014 (32)	RCT	23	11M, 12F; Age 72.0±9.6 y; PS: 11L, 12R; Type: 23I, 0H; Acute and early subacute stage	Electronic dynamometer, Digital Grip/Pinch Analyser (kg)	Grip strength	T_0: 1d / T_1: 29d	2.3 (4.6) / 3.1 (4.0)	NR / NR	T_0 vs T_1	0.18 (>0.05)	NR	30%
					Pinch strength	T_0: 1d / T_1: 29d	0.7 (1.4) / 0.8 (1.2)	NR / NR	T_0 vs T_1	0.08 (>0.05)	NR	10%
Au-Yeung 2014 (32)	RCT	21	11M, 10F; Age 68.4±9.9 y; PS: 12L, 9R; Type: 21I, 0H; Acute and early subacute stage	Electronic dynamometer, Digital Grip/Pinch Analyser (kg)	Grip strength	T_0: 1d / T_1: 29d	0.9 (2.7) / 5.6 (7.4)	NR / NR	T_0 vs T_1	0.97 (>0.05)	NR	30%
					Pinch strength	T_0: 1d / T_1: 29d	0.5 (1.3) / 1.7 (2.2)	NR / NR	T_0 vs T_1	0.67 (>0.05)	NR	10%
Bohannon 1995 (33)	Long.	10	4M, 6F; Age 66.7 y; PS: 2L, 8R; Type: NR; Acute and early subacute stage	Ametek Cadet Force gauge dynamometer (N)	Shoulder abductors	*Mean (range)* T_0: 6d / T_1: 11d	*Mean (range)* 27.6 (0.0–90.7) / 34.7 (0.0–93.4)	*Mean (range)* NR / NR	T_0 vs T_1	NA (0.180)	NR	0%
					Elbow flexors	T_0: 6d / T_1: 11d	28.0 (0.0–67.6) / 32.9 (0.0–85.4)	NR / NR	T_0 vs T_1	NA (0.109)	NR	0%
				Jamar Hand-held dynamometer (N)	Grip strength	T_0: 6d / T_1: 11d	44.0 (0–164.5) / 52.0 (0–160.1)	NR / NR	T_0 vs T_1	NA (0.317)	NR	0%
Canning 2004 (35)	Long.	22	11M, 11F; Age 68.4±6.6 y; PS: 10L, 12R; Type: NR; Early subacute stage	Load cell (Nm)	Elbow flexors and extensors	T_0: 21d / T_1: 35d / T_2: 49d / T_3: 63d / T_4: 77d	14.1 (9.4) / 16.4 (10.8) / 17.5 (10.8) / 18.8 (10.8) / 19.1 (10.3)	26.9 (NR) / NR / NR / NR / NR	T_0 vs T_1 / T_1 vs T_2 / T_2 vs T_3 / T_3 vs T_4 / T_0 vs T_2 / T_0 vs T_3 / T_0 vs T_4	0.22 (NR) / 0.10 (NR) / 0.12 (NR) / 0.03 (NR) / 0.33 (NR) / 0.46 (NR) / 0.49 (NR)	NA / NR / NR / NR / NR / NR / NR	0% / 0% / 0% / 0% / 0% / 0% / 0%
Carin-Levy 2006 (36)	Long.	18	11M, 7F; Age 66.0±11.5 y; PS: NR; Type: NR; Acute and early subacute stage	Lafayette Hand-held dynamometer (N)	Grip strength	T_0: 7d / T_1: 14d / T_2: 21d / T_3: 28d	*Median (IQR)* 78.5 (0–188.7) / 93.2 (51.5–186.3) / 88.3 (0–245.2) / 103 (83.4–227.9)	*Median (IQR)* 171.6 (103.0–318.7)* / 264.8 (109.1–345.6)* / 122.6 (107.9–294.2)* / 245.2 (117.7–348.1)*	T_0 vs T_1 / T_1 vs T_2 / T_2 vs T_3 / T_0 vs T_2 / T_0 vs T_3	NA (NS) / NA (NS) / NA (NS) / NA (NS) / NA (NS)	NA (NS) / NA (NS) / NA (NS) / NA (NS) / NA (NS)	22% / 6% / 0% / 28% / 28%

Table I (Continued). Muscle strength

UPPER LIMB (Continued)

First author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Change in time			
									Time point	ES PS (p-value)	ES NPS (p-value)	Drop-out ratio
Chen 2005 (37)	RCT	14	10M, 4F / Age 59.6±12.0 y / PS: 8L, 6R / Type: 8I, 6H / Early subacute stage	Jamar Hand-held dynamometer (kg)	Grip strength	T_0: 12d / T_1: 19d / T_2: 26d / T_3: 33d / T_4: 40d / T_5: 47d	0.0 (0.0) / 0.0 (0.0) / 0.29 (0.86) / 0.50 (1.23) / 0.65 (1.35) / 0.97 (1.68)	NR / NR / NR / NR / NR / NR	T_0 vs T_1 / T_1 vs T_2 / T_2 vs T_3 / T_3 vs T_4 / T_4 vs T_5 / T_0 vs T_2 / T_0 vs T_3 / T_0 vs T_4 / T_0 vs T_5	0.00 (≥.05) / 0.65 (NR) / 0.20 (NR) / 0.11 (NR) / 0.21 (NR) / 0.65 (≥.05) / 0.79 (≥.05) / 0.93 (<0.05*) / 1.12 (<0.05*)	NR / NR / NR / NR / NR / NR / NR / NR / NR	0% / 0% / 0% / 0% / 0% / 0% / 0% / 0% / 0%
Choi 2014 (38)	RCT	10	5M, 5F / Age 65.7±11.3 y / PS: 6L, 4R / Type: 6I, 4H / Early subacute stage	Hand-held dynamometer (kg)	Grip strength	T_0: 23d / T_1: 51d	6.6 (3.7) / 12.1 (5.4)	NR / NR	T_0 vs T_1	1.16 (0.005*)	NR	0%
Cortes 2017 (39)	Long.	18	9M, 9F / Age 55.0±12.9 y / PS: NR / Type: 18I, 0H / Early subacute stage	MicroFET2 Hand-held dynamometer (N)	Elbow flexors	T_0: 11d / T_1: 37d	*Z-Score (SE)* −3.7 (0.4) / −3.1 (0.2)	*Z-Score (SE)* NR / NR	T_0 vs T_1	NA (0.008*)	NR	6%
Ghaziani 2018 (40)	RCT	49	25M, 24F / Age 71.0 y / PS: NR / Type: 37I, 12H / Acute and early subacute stage	Device NR (kg)	Grip strength	T_0: 7d / T_1: 28d	12.0 (13.0) / 16.5 (12.8)	NR / NR	T_0 vs T_1	0.35 (<0.0001*)	NR	8%
Groisser 2014 (41)	Long.	10	5M, 5F / Age 52.6±5.6 y / PS: 8L, 2R / Type: NR / Acute and early subacute	Digital dynamometer (unit NR)	Grip strength	T_0: 7d / T_1: 60d	*% Median CL hand* 0.0 / 8.89	*% Median CL hand* NR / NR	T_0 vs T_1	NA (<0.001*)	NR	0%
Heller 1987 (42)	Long.	56	24M, 32F / Age 68.1±11.4 y / PS: 25L, 28R / Type: NR / Acute and early subacute stage	Hand-held dynamometer (mm Hg)	Grip strength	T_0: 4d / T_1: not specified	NR / NR	NR / NR	T_0 vs T_1	NR	NR	NR
Hosomi 2016 (43)	RCT	21	13M, 8F / Age 63.2±12.5 y / PS: 8L, 13R / Type: 12I, 9H / Early subacute stage	Device NR (kg)	Grip strength	T_0: 45d / T_1: 50d / T_2: 57d / T_3: 74d	7.1 (8.6) / 7.8 (8.4) / 8.2 (8.9) / 8.3 (8.6)	26.3 (9.6) / 26.4 (9.7) / 25.7 (9.7) / 26.8 (9.8)	T_0 vs T_1 / T_1 vs T_2 / T_2 vs T_3 / T_0 vs T_2 / T_0 vs T_3	0.08 (NR) / 0.05 (NR) / 0.01 (NR) / 0.12 (NR) / 0.14 (0.077)	0.01 (NR) / −0.07 (NR) / 0.11 (NR) / −0.06 (NR) / 0.05 (0.388)	0% / 0% / 0% / 0% / 0%
Kattenstroth 2018 (45)	RCT	23	16M, 7F / Age 59.0 y / PS: 13L, 10R / Type: 23I, 0H / Early subacute stage	Jamar Hand-held dynamometer, (kg)	Grip strength	T_0: 28d / T_1: 40d	20.44 (13.56) / 21.28 (10.90)	35.21 (11.43) / 34.60 (10.58)	T_0 vs T_1	0.07 (0.601)	−0.05 (0.494)	36%

Table I (Continued). Muscle strength

First author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Change in time			
									Time point	ES PS (p-value)	ES NPS (p-value)	Drop-out ratio
UPPER LIMB (Continued)												
Langhammer 2009 (47)	RCT	40	22M, 18F Age 72.0 ± 13.6 y PS: 19L, 21R Type: NR Acute and early subacute stage	Martin Vigorimeter Hand-held dynamometer (Bar)	Grip strength	T_0: acute stage, not specified T_1: T_0 + 16d	0.41 (0.26) 0.48 (0.29)	NR NR	T_0 vs T_1	0.29 (NR)	NR	13%
Larsen 2017 (48)	Long.	15	13M, 2F Age 59.0 ± 15.0 y PS: 7L, 8R Type: 15I, 0H Acute and early subacute stage	Load cell (N)	Pinch strength	T_0: 3d T_1: 38d	34.0 (14.0) 40.0 (14.0)	NR NR	T_0 vs T_1	0.42 (0.04*)	NR	13%
Liuzzi 2014 (50)	Long.	11	7M, 4F Age 63.2 ± 3.0 y PS: 6L, 5R Type: NR Acute and early subacute stage	Whole hand dynamometer (kg)	Grip strength	T_0: 1d T_1: 3d T_2: 7d T_3: 49d	22.5 (15.3) 23.9 (15.1) 25.5 (15.4) 29.3 (16.4)	35.1 (9.7) 33.3 (13.3) 34.4 (12.8) 34.5 (13.1)	T_0 vs T_1 T_1 vs T_2 T_2 vs T_3 T_0 vs T_2 T_0 vs T_3	0.09 (NR) 0.10 (NR) 0.23 (NR) 0.19 (NR) 0.41 (<0.05*)	−0.15 (NR) 0.08 (NR) 0.01 (NR) −0.06 (NR) −0.05 (NR)	0% 0% 0% 0% 0%
Matsuura 2015 (51)	RCT	10	5M, 5F Age 74.4 ± 12.7 y PS: 5L, 5R Type: 10I, 0H Early subacute stage	Hand-held dynamometer (kg)	Grip strength	T_0: 9d T_1: 14d	15.0 (2.1) 15.9 (2.5)	22.4 (NR) 23.1 (0.6)	T_0 vs T_1	0.39 (NR)	NA (NR)	0%
Noskin (2007) (53)	Long.	30	12M, 18F Age 62.0 ± 11.0 y PS: 18L, 12R Type: NR Acute and early subacute stage	Hand-held dynamometer (kg)	Grip strength	T_0: 2d T_1: 7d	Z-Score −1.1 −1.0	Z-Score −3.1 −2.6	T_0 vs T_1	NA (NR)	NA (NR)	27%
Powell 1999 (59)	RCT	30	14M, 16F Age 66.4 ± 12.5 y PS: 20L, 10R Type: NR Early subacute stage	Strain gauge (Nm)	Wrist extensors	T_0: 22d T_1: 50d T_2: 78d	Median (IQR) 0.7 (0.0–2.0) 0.9 (NR) 0.9 (NR)	Median (IQR) NR (NR) NR (NR) NR (NR)	T_0 vs T_1 T_1 vs T_2 T_0 vs T_2	NA (NR) NA (NR) NA (NR)	NR NR NR	7% 0% 7%
				Jamar Hand-held dynamometer (kg)	Grip strength	T_0: 22d T_1: 50d T_2: 78d	0.0 (0.0–8.5) NR (NR) NR (NR)	NR (NR) NR (NR) NR (NR)	T_0 vs T_1 T_1 vs T_2 T_0 vs T_2	NA (NR) NR NR	NR NR NR	7% 0% 7%
Prigatano 1997 (60)	Long.	51	29M, 22F Age 69.5 ± 13.0 y PS: 24L, 27R Type: 24I, 20H Early subacute stage	Stoetting hand dynamometer test	Grip strength	T_0: 17d T_1: 28d	NR NR	NR NR	T_0 vs T_1	NR	NR	0%

Table I (Continued). Muscle strength

First author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS^a $(T_x-T_0)/T_0$ (SD)	NPS^a $(T_x-T_0)/T_0$ (SD)	Change in time: Time point	ES PS (p-value)	ES NPS (p-value)	Drop-out ratio
UPPER LIMB (Continued)												
Renner 2009 (61)	Long.	16	7M, 9F Age 65.0±10.4 y PS: 12L, 4R Type: 16I, 0H Early subacute stage	Piezoelectric force sensor (Nm)	Elbow flexors	T_0: 29d; T_1: 50d; T_2: 71d	0.48 (0.84); 0.78 (0.99)	NR; NR	T_0 vs T_1; T_1 vs T_2; T_0 vs T_2	NA (NR); NA (NR); NA (NR)	NR; NR; NR	0%; 0%; 0%
					Elbow extensors	T_0: 29d; T_1: 50d; T_2: 71d	0.48 (0.83); 0.90 (1.67)	NR; NR	T_0 vs T_1; T_1 vs T_2; T_0 vs T_2	NA (NR); NA (NR); NA (NR)	NR; NR; NR	0%; 0%; 0%
					Wrist extensors	T_0: 29d; T_1: 50d; T_2: 71d	0.48 (0.83); 0.90 (1.67)	NR; NR	T_0 vs T_1; T_1 vs T_2; T_0 vs T_2	NA (NR); NA (NR); NA (NR)	NR; NR; NR	0%; 0%; 0%
				Digital multi-myometer (N)	Grip strength	T_0: 29d; T_1: 50d; T_2: 71d	0.62 (0.90); 0.73 (1.22)	NR; NR	T_0 vs T_1; T_1 vs T_2; T_0 vs T_2	NA (NR); NA (NR); NA (NR)	NR; NR; NR	0%; 0%; 0%
Suzuki 2011 (64)	Long.	21	10M, 11F Age 73.5±11.8 y PS: 4L, 17R Type: 17I, 4H Early subacute stage	μTAS MT-1 Hand-held dynamometer (Nm)	Elbow flexors	T_0: 7d; T_1: 14d; T_2: 21d; T_3: 28d	12.1 (13.7); 14.5 (14.4); 17.1 (16.3); 16.3 (15.5)	23.5 (14.1); 29.9 (18.7); 28.7 (16.4); 30.4 (17.4)	T_0 vs T_1; T_1 vs T_2; T_2 vs T_3; T_0 vs T_2; T_0 vs T_3	0.17 (>0.05); 0.17 (NR); −0.05 (NR); 0.33 (<0.0001*); 0.28 (0.001*)	0.38 (0.001*); 0.07 (NR); 0.10 (NR); 0.33 (0.009*); 0.43 (<0.0001*)	0%; 0%; 0%; 0%; 0%
					Elbow extensors	T_0: 7d; T_1: 14d; T_2: 21d; T_3: 28d	9.6 (10.1); 13.2 (14.1); 13.1 (13.4); 12.3 (11.7)	18.1 (9.7); 21.3 (11.8); 21.4 (10.9); 22.4 (13.3)	T_0 vs T_1; T_1 vs T_2; T_2 vs T_3; T_0 vs T_2; T_0 vs T_3	0.29 (0.006*); 0.01 (NR); −0.06 (NR); 0.29 (0.008*); 0.24 (0.046*)	0.29 (0.038*); 0.01 (NR); 0.08 (NR); 0.31 (0.027*); 0.37 (0.003*)	0%; 0%; 0%; 0%; 0%
				Jamar Hand-held dynamometer (kg)	Grip strength	T_0: 7d; T_1: 14d; T_2: 21d; T_3: 28d	7.6 (9.2); 8.8 (9.4); 9.8 (10.4); 10.0 (10.6)	16.3 (8.7); 19.1 (9.5); 19.4 (9.0); 20.2 (9.1)	T_0 vs T_1; T_1 vs T_2; T_2 vs T_3; T_0 vs T_2; T_0 vs T_3	0.13 (>0.05); 0.10 (NR); 0.02 (NR); 0.22 (0.012*); 0.24 (0.005*)	0.30 (0.001*); 0.03 (NR); 0.09 (NR); 0.34 (<0.0001*); 0.43 (<0.0001*)	0%; 0%; 0%; 0%; 0%
Turner 2012 (65)	Long.	10	5M, 5F Age 68.0±4.0 y PS: 5L, 5R Type: 7I, 3H Early subacute stage	Hand joystick robotic device, IMT2 shoulder/arm robot (N)	Shoulder flexors	T_0: 20d; T_1: 27d; T_2: 34d; T_3: 41d; T_4: 48d	25.0 (9.5); 23.0 (19.0); 26.0 (15.8); 24.0 (15.8); 23.0 (15.8)	NR; NR; NR; NR; NR	T_0 vs T_1; T_1 vs T_2; T_2 vs T_3; T_3 vs T_4; T_0 vs T_2; T_0 vs T_3; T_0 vs T_4	−0.13 (>0.05); 0.17 (>0.05); −0.12 (>0.05); −0.06 (>0.05); 0.08 (>0.05); 0.08 (>0.05); −0.15 (>0.05)	NR; NR; NR; NR; NR; NR; NR	0%; 0%; 0%; 0%; 0%; 0%; 0%
					Shoulder Extensors	T_0: 20d; T_1: 27d; T_2: 34d; T_3: 41d; T_4: 48d	19.0 (12.6); 15.0 (9.5); 25.0 (15.8); 22.0 (15.8); 27.0 (15.8)	NR; NR; NR; NR; NR	T_0 vs T_1; T_1 vs T_2; T_2 vs T_3; T_3 vs T_4; T_0 vs T_2; T_0 vs T_3; T_0 vs T_4	−0.35 (>0.05); 0.76 (>0.05); −0.18 (>0.05); 0.30 (>0.05); 0.40 (>0.05); 0.20 (>0.05); 0.54 (>0.05)	NR; NR; NR; NR; NR; NR; NR	0%; 0%; 0%; 0%; 0%; 0%; 0%

Table I (Continued). Muscle strength

First author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Change in time Time point	ES PS (p-value)	ES NPS (p-value)	Drop-out ratio
UPPER LIMB (Continued)												
Turner 2012 (65)	Long.	10	5M, 5F Age 68.0±4.0 y PS: 5L, 5R Type 7I, 3H Early subacute stage	Hand joystick robotic device, IMT2 shoulder/arm robot (N)	Shoulder Abductors	T_0: 20d	22.0 (9.5)	NR	T_0 vs T_1	0.08 (>0.05)	NR	0%
						T_1: 27d	23.0 (15.8)	NR	T_1 vs T_2	0.13 (>0.05)	NR	0%
						T_2: 34d	25.0 (12.6)	NR	T_2 vs T_3	-0.38 (>0.05)	NR	0%
						T_3: 41d	20.0 (12.6)	NR	T_3 vs T_4	0.00 (>0.05)	NR	0%
						T_4: 48d	20.0 (12.6)	NR	T_0 vs T_2	0.26 (>0.05)	NR	0%
									T_0 vs T_3	-0.17 (>0.05)	NR	0%
									T_0 vs T_4	-0.17 (>0.05)	NR	0%
					Shoulder Adductors	T_0: 20d	10.0 (12.6)	NR	T_0 vs T_1	0.26 (>0.05)	NR	0%
						T_1: 27d	13.0 (9.5)	NR	T_1 vs T_2	0.30 (>0.05)	NR	0%
						T_2: 34d	16.0 (9.5)	NR	T_2 vs T_3	0.17 (>0.05)	NR	0%
						T_3: 41d	18.0 (12.6)	NR	T_3 vs T_4	-0.43 (>0.05)	NR	0%
						T_4: 48d	13.0 (9.5)	NR	T_0 vs T_2	0.52 (>0.05)	NR	0%
									T_0 vs T_3	0.61 (>0.05)	NR	0%
									T_0 vs T_4	0.26 (>0.05)	NR	0%
Umeki 2019 (66)	RCT	25	14M, 11F Age 65.3±14.1 y PS: 11L, 14R Type 14I, 11H Acute and early subacute stage	Takei Hand dynamometer (kg)	Grip strength	T_0: 6d	17.7 (13.9)	NR	T_0 vs T_1	0.12 (>0.05)	NR	0%
						T_1: 16d	19.4 (14.6)	NR				
Vanbellingen 2017 (67)	Long.	82	47M, 35F Age 67.9±13.8 y PS: 0L, 82R Type 61I, 21H Early subacute stage	Jamar Hand-held dynamometer (kg)	Grip strength	T_0: 11d	19.7 (11.1)	NR	T_0 vs T_1	0.25 (<0.0001*)	NR	0%
						T_1: 44d	22.5 (10.3)	NR				
Vanoglio 2016 (68)	RCT	15	7M, 8F Age 73.0±14.0 y PS: 10L, 5R Type 9I, 6H Early subacute stage	Jamar Plus+ Hand-held dynamometer (kg/BMI)	Grip strength	T_0: 17d	0.19 (0.43)	NR	T_0 vs T_1	0.06 (0.085)	NR	13%
						T_1: 59d	0.22 (0.48)					
Vanoglio 2016 (68)	RCT	15	7M, 8F Age 73.0±14.0 y PS: 10L, 5R Type 9I, 6H Early subacute stage	Jamar Plus+ Hand-held dynamometer (kg/BMI)	Pinch strength	T_0: 17d	0.04 (0.07)	NR	T_0 vs T_1	0.12 (0.087)	NR	13%
						T_1: 59d	0.05 (0.09)	NR				

n: number of participants; PS: paretic side; NPS: non-paretic side; ES: effect size; Long.: longitudinal; RCT: randomized controlled trial; M: male; F: female; L: left; R: right; I: ischaemic; H: haemorrhagic; T: time-point of evaluation; d: mean days after stroke; NR: not reported; NS: not significant; NA: not analysed; IQR: interquartile range; SD: standard deviation; N: Newton; kg: kilogram; BMI: body mass index; Nm: Newton meter; mmHg: millimetres of mercury; kg/f: kilogram/force.
[a]Values of the paretic and non-paretic side are reported as means and standard deviations unless otherwise mentioned.
*Statistically significant.
Studies reporting differences between the paretic and non-paretic side are marked with † (no difference between both sides ($p \geq 0.05$)) or ‡ (significant difference between both sides ($p < 0.05$)).

Table II. Muscle size

Author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Time point	ES PS (p-value)	ES NPS (p-value)	Drop-out ratio
CROSS-SECTIONAL AREA (UPPER LIMB)										Change in time		
Carin-Levy 2006 (36)	Long.	18	11M, 7F Age 66.0±11.5 y PS: NR Type: NR Acute and early subacute stag	Skin fold measurements (cm²)	Upper arm muscles	T_0: 7d T_1: 14d T_2: 21d T_3: 28d	*Median (IQR)* 60.5 (58.1–62.8) 65.3 (58.3–2.6) 60.2 (44.0–76.8) 64.3 (58.3–75.6)	*Median (IQR)* 62.9 (61.1–64.8) 66.0 (62.2–68.7)† 60.1 (44.9–75.8)† 65.5 (59.4–72.0)†	T_0 vs T_1 T_1 vs T_2 T_2 vs T_3 T_0 vs T_2 T_0 vs T_3	NA (NS) NA (NS) NA (NS) NA (NS) NA (NS)	NA (NS) NA (NS) NA (NS) NA (NS) NA (NS)	22% 6% 0% 28% 28%
					Forearm muscles	T_0: 7d T_1: 14d T_2: 21d T_3: 28d	*Median (IQR)* 35.9 (33.3–38.5) 47.2 (41.4–48.9) 43 (34.2–50.1) 47.2 (42.0–50.5)	*Median (IQR)* 45.3 (37.4–47.7)† 45.9 (43.3–48.2)† 42.8 (34.9–51.4)† 45.9 (41.8–49.7)†	T_0 vs T_1 T_1 vs T_2 T_2 vs T_3 T_0 vs T_2 T_0 vs T_3	NA (NS) NA (NS) NA (NS) NA (NS) NA (NS)	NA (NS) NA (NS) NA (NS) NA (NS) NA (NS)	22% 6% 0% 28% 28%
CROSS-SECTIONAL AREA (LOWER LIMB)												
Carin-Levy 2006 (36)	Long.	18	11M, 7F Age 66.0±11.5 y PS: NR Type: NR Acute and early subacute stag	Skin fold measurements (cm²)	Thigh muscles	T_0: 7d T_1: 14d T_2: 21d	*Median (IQR)* 143.6 (118.2–169.0) 162.7 (133.4–171.7) 155.7 (113.4–157.1)	*Median (IQR)* 155.4 (123.6–187.1)† 163.2 (136.3–170.7)† 133.5 (107.2–170.7)†	T_0 vs T_1 T_1 vs T_2 T_2 vs T_3	NA (NS) NA (NS) NA (NS)	NA (NS) NA (NS) NA (NS)	22% 6% 0%
						T_3: 28d	148.2 (115.5–168.2)	152.8 (120.6–159.7)†	T_0 vs T_2 T_0 vs T_3	NA (NS) NA (NS)	NA (NS) NA (NS)	28% 28%
Carin-Levy 2006 (36)	Long.	18	11M, 7F Age 66.0±11.5 y PS: NR Type: NR Acute and early subacute stag	Skin fold measurements (cm²)	Calf muscles	T_0: 7d T_1: 14d	*Median (IQR)* 65.6 (63.0–106.7) 94.2 (83.6–101.8)	*Median (IQR)* 69.5 (64.9–105.5)† 96.7 (78.0–97.7)†	T_0 vs T_1 T_1 vs T_2	NA (NS) NA (NS)	NA (NS) NA (NS)	22% 6%
						T_2: 21d T_3: 28d	80.2 (61.1–100) 94.7 (76.7–101.5)	82.0 (60.1–101.5)† 95.6 (71.4–99.5)†	T_2 vs T_3 T_0 vs T_2	NA (NS) NA (NS)	NA (NS) NA (NS)	0% 28%
									T_0 vs T_3	NA (NS)	NA (NS)	28%
MUSCLE THICKNESS (UPPER LIMB)												
Moukas 2002 (52)	Long.	16	8M, 8F Age 61.0±11.0 y PS: NR Type: NR Acute and early subacute stage	Ultrasound imaging, M-mode, 10 MHz transducer (cm)	Elbow extensors	T_0: 1d T_1: 11d	2.21 (0.43) 1.78 (0.40)	NR NR	T_0 vs T_1	–1.01 (<0.001*)	NR	0%
MUSCLE THICKNESS (LOWER LIMB)												
Kokura 2020 (46)	Long.	57	23M, 34F Age 82.1±7.6 y PS: 29L, 28R Type: 45I, 12H Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (mm)	Knee extensors	T_0: 1d T_1: 7d T_2: 14d T_3: 21d T_4: 28d	25.6 (7.2) 23.6 (7.7) 22.6 (7.6) 22.1 (7.3) 21.3 (7.1)	25.0 (7.7) 24.4 (7.2) 23.6 (7.6) 23.5 (6.9) 23.3 (6.8)	T_0 vs T_1 T_1 vs T_2 T_2 vs T_3 T_3 vs T_4 T_0 vs T_2 T_0 vs T_3 T_0 vs T_4	–0.27 (<0.001*) –0.13 (NR) –0.07 (NR) –0.11 (NR) –0.40 (<0.001*) –0.48 (<0.001*) –0.60 (<0.001*)	–0.08 (>0.05) –0.11 (NR) –0.01 (NR) –0.03 (NR) –0.18 (<0.05*) –0.20 (<0.05*) –0.23 (<0.05*)	0% 0% 0% 0% 0% 0% 0%

Table II (Continued). Muscle size

Author (year)	Study design	n	Subject features	Measuring device (unit)	Assessed muscle group	Evaluation time	PS[a]	NPS[a]	Time point	ES PS (p-value)	ES NPS (p-value)	Drop-out ratio
MUSCLE THICKNESS (LOWER LIMB) (Continued)												
		39	19M, 20F; Age 80.8±9.8 y; PS: 22L, 17R; Type: 28I, 11H; Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (mm)	Knee extensors	T_0: 1d; T_1: 7d; T_2: 14d; T_3: 21d; T_4: 28d	26.7 (6.7); 24.4 (6.8); 23.4 (6.7); 21.7 (5.8); 21.4 (6.2)	26.4 (7.5); 24.8 (6.8); 24.2 (7.0); 23.6 (6.9); 22.6 (6.4)	T_0 vs T_1; T_1 vs T_2; T_2 vs T_3; T_3 vs T_4; T_0 vs T_2; T_0 vs T_3; T_0 vs T_4; T_0 vs T_1	−0.34 (<0.05*); −0.15 (NR); −0.27 (NR); −0.05 (NR); −0.49 (<0.001*); −0.79 (<0.001*); −0.81 (<0.001*); −0.84 (<0.001*)	−0.22 (<0.05*); −0.09 (NR); −0.09 (NR); −0.15 (NR); −0.30 (<0.001*); −0.39 (<0.001*); −0.54 (<0.001*); −0.59 (<0.001*)	0%; 0%; 0%; 0%; 0%; 0%; 0%; 0%
Nozoe 2016 (54)	Long.	31	22M, 9F; Age 70.3±12.8 y; PS: 17L, 14R; Type: 18I, 13H; Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (mm)	Knee extensors	T_0: 2d; T_1: 16d	28.0 (7.1); 22.1 (6.8)	28.6 (7.3); 24.1 (7.7)‡	T_0 vs T_1	−0.84 (<0.001*)	−0.59 (<0.001*)	0%
Nozoe 2017 (56)	CCT	10	7M, 3F; Age 63.1±11.4 y; PS: 6L, 4R; Type: NR; Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (cm)	Knee extensors	T_0: 2d; T_1: 16d	3.07 (0.60); 2.20 (0.68)	3.29 (0.59); 2.62 (0.92)	T_0 vs T_1	−1.30 (.005*)	−0.85 (.005*)	0%
Nozoe 2018 (55)	Long.	17	4M, 13F; Age 66.0±11.0 y; PS: NR; Type: NR; Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (cm)	Knee extensors	T_0: 3d; T_1: 17d	2.98 (0.72); 2.67 (0.74)	NR; NR	T_0 vs T_1	−0.41 (.001*)	NR	0%
Nozoe 2020a (57)	Long.	55	41M, 14F; Age 65.0±10.0 y; PS: 31L, 24R; Type: 27I, 28H; Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (%)	Knee extensors	T_0: 7d; T_1: 21d	$MD\ T_1-T_0\ (SD)$ −16.9 (14.7)	$MD\ T_1-T_0\ (SD)$ −11.3 (12.7)	T_0 vs T_1	NA (NR)	NA (NR)	0%
Nozoe 2020b (58)	Long.	18	14M, 4F; Age 66.3±10.3 y; PS: 7L, 11R; Type: 10I, 8H; Acute and early subacute stage	Ultrasound imaging, B-mode, 8 MHz transducer (cm)	Knee extensors	T_0: 2d; T_1: 16d	*Median (IQR)* 3.1 (1.7); 2.6 (1.4)	*Median (IQR)* 3.5 (1.4)†; 2.9 (1.4)‡	T_0 vs T_1	NA (.014*)	NA (.003*)	0%
LEAN MUSCLE MASS (LOWER LIMB)												
Jorgensen 2011 (44)	Long.	12	Not able to walk by 2 months; Acute and early subacute stage	DEXA scanner (gr)	Lower limb	T_0: 7d; T_1: 56d	6796.42 (1529.94); 6294.92 (1154.28)	6832.83 (1315.65); 6518.58 (1282.65)	T_0 vs T_1	−0.36 (<0.05*)	−0.23 (<0.05*)	11%
		13	Able to walk by 2 months; Acute and early subacute stage	DEXA scanner (gr)	Lower limb	T_0: 7d; T_1: 56d	7074.31 (1482.91); 6931.23 (1389.81)	6945.69 (1420.88); 6871.38 (1363.01)	T_0 vs T_1	−0.10 (>0.05)	−0.05 (>0.05)	11%

n: number of participants; PS: paretic side; NPS: non-paretic side; ES: effect size; Long.: Longitudinal; CCT: clinical controlled trial; M: Male; F: female; L: left; R: right; I: ischaemic; H: haemorrhagic; T: time-point of evaluation; d: mean days after stroke; NR: not reported; NS: not significant; NA: not analysed; gr: gram; Cm: centimetres; mm: millimetres; IQR: interquartile range; MD: mean difference; SD: standard deviation.
[a]Values of the paretic and non-paretic side are reported as means and standard deviations unless otherwise mentioned*Statistically significant Studies reporting differences between the paretic and non-paretic side are marked with † (no difference between both sides ($p≥0.05$)) or ‡ (significant difference between both sides ($p<0.05$)).

(32, 37, 38, 40, 47, 49, 56, 59, 63, 66, 68) or a placebo intervention combined with usual care (32, 43, 45, 51).

Patient characteristics
In total, 1,097 stroke survivors (598 males, 499 females; mean age 67 years) participated in the included studies. Muscle characteristics of the subjects were assessed in the acute and early subacute stage post-stroke (32, 33, 36, 40–42, 44, 46–48, 50, 52–54, 56–58, 66) or exclusively measured in the acute (55) or early subacute stage (Tables I and II) (31, 34, 35, 37–39, 43, 45, 49, 51, 59–65, 67, 68).

Outcome measure characteristics
Data extraction revealed 4 outcome measures of interest: muscle strength (i.e. lower limb (31, 34, 36, 49, 62, 63), upper limb (31, 33, 35, 39, 59, 61, 64, 65), grip (32, 33, 36–38, 40–43, 45, 47, 50, 51, 53, 59–61, 64, 66–68) and pinch strength (32, 48, 68)), muscle thickness (46, 52, 54–58), muscle cross-sectional area (CSA) (36) and lean muscle mass (44). No data on muscle fibre characteristics were reported. The preferred assessment tool to objectively quantify muscle strength was a hand-held dynamometer, which was used in the majority of the included studies (73%) (31–34, 36-39, 41, 42, 45, 47, 49–51, 53, 59, 62, 64, 66–68). Muscle CSA was determined via anthropometric skin fold measurements (36), whereas a Dual Energy Xray absorptiometry (DEXA) scanner and an ultrasound system were used to respectively measure lean muscle mass (44) and muscle thickness (46, 52, 54–58). The assessed muscle groups in the lower limb were hip flexors (31, 34), knee extensors (31, 34, 36, 46, 49, 54–58, 62, 63), knee flexors (49, 63) and ankle dorsiflexors (31, 34). The muscles of the upper extremity being evaluated were the shoulder abductors (31, 33, 65), adductors (65), flexors (65) and extensors (65), elbow flexors (31, 33, 35, 39, 61, 64) and extensors (31, 35, 52, 61, 64), and wrist extensors (31, 59, 61). Studies focused mainly on the evaluation of the muscle groups on the paretic side. Data of the non-paretic side were reported in less than half of the included trials (45%) (31, 34, 36, 43–46, 49–51, 53, 54, 56–58, 62–64).

Quality assessment
Fig. 2 represents a summary of the authors' judgement about each risk of bias item. Sampling bias was rated "high" in 30 studies because recruitment of the target population took place in only 1 centre or because a specific target population was recruited for the study (31, 32, 36–46, 48–52, 54–59, 61, 62, 64, 65, 67, 68). The remaining 8 studies were rated "unclear" (33–35, 47, 53, 60, 63, 66). Due to insufficiently reported information about 1 of the pre-specified confounding variables, confounding bias was rated "unclear" in 26 studies (32, 33, 35–40, 43, 44, 46, 47, 49, 50, 52, 54–60, 62, 64, 66, 68), whereas the remaining 12 studies were rated "high" because of the large age differences at study onset (31, 34, 41, 42, 45, 48, 51, 53, 61, 63, 65, 67). Performance bias was unclear in every study because there was insufficient information about the timing of the assessments during the day. Detection bias was low in 27 studies (31–34, 37–39, 41, 42, 44–47, 49–52, 54–58, 61, 64, 66–68) and unclear in the remaining 11 studies because information about the measurement device was insufficiently reported (35, 36, 40, 43, 48, 53, 59, 60, 62, 63, 65). Attrition bias was rated "low" in 15 studies (38, 40, 43, 46–51, 54, 57, 59, 60, 65, 68), "unclear" in 16 (31–35, 41, 42, 45, 52, 55, 61–64, 66, 67) and "high" in the other 7 studies (36, 37, 39, 44, 53, 56, 58). Only 6 of the included studies reported a pre-specified protocol and therefore reporting bias was rated "low" (40, 43, 45, 51, 66, 68), whereas reporting bias of the other 32 studies was rated "unclear" (31–39, 41, 42, 44, 46–50, 52–65, 67).

Synthesis of the results
The means, SDs, significance values and effect sizes of all included studies are shown in Tables I and II.
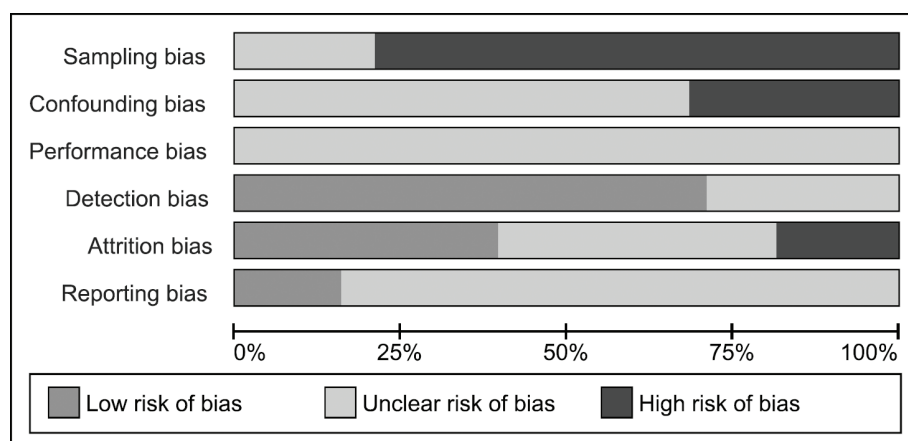

Fig. 2. Risk of bias assessment.

Twelve studies did not report mean values and SDs and were excluded from quantitative data-analysis and therefore will not be discussed in the following paragraphs (33, 35, 36, 39, 41, 42, 53, 57–61). Detailed information about these studies is reported in Tables I and II.

Muscle strength
The examined muscle groups of the lower limbs (i.e. hip flexors, knee flexors, knee extensors and ankle dorsiflexors), measured within the early subacute stage, showed a significant increase in muscle strength on the paretic side with moderate, positive effect sizes ($p < 0.05$, g_H: 0.34–0.70) (31, 34, 62, 63). A single study did not report significant changes in knee flexors and extensors, but did find a similar trend towards an increase in muscle strength over time with positive, small effect sizes (knee extensors: $p = 0.07$, g_H: 0.31; knee flexors: $p = 0.27$, g_H: 0.21) (49). Concerning the non-paretic side, muscle strength of the lower limbs significantly increased in the hip flexors ($p < 0.05$, g_H: 0.24–0.25) and ankle dorsiflexors ($p < 0.05$, g_H: 0.26–0.31) (31, 34), whilst studies that investigated the knee extensors and flexors reported mixed results ($p < 0.001$ to $p > 0.05$, g_H: 0.06–0.28) (31, 34, 49, 62, 63).

The muscle groups of the upper limbs were assessed in the early subacute stage after stroke. Studies reported a significant increase over time for elbow flexors, elbow extensors and wrist extensors on the paretic side with small to moderate effect sizes ($p < 0.001$ to $p = 0.046$, g_H: 0.17–0.40) (31, 64). Changes in muscle strength of the shoulder abductors were inconsistent between studies ($p < 0.001$ to $p > 0.05$, g_H: –0.15 to 0.28) (31, 65). The muscle groups of the shoulder flexors, extensors and adductors were examined only in a single study which showed non-significant changes over time ($p > 0.05$, g_H: –0.43 to 0.76) (65). Regarding the non-paretic side, studies reported a significant increase for the wrist extensors ($p < 0.001$, g_H: 0.23) (31), a non-significant change over time for the shoulder abductors ($p > 0.001$, g_H: 0.16) (31) and mixed results for the elbow flexors and extensors ($p < 0.05$ to $p > 0.001$, g_H: –0.05 to 0.43) (31, 64).

Studies that measured grip strength within the early subacute stage demonstrated positive effect sizes representing an increase over time. However, significance values and the size of the effects showed large discrepancies between studies measuring grip strength on the paretic side, with non-significant changes and small effect sizes being reported on the paretic side ($p > 0.05$, g_H: 0.01–0.14) (43, 45, 68), whilst other studies showed a significant increase with small to large effect sizes ($p < 0.05$, g_H: 0.25–1.16) (37, 38, 64, 67). This variability is also presented in studies evaluating grip strength changes between the acute and early subacute stage with effect sizes ranging from small to large (g_H: 0.12–0.97) and both significant (40, 50) and non-significant (32, 66) changes are found. Studies investigating grip strength on the non-paretic side showed an overall non-significant change over time, with only 1 study reporting significant changes with moderate, positive effect sizes ($p < 0.05$, g_H: 0.33–0.38) (64).

Pinch strength was examined in 1 study within the early subacute stage, which showed a non-significant change over time on the paretic side with a small effect size ($p = 0.087$, $g_H = 0.12$) (68). Two other studies reported pinch strength data assessed between the acute and early subacute stage with small to moderate positive effect sizes (g_H: 0.08–0.67) representing an increase on the paretic side ($p = 0.04$ and $p > 0.05$) (32, 48). No studies examined pinch strength on the non-paretic side.

Muscle thickness
Muscle thickness was measured in the muscle groups of the knee extensors (46, 54–57) and elbow extensors (52). Studies assessing stroke survivors between the acute and early subacute stage found a significant decrease in muscle thickness of the knee extensors on the paretic side with moderate to large effect sizes ($p < 0.001$ to $p < 0.05$, g_H: –0.40 to –1.30), whereas small to large effects were observed on the non-paretic side ($p < 0.001$ to $p < 0.05$; g_H: –0.18 to –0.85). One study reported changes in the knee extensors' muscle thickness within the acute and early subacute stage, showing a significant decrease on both sides ($p < 0.05$, g_H: –0.01 to –0.34) (46). Although the elbow extensors were only addressed in a single study, a large negative effect size was found representing a significant decrease in muscle thickness between the acute and early subacute stage ($p < 0.001$, $g_H = –1.01$) (52).

Lean muscle mass
Jorgensen et al.'s study was the only one investigating lean muscle mass in the early stage post-stroke (44). They divided the stroke population into 2 subgroups based on the subjects ambulation type. Results showed a significant decrease in lean muscle mass on the paretic and non-paretic side for patients who were not able to walk 2 months post-stroke with small to moderate effect sizes (paretic side: $p < 0.05$, $g_H = –0.36$; non-paretic side: $p < 0.05$, $g_H = –0.23$). In contrast, subjects who were ambulant after 2 months showed no significant decrease in lean muscle mass on both sides (paretic side: $p > 0.05$, $g_H = –0.10$; non-paretic side: $p > 0.05$, $g_H = –0.05$).

Cross-sectional area

Only 1 study investigated the cross-sectional area in the acute and subacute phase after stroke, using skin-fold measurements (cm^2) of the upper arm muscles, forearm muscles, tight muscles and calf muscles. No significant changes were reported between the different time-points for the paretic and the non-paretic side.

DISCUSSION

Summary of the evidence

The aim of this systematic review was to synthesize available evidence describing the time-course of peripheral skeletal muscle changes measured by objective, quantitative assessment methods in the first 3 months post-stroke.

A total of 38 studies investigating time-related changes in muscle characteristics in 4 different outcome measures were identified. In general, the results revealed an overall mean increase in muscle strength on the paretic side, whereas muscle thickness in the upper and lower limb decreased. Lean muscle mass and muscle CSA were only examined in a single study, but results showed a trend towards a decrease in lean muscle mass in the lower limbs of non-ambulant stroke survivors, whereas muscle CSA seemed to remain unchanged in the early subacute stages post-stroke. Similar results were found on the non-paretic side, but these changes were smaller compared with the paretic side.

The general increase in muscle strength in the first 3 months of stroke recovery is probably due to inpatient rehabilitation, where clinicians nowadays are using a broad range of evidence-based interventions to improve motor recovery (2). In addition, spontaneous recovery mechanisms will contribute to this early gain in muscle strength (21). Despite the overall increase in muscle strength, which might indicate early recovery, results should be interpreted with caution.

The benefits of early stroke rehabilitation are beyond doubt, yet the calculated effect sizes for muscle strength were generally small to moderate, indicating that there is still room for improvement. Moreover, an early decrease in muscle thickness was found despite participants receiving conventional therapy. This finding is in line with previous research that reported stroke-induced muscle wasting (7, 8). Moreover, it seems that this phenomenon is not only due to sarcopaenia (i.e. age-related loss of muscle mass and muscle strength) since stroke survivors show higher prevalence rates of muscle wasting compared with healthy people, even after controlling for age, sex and race (69). These results might indicate that more attention for specific therapy regimens, directly aimed at

the level of the skeletal muscle, is warranted to prevent loss of function and to optimize recovery (70).

One might question if the observed changes in muscle strength are the result of true changes in the underlying physiology and mechanical properties of the skeletal muscle or due to neural adaptation. Understanding of "how" muscle strength changes are achieved early after stroke is essential to better understand the complex stroke recovery process. Besides the increase in muscle strength, the results of this review revealed a concomitant decrease in muscle thickness, which might seem contradictory at first sight. Yet, previous research has shown that there is no one-to-one relationship between those 2 parameters, suggesting that other factors contribute to the recovery of muscle strength (71). One such factor, besides neuromuscular changes, may be the architectural properties of the skeletal muscle, which play an integer role in the force-generation process. Muscle fibre length, pennation angle and physiological CSA are deemed the most important architectural parameters and therefore, structural changes of these properties might influence force production (15). However, to the best of our knowledge, the impact of such changes on force production has not been investigated in (sub)acute stroke patients, and, therefore, this should be considered speculative and warrants further investigation. Nevertheless, previous research in chronic stroke survivors has already presented evidence that changes in the architecture of the muscle occur (i.e. decreased fibre length) and contribute to strength deficits (16), but no information for (sub)acute stroke patients is available. Only a single study measuring muscle CSA was included in this systematic review, which made it difficult to draw uniform conclusions towards its influence on recovery (36). Therefore, the structure-function relationship in the early recovery process after stroke remains unclear because no other studies investigating the architectural properties were found during the systematic search of this review.

Furthermore, the results reported by the included studies were highly variable, with effect sizes ranging from small to large and noticeable discrepancies in the significance values. This heterogeneity is likely due to researchers using different measurement tools, units, and procedures to address their outcome measure and variable time-windows to assess muscle changes. In addition, stroke research has shown that recovery profiles vary greatly between individual stroke survivors (72). This might raise the question of whether different processes underlie recovery for subjects recovering better and faster compared with others. Indeed, the results reported by all of the included studies are summarized values (e.g. means) which represent stroke recovery at group level. However,

with the different recovery profiles in mind, it might be interesting to closely observe individual muscle changes rather than focusing on the group level. Although none of the trials in this systematic review statistically established these individual muscle trajectories, some of the authors plotted individual data in figures (39, 55) or additional tables (50). Cortes et al., for example, illustrated the time-course of biceps muscle strength for each individual stroke participant (39). This figure shows a clear diversity in the recovery patterns of stroke survivors and confirms that not every patient has the same potential to recover after a stroke incident. Knowledge of the underlying mechanisms contributing to this large recovery variability within the stroke population is fundamental for both research and clinical practice. The possibility to distinguish subgroups within a certain population would make it easier to select a specific group for testing a given treatment or personalize therapeutic stroke interventions (4, 73).

Study limitations

This systematic review has a number of limitations. An important key issue was the large variability between the included studies, which made it difficult to compare results. By dividing the time after stroke into clear cut-off phases, as suggested by the Stroke Consortium (4), we tried to facilitate comparison. However, timing of the measurements regarding stroke onset differed greatly between the included studies. Research has shown that most recovery occurs in the first 3 months post-stroke, but knowledge about the exact time-window during which muscle-related recovery takes place remains unclear.

Another constraint was the sources of bias in the included trials. The overall high risk of sampling bias is important to consider, since most studies recruited participants in only 1 centre or recruiting a specific target population (e.g. subjects with low baseline strength). Although the patient's baseline level of functioning and stroke severity were not taken into account in this systematic review, it might be noticed that this will probably have clinical implications towards the reported muscle changes. In stroke recovery, a rule of thumb is that subjects with initially more severe deficits are less likely to make a good recovery. However, not every patient seems to fit this proportional recovery rule (74). This once again highlights the importance of reporting individual changes over time and the need to specify clear subgroups in stroke survivors.

Furthermore, the pre-specified confounding variables were insufficiently reported in most studies, especially nutrition, smoking and physical activity status, which could result in a potential bias as these confounding factors might have an influence on muscle changes post-stroke.

Finally, studies that used surface electromyography as a measuring device to assess muscle activity were excluded from this systematic review because data are likely to be influenced by the position of the electrodes, the analysis methods, rapportage of the results, which would complicate comparison between studies (75). However, the results of these measurements could be of important clinical relevance and might therefore be an interesting topic for future research.

Future research

This review gathered all information about skeletal muscle changes in the acute and early subacute stroke population, yet it also uncovered important shortcomings in the existing stroke literature that should be considered in future research about this topic.

First, this review identified a lack of studies investigating architectural properties in the first 3 months after stroke. Future studies addressing these outcome measures are recommended, as they might help to better understand the recovery process.

Secondly, standardized time-intervals to assess post-stroke muscle changes are lacking and causing a large heterogeneity between studies. Although the time after stroke was divided into phases in this review, the evaluation time-points did not entirely fit into these clear-cut sequences. Defining critical time-points in stroke rehabilitation to explore muscle trajectories in a uniform matter and to determine the optimal timing to implement interventions is recommended.

Thirdly, muscle changes are only reported at group level. Since stroke patients show an individual recovery pattern, it seems advisable to report individual muscle trajectories rather than trajectories at group level. Research into those individual trajectories would make it possible to define subgroups within the stroke population for research or clinical purpose and might permit future research to investigate the effects of interventions tailored to these specific patient profiles.

Finally, potential confounding factors, which might have an influence on peripheral muscle changes, were only taken into account to a limited extent. A number of these confounding factors are already proposed in this review within the context of confounding bias and based on experts' advice (e.g. age, nutrition, physical activity) (Appendix 2). These suggested confounding factors are not exhaustive and should be further explored in future research.

CONCLUSION

Skeletal muscle changes in the first 3 months of stroke recovery show a clear trajectory at the group level on the paretic side, with an increase in strength (muscle strength, grip strength and pinch strength) and a decrease in muscle thickness, whereas lean muscle mass and muscle CSA were insufficiently investigated to draw firm conclusions. More attention on specific therapy regimens, directly aimed at the skeletal muscle, is warranted to prevent loss of function and to optimize recovery post-stroke. Understanding of "how" muscle strength changes are achieved early after stroke could lay important foundations for advances in future stroke rehabilitation interventions.

The authors have no conflicts of interest to declare.

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