

Research Article

Children's growth and motor development following a severe burn: a systematic review

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Abstract

Background: The epidemiological data on post-burn growth, body composition and motor development is ambiguous and scattered. The aim of this systematic review was therefore to summarize the current body of evidence on post-burn growth, body composition and motor development in children.

Methods: A literature search was conducted in PubMed, EMBASE and Web of Science up to March 2021. We considered observational studies that reported (1) metrics on weight, height, body composition, bone mineral content, bone mineral density or motor development, in (2) paediatric burn patients and (3) published in a peer-reviewed journal.

Results: A total of 16 studies were included. Each of the included studies used quantitative methods, but with differing methodology: prospective cohort studies ($n=8$), retrospective chart reviews ($n=3$), case-control studies ($n=2$), cross sectional studies ($n=2$) and a retrospective cohort study ($n=1$). When combined, the included studies represented 2022 paediatric burn patients, with a mean age of $7.7 (\pm 3.2)$ years. The average burn size was $52.8\% (\pm 12.7\%)$ of the total body surface area. Identified outcome measures included weight ($n=12$), height ($n=7$), muscular strength ($n=4$), bone mineral content ($n=5$), bone mineral density ($n=5$), body mass index ($n=3$), fat mass ($n=5$), lean body mass ($n=7$) and fine and gross motor development ($n=1$).

Conclusions: Following an initial decline, patients' growth and motor development started to recover during the first or second year post-burn. Nonetheless, burns may have a profound and prolonged effect on the paediatric burn patients' muscular strength, bone mineral content and lean body mass. It should be noted that the vast majority of studies included only patients with burns covering $\geq 30\%$ total body surface area. The evidence presented in this review may thus not be representative of the whole paediatric burn population.

Key words: Burns, Children, Weight, Height, Bone, Muscle, Motor function

Highlights

- Given the average burn size of 52.8% ($\pm 12.7\%$) total burn surface area, the evidence presented in this review was not representative of the whole paediatric burn population.
- Following an initial decline, patients' growth and motor development started to recover during the first or second year post-burn.
- Further research is needed to establish the effect of less extensive burn injuries on paediatric burn patients' growth and motor development.

Background

Burns are prevalent, representing the fifth most common cause of non-fatal injuries in children worldwide [1]. Severe burns induce a hypermetabolic state where the release of stress hormones and pro-inflammatory mediators leads to an increase in heart rate, blood pressure, respiratory rate, glucose consumption, peripheral insulin resistance, glycogenolysis, proteolysis and futile substrate cycling [2,3]. This hypermetabolic state typically commences after 72–96 h and can persist up to 36 months after the initial burn [4,5]. It is the magnitude and long-term persistence of the hypermetabolic state that makes it stand out from a similar response in patients suffering trauma or critical illness [3].

Increased energy expenditure during the hypermetabolic state leads to whole-body catabolism. In paediatric patients, this raises questions regarding the short- and long-term effects on body composition, growth and motor development. Back in 1990, Rutan and Herndon first reported growth arrest in paediatric patients who had sustained burns $>40\%$ of the total body surface area (TBSA) [6]. This growth arrest was most profound during the first year post-burn, resolving to near normal after 3 years. Numerous studies have since reported on the effect of burns on paediatric patients' body composition, growth and motor development [2,7–10].

However, the epidemiological data on post-burn growth, body composition and motor development is ambiguous and scattered. The aim of this review was therefore to summarize the current body of evidence on these three factors in children.

Methods

This study is reported following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement of 2009 [11]. The protocol was registered to the International Prospective Register of Systematic Reviews (PROSPERO) on 18 February 2021 (ID: CRD42021229499).

Search strategy

A comprehensive search was performed in PubMed, EMBASE and Clarivate Analytics/Web of Science Core Collection from inception to March 2021, in collaboration with a medical information specialist (JCFK). The search included controlled terms and free text terms for synonyms of 'children' or 'infants' or 'paediatric' combined with synonyms of 'burns' and 'growth' or 'body composition' or 'anthropometry' or

'motor skills'. The search was performed without restrictions for methodology, date or language. The full search strategies can be found in supplementary Tables 1–3 (see online supplementary material). Reference lists of included studies were screened for relevant studies that may have been missed by the search.

Study selection

We considered observational studies that reported (1) metrics on weight, height, body composition, bone mineral content (BMC), bone mineral density (BMD) or motor development, in (2) paediatric burn patients and (3) published in a peer-reviewed journal. Language restrictions were set to English and Dutch. Intervention studies, case reports, case series, reviews, comments, letters and studies conducted in animals or adult subjects (≥ 18 years old) only were excluded. Screening based on title, abstract and full-text was conducted independently by two investigators (MDC, MGAB), including one content expert (MGAB). Investigator disagreements about article eligibility were resolved through discussion with a third investigator (AP). The screening procedure was conducted with the use of the web-based platform RAYYAN (<https://www.rayyan.ai>).

Risk of bias assessment

For all included studies, the risk of bias was examined by two independent investigators (MDC, MGAB) using the Newcastle–Ottawa Quality Assessment Scale for case control and cohort studies [12]. A study could be awarded a maximum of one star for each item within the selection and exposure categories. A maximum of two stars could be awarded for comparability. The overall rating was used as an indication of a study's quality and overall certainty of evidence.

Data extraction and analysis

Data was extracted using a standardized data extraction method adapted from the Cochrane Collaboration model (MDC, MGAB). The extracted data included information about the (1) setting; (2) methods: study aim, study design, study period; (3) characteristics of the study population: inclusion and exclusion criteria, sample size, age distribution, sex, TBSA burned, TBSA full-thickness burned, aetiology, drug therapies, (rehabilitative) exercise and nutritional support; and (4) outcome measures.

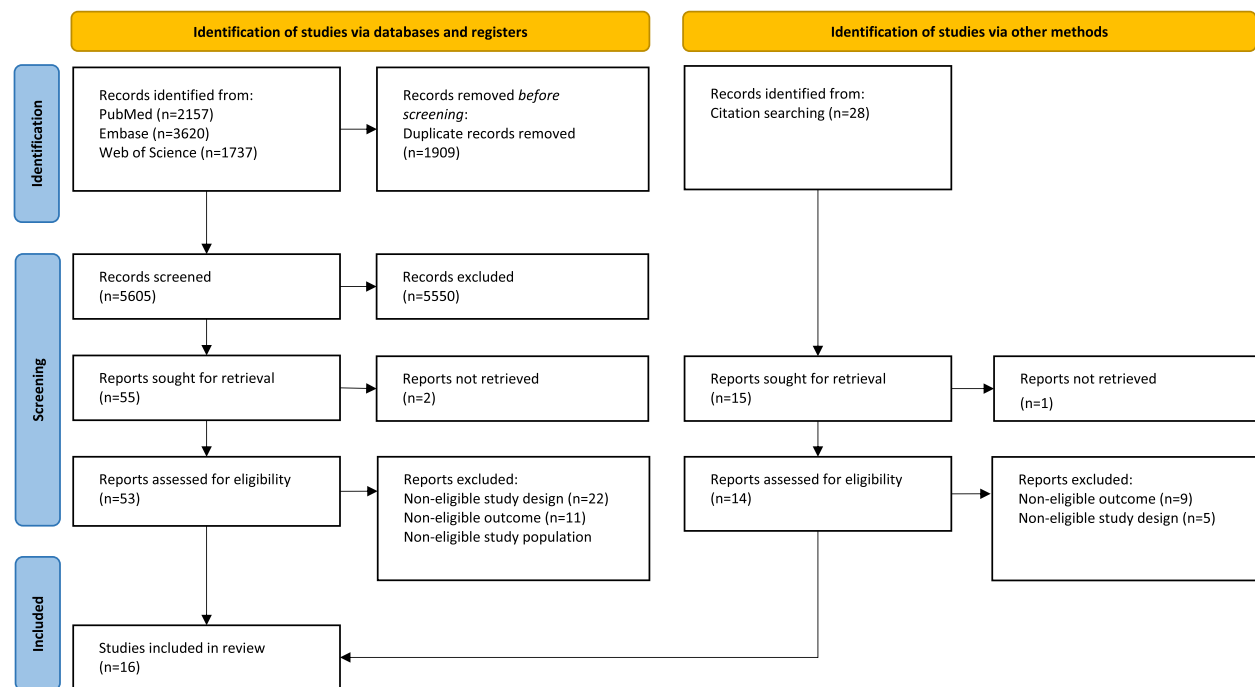


Figure 1. PRISMA 2020—flow diagram

Identified outcome measures were categorized as weight, height, muscular strength, bone, body composition and motor development. A list of all identified outcome measures and their corresponding measurement units is available in supplementary Table 4 (see online supplementary material). Common outcome measures included Z-scores and percentiles. A Z-score represents the number of standard deviations between an observation and the mean of the population. A percentile is the value below which a given percentage of observations falls; the 50th percentile represents the median of the population.

The extracted data did not allow for meta-analysis due to considerable heterogeneity in outcome measures, measurement units and methodology. Instead, the extracted data was analysed using narrative analysis.

Results

Study selection

The systematic literature search identified a total of 7514 records across PubMed ($n = 2157$), Embase ($n = 3620$) and Web of Science ($n = 1737$). After de-duplication, a total of 5605 records remained, from which 55 underwent full-text screening following the review of titles and abstracts. Reasons for exclusion during full-text screening included (1) non-eligible study design ($n = 22$), (2) non-eligible outcome measure ($n = 11$), (3) non-eligible study population ($n = 4$), and (4) no full-text available ($n = 2$). Following full-text screening, an additional 28 records were identified from the reference lists of included studies by manual search. Of these, 13 records were excluded based on the title and abstract. The remaining

15 records were excluded during full-text screening, based on: (1) non-eligible outcome measures ($n = 9$), (2) non-eligible study designs ($n = 5$), or (3) the full-text was not available ($n = 1$). Figure 1 shows the flow diagram for the study selection process.

Study characteristics and quality

A total of 16 records met the previously mentioned eligibility criteria (Table 1). All studies were published in English between 1990 and 2021. The majority of studies originated from the USA ($n = 13$; 81%), specifically the Shriners' Burns Hospital for Children in Galveston, TX. Each of the included studies used quantitative methods, but with differing methodology: prospective cohort studies ($n = 8$), retrospective chart reviews ($n = 3$), case-control studies ($n = 2$), cross sectional studies ($n = 2$) and a retrospective cohort study ($n = 1$). The number of participants in the reviewed studies ranged from 21 to 977.

When combined, the included studies represented 2022 paediatric burn patients, with a mean age of $7.7 (\pm 3.2)$ years (Table 2). In total, 13 out of 16 studies concerned only patients with severe burns; defined by the American Burn Association as burns covering $>10\%$ TBSA in children aged <10 years old, $>20\%$ TBSA in children aged ≥ 10 years old, or full-thickness burns covering $>5\%$ TBSA [13]. Consequently, the average burn size was $52.8\% (\pm 12.7)$ TBSA, with an average full-thickness burn of $38.8\% (\pm 20.1)$ TBSA (Table 2). Four studies reported the administration of anabolic or anticatabolic agents [2,9,14,15], two of which disclosed that patients previously or concurrently participated in clinical trials or rehabilitative exercise programmes [14,15].

Table 1. Characteristics of included studies

Author	Year	Country	Setting	Study design	Inclusion criteria	Exclusion criteria	Controls	Sample size (n)	
								Patients	Controls
Alloju <i>et al.</i> [8]	2008	USA	Hospital Post-discharge	Case-control study	Subjects (1) aged 6–17 years old; (2) with a burn covering $\geq 40\%$ TBSA.	(1) Leg amputation; (2) anoxic brain injury; (3) psychological disorders; (4) quadriplegia; (5) severe behaviour or cognitive disorders.	Age-matched non-burned children	33	46
Cambiaso-Daniel, <i>et al.</i> [15]	2017	USA	Hospital	Retrospective chart review	Subjects (1) with a hospital admission between 2000–2015; (2) with a burn covering $\geq 30\%$ TBSA; (3) with a body composition scan (DEXA) during their acute hospital admission; (4) with a burn including at least one side of the upper and lower extremity.	Subjects (1) who received anabolic agents, including growth hormone and oxandrolone; (2) who underwent early exercise interventional programmes; (3) without a body composition scan (DEXA) within 2 weeks before discharge, or at least 2 weeks between admission and discharge scans.	–	24	–
Cambiaso-Daniel <i>et al.</i> [14]	2018	USA	Post-discharge	Case-control study	Subjects (1) aged > 7 years old; (2) with a burn covering $> 30\%$ TBSA; (3) who participated in a rehabilitative exercise training programme of 6 or 12 weeks.	Subjects with (1) non-thermal injuries; (2) amputation of extremities.	Non-burned children	40	40
Childs <i>et al.</i> [16]	1990	UK	Hospital	Prospective cohort study	Subjects with a burn covering $> 10\%$ TBSA.	–	–	21 ^a	–
Disseldorp <i>et al.</i> [17]	2015	NL	Post-discharge	Cross-sectional study	Subjects (1) aged 6–17 years old; (2) admitted to a Dutch burn centre between 0.5–5 years ago; (3) with a burn covering $\geq 10\%$ TBSA, or a length of stay of > 6 weeks.	Subjects with (1) extensive pre-existing comorbidity or mental disability; (2) insufficient Dutch language proficiency.	Age- and sex-matched norm values	24	–
Hart <i>et al.</i> [18]	2000	USA	Post-discharge	Prospective cohort study	Subjects (1) aged < 18 years old; (2) with a burn covering $> 40\%$ TBSA; (3) who received acute burn treatment at Shriners' Burns Hospital, Galveston. Subjects who have provided consent to return at 6, 9, and 12 months post-burn.	–	–	25	–
Jeschke <i>et al.</i> [5]	2011	USA	Hospital Post-discharge	Prospective cohort study	Subjects (1) with a burn covering $> 30\%$ TBSA; (2) admitted to Shriners' Burns Hospital for Children between 1998–2008; (3) who required at least one surgical intervention; (4) who consented to the approved experimental study protocol.	–	Non-burned children	977	–
Kazis <i>et al.</i> [22]	2016	USA	Post-discharge	Prospective cohort study	Subjects (1) aged < 5 years old; (2) with a burn covering $> 20\%$ TBSA; (3) with a burn of any size to a critical area, such as face, hands, feet, or genitalia.	–	Non-burned children or infants recruited from well-baby clinics and other paediatric settings	336	285

(Continued)

Table 1. Continued

Author	Year	Country	Setting	Study design	Inclusion criteria	Exclusion criteria	Sample size (n)	
							Patients	Controls
Klein <i>et al.</i> [9]	1995	USA	Hospital	Prospective cohort study	Subjects with a burn covering $\geq 40\%$ TBSA.	–	24	29
							Non-burned children aged 2.5–18.0 years old who had received oral tetracycline and then underwent elective orthopaedic surgery.	
Klein <i>et al.</i> [10]	1995	USA	Hospital	Cross-sectional	–	–	68	–
Mittendorf <i>et al.</i> [7]	1995	USA	Post-discharge Hospital	Retrospective cohort study	Subjects (1) aged between 2–16 years old; (2) with a burn covering 40–90% TBSA.	–	13	14
			Post-discharge				Burn subjects who decreased their weight for height during the first year of follow-up	
Prelack <i>et al.</i> [19]	2007	USA	Hospital	Retrospective chart review	Subjects (1) admitted to Shriners Burns Hospital for Children between 1970–1995; (2) aged > 1 month and < 13 years old; (3) with a burn covering $> 30\%$ TBSA; (4) in need of ≥ 3 hospital admissions for reconstructive surgery after the initial admission.	Subjects [(1) with pre-existing medical conditions, such as inborn errors of metabolism, malabsorptive conditions, or kidney, cardiac, or other major organ disease that might have a negative impact on growth; (2) who resided in a foreign country; (3) amputation of the lower limbs.	159	–
Przkora <i>et al.</i> [2]	2006	USA	Post-discharge	Prospective cohort study	Subjects (1) aged < 18 years old; (2) with a burn covering $\geq 40\%$ TBSA; (3) available for studies after hospital discharge.	–	25	20
Przkora <i>et al.</i> [20]	2008	USA	Post-discharge	Prospective cohort study	Subjects (1) aged ≤ 18 years old; (2) with a burn covering $\geq 40\%$ TBSA; (3) who are available for follow-up starting at hospital discharge, 6, 9, 12, 18, and 24 months post-burn.	–	9	15
							Burn subjects aged 4–17.9 years old at baseline	
Rutan <i>et al.</i> [6]	1990	USA	Hospital	Retrospective chart review	Subjects (1) admitted to Shriners Burns Hospital for Children between 1982–1986; (2) aged > 2 years old; (3) with a thermal burn covering $> 40\%$ TBSA, with $> 10\%$ TBSA full-thickness.	–	80	–
							Age- and sex-matched norm values	
Windle <i>et al.</i> [21]	2004	UK	Hospital	Prospective cohort study	Subjects (1) with a thermal injury; (2) who got referred for nutrition support between 2001–2003.	Subjects who (1) did not survive; (2) had incomplete weight or height data and suspicion of weight inaccuracy; (3) had limb amputation during hospital stay.	22	–

NL the Netherlands, TBSA total body surface area, DEXA dual energy X-ray absorptiometry

^aChilds C. *et al.* studied a group of children during their hospital stay (n = 11) and a group of children attending the outpatient clinic (n = 10). Some of the children who were included in the study during their hospital, were also included in the group of children attending the outpatient clinic. So, the sample size of n = 22 did not constitute of unique cases.

Table 2. Characteristics of the study population

Study	Male, n (%)	Age, mean (SD)		TBSA burned, mean (SD)	Full-thickness burn, mean (SD)	Aetiology (%)	Drug therapies ^a	Rehabilitative exercise ^b	Nutrition support
		Patients	Controls						
Alloju <i>et al.</i> 2008 [8]	25 (75.0)	24 (52.0)	11.8 (3.4)	12.1 (2.6)	56.0 (15.0)	–	–	–	–
Cambiaso-Daniel <i>et al.</i> 2017 [15]	18 (75.0)	–	10.0 (5.0)	–	59.0 (17.0)	–	Yes	–	Yes
Cambiaso-Daniel <i>et al.</i> 2018 [14]	14 (35.0)	14 (35.0)	13.2 (2.9)	–	49.0 (15.0)	–	Yes	Yes	–
Childs <i>et al.</i> 1990 [16]	7 (64.0)	–	5.26 (4.2)	–	25.8 (14.6)	Scald (64.0)	–	–	Yes
Disseldorp <i>et al.</i> 2015 [17]	14 (58.3)	–	11.3 (–)	–	18.1 (–)	–	–	–	–
Hart <i>et al.</i> 2000 [18]	15 (60.0)	–	7.6 (1.5)	–	64.5 (12.9)	–	–	–	–
Jeschke <i>et al.</i> 2011 [5]	627 (64.0)	–	7.5 (5.3)	–	50.0 (20.0)	Flame (74.0) Scald (21.0) Other (25.0)	–	–	Yes
Kazis <i>et al.</i> 2016 [22]	196 (58.4)	139 (48.9)	2.0 (1.2)	2.4 (1.3)	18.0 (18.1)	Scald (59.3) Flame (22.5) Contact (14.7) Electrical (0.6) Chemical (0.0) Other (3.0)	–	–	–
Klein <i>et al.</i> 1995 [9]	17 (71.0)	–	11.5 (3.6)	–	63.0 (16.0)	–	Yes	–	Yes
Klein <i>et al.</i> 1995 [10]	38 (55.9)	–	8.0 (2.4)	–	–	–	–	–	Yes
Mittendorfer <i>et al.</i> 1995 [7]	10 (76.9)	9 (64.3)	9.7 (1.1)	5.6 (1.2)	59.0 (3.4)	–	–	–	–
Prelack <i>et al.</i> 2007 [19]	73 (46.0)	–	5.3 (3.3)	–	54.5 (19.5)	46.3 (23.7)	–	–	–
Przkora <i>et al.</i> 2006 [2]	17 (68.0)	12 (60.0)	9.3 (5.6)	11.3 (2.8)	64.0 (15.0)	53.0 (24.0)	–	–	–
Przkora <i>et al.</i> 2008 [20]	7 (77.8)	11 (73.3)	2.2 (0.7)	10.9 (5.2)	57.0 (11.0)	41.0 (19.0)	Yes	–	–
Rutan <i>et al.</i> 1990 [6]	51 (63.8)	–	8.6 (4.1)	–	60.0 (15.0)	46.0 (24.0)	–	–	Yes
Windle <i>et al.</i> 2004 [21]	10 (44.4)	–	3.0 (–)	–	20.4 (11.8)	7.6 (9.7)	–	–	Yes

SD standard deviation, TBSA total body surface area
^aStudies reported the administration of propranolol, oxandrolone, recombinant human growth hormone, glucagon-like peptide, fenofibrate, ketoconazole, and metformin ^bStudies reported the participation in a 6–12-week rehabilitative exercise programme

Table 3. Assessment of risk of bias

Study	Selection	Comparability	Outcome	Total no. of stars
Alloju <i>et al.</i> 2008 ^a [8]	★★★	★★	★★	★★★★★★
Cambiaso-Daniel <i>et al.</i> 2017 [15]	★★	★	★★★	★★★★★★
Cambiaso-Daniel <i>et al.</i> 2018 ^a [14]	★★	★★	★★	★★★★★★
Childs <i>et al.</i> 1990 [16]	★★	–	★★	★★★★
Disseldorp <i>et al.</i> 2015 [17]	★★★★	–	★★	★★★★
Hart <i>et al.</i> 2000 [18]	★★★★	–	★★★	★★★★★★
Jeschke <i>et al.</i> 2011 [5]	★★★★	–	★★	★★★★
Kazis <i>et al.</i> 2016 [22]	★★	★★	★	★★★★
Klein <i>et al.</i> 1995 [9]	★★★★	★	★★★	★★★★★★
Klein <i>et al.</i> 1995 [10]	★★	★	★	★★★★
Mittendorfer <i>et al.</i> 1995 [7]	★★	★	★★	★★★★
Prelack <i>et al.</i> 2007 [19]	★★	★	★★	★★★★
Przkora <i>et al.</i> 2006 [2]	★★	–	★★★	★★★★
Przkora <i>et al.</i> 2008 [20]	★★	–	★★	★★★★
Rutan <i>et al.</i> 1990 [6]	★★★★	★	★★	★★★★★★
Windle <i>et al.</i> 2004 [21]	★★★★	–	★★	★★★★

Note: a study could be awarded a maximum of one star for each item within the selection and exposure categories. A maximum of two stars could be awarded for comparability. The maximum number of stars in total is nine.

^aCase-control study

Results from the risk of bias assessment are summarized in Table 3. Based on the Newcastle–Ottawa Quality Assessment Scale, the included studies were of moderate quality with an overall rating between 4 and 7 out of 10.

Weight

Weight was reported as Z-score(s) ($n=2$), (kilo)grams ($n=4$), percent change ($n=4$), number of subjects who increased or decreased their weight ($n=1$), and the prevalence of low and stunted weight ($n=2$). Comparisons were drawn with admission values, non-burned peers, different age group(s), different time interval(s) or paediatric burn subjects with a burn covering $\geq 40\%$ of TBSA [2,5–7,14–21].

There was no statistically significant difference in weight between paediatric burn subjects and non-burned peers following discharge and up to 10 years post-burn [5,17,19]. This may be dependent on burn size, as Prelack *et al.* demonstrated significantly lower weight-for-age Z-scores in subjects with a burn covering $\geq 40\%$ of TBSA during the first 1.5 years post-burn [19].

During hospital stay, subjects' weight reduced by 1–15.7% [15,16,21]. In accordance, Jeschke *et al.* and Rutan and Herndon reported a significant increase in subjects who fell below the median weight following admission and up to 3 years post-burn ($p \leq 0.05$) [5,6]. The prevalence of stunted weight ($\leq -2SD$) also showed a transient but significant increase at 1 year post-burn [6].

Hart *et al.* reported no significant change in weight throughout 12 months of follow-up among 25 subjects with burn covering $\geq 40\%$ of TBSA. This included a lack of weight gain that is to be expected with children's natural development and growth [18].

Depending on age, it took >1 year for paediatric burn subjects to significantly improve their weight following a

burn [2,5–7,20]. According to Mittendorfer *et al.*, subjects below the age of 8 years were more prone to net weight loss ($p < 0.05$), whereas subjects above the age of 8 years were more prone to weight gain, including during the first year post-burn. Observed early weight gain led to continuous weight gain, followed by overweight [7].

Height

Among the seven studies that reported on height, measures included Z-score(s) for age ($n=1$), percentile(s) for age ($n=2$), height in centimetres ($n=2$), percent change ($n=2$) and the prevalence of low and stunted height ($n=2$) [2,5,6,14,17,19,20].

There was no statistically significant difference in height between paediatric burn subjects and non-burned peers from discharge up to 5 years after burn [14,17]. Even though one study did report a significant deviation in height, the authors suggested this may have been due to a faulty reference population [19].

However, there are indications that paediatric burn subjects experience growth deceleration [5,6,19]. Among the included studies, 36.0–55.0% of paediatric burn subjects fell below the median height-for-age at admission. This group increased to 69.0–76.0% at 1 year post-burn, 75.0–76.0% at 2 years post-burn and 40.0–70.0% at 3 years post-burn [5,6]. Prelack *et al.* reported a significant decrease in height-for-age Z-scores from 6 months up to 5 years after burn, resulting in a moderate height deficit of 1.6–5.8 cm, depending on the subject's age [19].

Moreover, Rutan *et al.* reported a significant increase in the prevalence of stunted growth among paediatric burn subjects, from 3.0–10.0% at admission to 30.0–41.0% at 1–2 years after burn. At 3 years after burn, the prevalence of stunted growth among paediatric burn subjects varied from

8.0 to 20.0% [6]. Similarly, Prelack *et al.* observed stunted growth in 17 out of 159 (10.7%) paediatric burn subjects [19].

Two studies demonstrated that paediatric burn subjects' growth improved at ~1–2 years after burn [2,5]. Whether and when subjects completely restore their growth may be dependent on age and burn size. Infants and toddlers showed a significantly higher increase in height when compared to older children [20], whereas paediatric burn subjects with burns covering $\geq 50\%$ of their TBSA, did not completely restore their growth Z-score throughout 10 years of follow-up [19].

Muscular strength

Muscular strength was assessed using isokinetic dynamometry and reported as peak torque (N) (Nm), total work (J) and Z-score(s) [8,14,17]. According to Alloju *et al.* and Cambiaso-Daniel *et al.*, paediatric burn subjects generated significantly lower peak torque in comparison to their non-burned peers at discharge, 3 months, 6 months and 3.5 years post-burn, with lean body mass-normalized peak torque values being at 60–85% relative to their non-burned peers [8,14]. However, peak torque values reported by Disseldorp *et al.* were below the norm but within normal ranges and were not statistically significant at an average of 3 years post-burn [17].

Similarly, paediatric burn subjects generated significantly lower total work values with total work among paediatric burn subjects (46.9 J) being at 55.5% relative to their non-burned peers at 6 months post-burn [8].

BMC

BMC was reported in mean (kilo)grams ($n=4$) and percentages ($n=2$), compared to admission values, non-burned peers and different age group(s) [2,5,14,15,20]. BMC was estimated using the dual-energy X-ray absorptiometry method (DEXA).

Relative to their non-burned peers, paediatric burn patients' BMC remained significantly decreased up to 3.5 years after burn [2,5,14]. Cambiaso-Daniel *et al.* observed a decrease in BMC of 9.0% ($p=0.12$) during the subjects' hospital stay, with an average time between DEXA scans of 34 days [15]. Following discharge, BMC did not increase significantly until the second year after burn [2,20]. In subjects aged 4–17.9 years old, BMC increased significantly more slowly, indicating that the recovery of BMC was dependent on the subject's age [20].

BMD

BMD was reported as Z-score(s), (g/cm^2) and the prevalence of an age-related Z-score below -1 and -2 . Comparisons were made with admission values, non-burned peers and norm values. BMD was estimated using DEXA [5,9,10,14,15].

The comparison of bone mineral density among paediatric burn patients and their non-burned peers remained inconclusive [5,9,14,15]. During hospital admission, Cambiaso-Daniel *et al.* observed a decrease in BMD of 7.0% ($p=0.14$)

during the subjects' hospital stay [15]. Similarly, Klein *et al.* demonstrated an increased prevalence of low and very low BMD among moderately burned ($<40\%$ TBSA) and severely burned ($\geq 40\%$ TBSA) paediatric burn subjects during hospital admission and following discharge. Among moderately burned subjects, the prevalence of an age-related Z-score below -1 and -2 was 31% ($p < 0.005$) and 6%, respectively. Among severely burned patients, the prevalence of an age-related Z-score below -1 and -2 was 60% ($p < 0.005$) and 27% ($p < 0.005$), respectively [10].

Body mass index

Body mass index (BMI) was reported as Z-score(s), ($\text{kg}/\text{height}^2$) or percentile(s), compared to non-burned peers and reference values [14, 17] or mean BMI over time [18]. Studies observed no significant deviations from reference values and non-burned peers from discharge until 5 years after burn [14,17]. In addition, within patients, BMI did not statistically significantly change over time [18].

Fat mass

Fat mass was reported as local fat mass in (kilo)grams ($n=1$), total fat mass in (kilo)grams ($n=3$) and change in fat mass ($n=3$), compared to non-burned peers, different age group(s) or different time interval(s) [5,14,15,18,20]. Fat mass was estimated using DEXA.

Two studies reported an increase in total fat mass between the time of injury and discharge ($p < 0.001$) [15], and between discharge and 3.5 years after burn ($p < 0.05$) [14]. On the other hand, results by Jeschke *et al.* and Hart *et al.* indicated that total fat mass did not significantly change over time [5,18].

Jeschke *et al.* also showed that throughout a 3-year follow-up period, the fat mass of study participants ($n=977$) was significantly lower compared to non-burned peers ($p < 0.05$) [5]. One study showed that the effect of burns on total fat mass did not differ across age categories ($p=0.19$) [20].

Lean body mass

Lean body mass was reported as local lean body mass in (kilo)grams ($n=2$), total lean body mass in (kilo)grams ($n=4$) and change in lean body mass ($n=4$), compared to non-burned peers, different age group(s) or different time interval(s) [2,5,8,14,15,18,20].

Four studies compared total lean body mass in paediatric burn subjects to non-burned peers, and each observed a significant decrease in lean body mass varying from 6 months until 3.5 years after burn [2,5,8,14]. Serial DEXA measurements indicated a loss of lean body mass from admission until 9 months after burn [15,18,20]. From 9–24 months, subjects gained lean body mass [2,18,20]. This may be dependent on the subjects' age. Przkora *et al.* compared the change in lean body mass in subjects aged <4 years old to subjects aged ≥ 4 years old. Infants and toddlers did not gain lean body mass until 12 months after burn, whereas subjects aged ≥ 4 years

old started gaining lean body mass from 6 months after burn onwards [20].

Fine and gross motor development

One study reported on fine and gross motor development following a burn in 336 paediatric patients up to 5 years old [22]. During the follow-up period of 48 months, fine and gross motor development were estimated using the Burns Outcome Questionnaire (BOQ) and compared to age-matched non-burned reference values. Note that higher BOQ scores indicate better functioning.

Initially, fine motor skills (49.8; 95% confidence interval [48.7–50.9]) was the least affected of all BOQ domains. Fine motor development improved over time and, regardless of burn size, the greatest change occurred in the first few months. However, burn size did affect the predicted recovery scores. In patients with a burn covering $\geq 20\%$ TBSA, the predicted recovery score was significantly lower ($p = 0.001$). Consequently, despite showing improvement, patients with a burn covering $\geq 20\%$ TBSA never reached the fine motor function of non-burned peers.

Gross motor development improved exponentially over time. In patients with a burn covering $< 20\%$ TBSA, gross motor development may even approach the functional level of non-burned peers. However, in patients with TBSA $\geq 20\%$, the predicted recovery scores were significantly lower ($p < 0.001$), whereas the rate of recovery was significantly higher ($p = 0.03$). Similar to fine motor development, patients with a burn covering $\geq 20\%$ TBSA never reached the gross motor function of non-burned peers.

Discussion

The current paper provides the first systematic overview of post-burn growth and motor development in paediatric patients. Evidence on the effect of a burn on paediatric burn patients' growth and motor development was limited. Overall, 16 studies met our inclusion criteria, 8 of which had a prospective study design. The vast majority of included studies were conducted in paediatric patients with extensive burns only (TBSA $> 30\%$). Unfortunately, we were unable to conduct a meta-analysis due to considerable heterogeneity in outcome measures, measurement units and methodology. Nevertheless, some trends could be noted.

Paediatric burn patients tended to decrease both their height- and weight-percentile following admission and up to several years post-burn. Depending on age, it took > 1 year for paediatric burn patients to significantly improve their height- and weight-percentile. Corresponding to this pattern, both Przkora *et al.* and Jeschke *et al.* documented elevated resting energy expenditure up to 24 and 36 months post-burn, respectively [2,5]. This physiological alteration was representative of a persistent hypermetabolic response. Nevertheless, there was no statistically significant difference in height and weight between paediatric burn patients and non-burned peers.

Two out of three studies reported significantly lower muscular strength among paediatric burn patients compared to non-burned peers [8,14]. However, one study by Disseldorp *et al.* reported that paediatric burn patients' muscular strength was below the norm but within the normal range at an average of 3 years post-burn [17]. It can be assumed that the paediatric burn patients included by Disseldorp *et al.* had greater muscular strength owing to a smaller average burn size (18.1% TBSA). The systemic physiological response following a burn is dependent on burn size [23]. Less extensive burns are more likely to result in a shorter length of hospital stay and immobilization.

Cambiaso-Daniel *et al.* observed a non-significant decrease in BMC and BMD during a time frame within the patient's hospital stay [15]. This was consistent with previous research among patients with prolonged bed rest, where statistically significant changes were not observed until several weeks following the injury [24]. After discharge, BMC and BMD remained decreased [2,10,20]. This prolonged effect was consistent with a decrease of overall bone formation and an increase in bone resorption, owing to both a post-burn inflammatory response and sedentary state [10,25–30]. Compared to non-burned peers, patients' BMC remained significantly decreased up to 3.5 years post-burn [2,5,14]. The comparison of BMD among paediatric burn patients and their non-burned peers was inconclusive [5,9,14].

Paediatric burn patients decreased their lean body mass following admission and up to 9 months post-burn [15,18,20]. From 9–24 months post-burn, paediatric burn patients started gaining lean body mass [2,18,20]. However, when compared to their non-burned peers, paediatric burn patients' lean body mass was significantly decreased up to 3.5 years post-burn [2,5,8,14].

The fine and gross motor skills of paediatric burn patients improved exponentially over time [22]. The recovery of fine and gross motor skills was dependent on burn size; the predicted recovery scores were significantly lower among paediatric patients with a burn covering $\geq 20\%$ TBSA. Consequently, despite showing improvement, patients with a burn covering $\geq 20\%$ TBSA did not reach the fine and gross motor function of non-burned peers at 2 years post-burn. It remains unclear whether paediatric patients could reach the fine and gross function of non-burned peers in due time, as a study period of 2 years may not suffice to depict full-recovery.

One of the strengths of this review was the systematic approach in accordance with the PRISMA Statement Guidelines; two independent investigators performed the study selection and risk of bias assessment. In addition, the search strategy was broad and performed in three databases: PubMed, EMBASE and Web of Science. Following this search, the reference lists of the included studies were also screened for relevant studies that may have been missed earlier. Consequently, it is unlikely that any relevant publications were missed.

The most important limitation of this systematic review was the lack of meta-analysis due to considerable

heterogeneity in outcome measures, measurement units and methodology. Furthermore, some limitations of the evidence should be considered.

First, 13 out of 16 studies included only paediatric patients with severe burns, resulting in an average burn size of 52.8% (± 12.7) TBSA, with an average full-thickness burn of 38.8% (± 20.1) TBSA. Yet, epidemiological studies have shown that most burns among paediatric patients are minor and concern $\leq 10\%$ TBSA [31–36]. The evidence presented in this review may thus not be representative of the whole paediatric burn population.

Second, the included studies were predominantly set in the USA, specifically the Shriners' Burns Hospital for Children in Galveston, TX ($n = 13$; 81%). The disproportionate representation of a single centre in this systematic review affects the generalizability of the evidence.

Third, the included studies did not account for the potential of effect modification by the patient's medical treatment and rehabilitation efforts. The magnitude of the effect of a burn on the patient's growth, body composition and motor development, may be dependent on the medical treatment received during hospital admission and the rehabilitation efforts after hospital discharge.

Fourth, the included studies date from 1990–2021, a time throughout which significant advances in clinical care have been made. The standard of care, including nutritional support and therapeutic agents, is thus likely to differ among the included studies. A confounding factor in the evaluation of growth and body composition is the administration of therapeutic agents with an anabolic or anticatabolic effect following a severe burn. Four of the included studies reported the administration of such therapeutic agents, including (1) propranolol: a β -adrenergic receptor blocker, or beta-blocker, that has been reported to promote the restoration of lean body mass and reduce tachycardia and resting energy expenditure [37–39]; (2) oxandrolone: a synthetic derivative of testosterone, that has been reported to reduce resting energy expenditure and promote the restoration of BMC and linear growth [37,38,40]; and (3) recombinant human growth hormone, that has been reported to reduce muscle wasting and promote wound healing, linear growth and weight maintenance [41–44]. Whilst two out of four studies reported no difference between patients who received a therapeutic agent and those who did not, the exact impact of this confounding factor remains unknown. None of the four studies provided data or sensitivity analyses on this subsample [2,9,14,15]. Among the remaining included studies, study participants did not receive therapeutic agents with an anabolic or anticatabolic effect [19], or it was unknown [5–8,10,16–18, 20–22].

Fifth, the overall quality of included studies was moderate, mainly due to the study size, insufficient comparability between the included patients and controls, and the risk of residual confounding. In fact, being subject to both bias and confounding is known to be one of the biggest limitations of a systematic review of observational evidence. Nevertheless,

observational evidence may be advantageous in the evaluation of long-term outcomes.

Conclusions

Following the initial decline, patients' growth and motor development started to recover during the first or second year post-burn. Nonetheless, burns may have a profound and prolonged effect on the paediatric burn patients' muscular strength, BMC and lean body mass. It should be noted that the vast majority of studies included only patients with burns covering $\geq 30\%$ TBSA. The evidence presented in this review may thus not be representative of the whole paediatric burn population. Further research is needed to establish the effect of less extensive burn injuries on paediatric burn patients' growth and motor development.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data will be made available upon reasonable request by e-mail to the corresponding author.

Conflicts of interest

The authors declare that they have no competing interests.

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Author's contributions

Concept and study design: MDC, MGAB, AP; Search strategy: JCFK; Title and abstract screening: MDC, MGAB, AP; Full-text screening: MDC, MGAB, AP; Manual search of reference lists: MDC, MGAB; Risk of bias assessment: MDC, MGAB; Data extraction and analysis: MDC, MGAB, AP; Manuscript preparation: MDC, MGAB, PPMZ, JCFK, AP.

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