Functioning beyond pediatric burns

physical activity, fatigue, and exercise capacity up to 5 years post burn

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CHAPTER 1: General introduction

GENERAL INTRODUCTION

A burn injury is considered one of the most traumatic injuries that can happen to a child [1]. Normal life is suddenly disrupted, and replaced by a period of hospital stay with painful treatment procedures, and being away from home, school, family and friends. Recovery from a burn injury can be lengthy and complex and children may have to deal with lifelong consequences [2-4]. In order to guide and optimize burn recovery and rehabilitation, insight in outcomes of functioning beyond pediatric burns is essential.

Pediatric burns

Each year, approximately 290 children are admitted to one of the three Dutch Burn Centers, located in Beverwijk, Groningen, and Rotterdam. The majority of them (~70%) is aged 0-4 years [5]. In this young age group, most burns are caused by hot fluids, like coffee or tea. In older children and adolescents, the cause of burn injury is more diverse (Figure 1) [5].

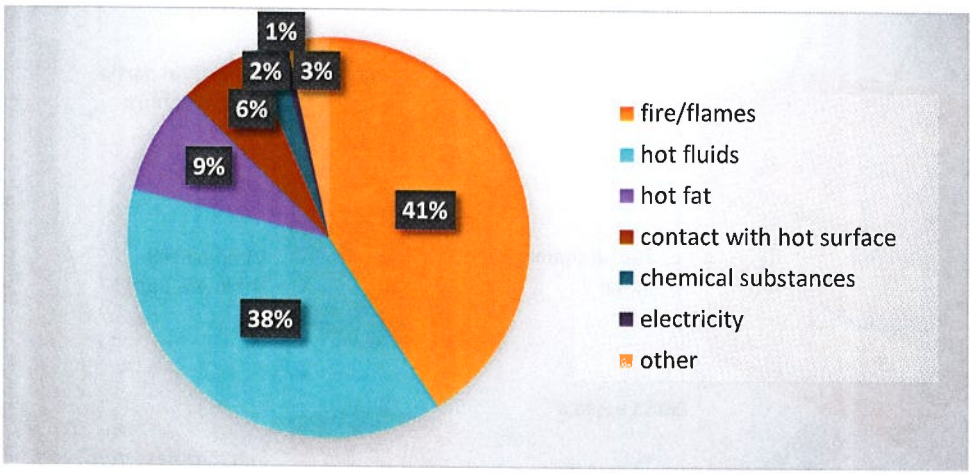

Figure 1. Causes of burns in children and adolescents (5-18 years) admitted to a Dutch burn center [5].

The **severity of burns** primarily depends on the extent and depth of the burn. The extent of burn wounds is mostly expressed as a percentage of total body surface area (**TBSA**). To visualize, the size of your hand palm including closed fingers matches approximately 1% of your TBSA (Figure 2).



Figure 2. Hand size reflects approximately 1% total body surface area (TBSA).

The depth of the burn is reflected in the layers of skin being damaged and depends on the causative agent, the temperature and duration of exposure, the thickness of the skin, and whether or not adequate cooling techniques were applied. In **epidermal burns** (e.g. sun burn), there is redness, pain and sometimes swelling, but no damage of the skin. For this reason, superficial burns are not taken into account when determining the extensiveness of a burn wound. **Partial-thickness burns** affect the epidermis and (part of) the dermis (Figure 3). Depending on the part of the dermis that has been saved, partial thickness burns are categorized as superficial or deep. Superficial partial thickness burns have the potential to heal spontaneously within 7-14 days, while deep partial thickness burns mostly require surgical intervention, i.e. skin grafting, as spontaneous healing takes too long and can result in suboptimal scars. In **full-thickness burns**, all layers of the skin are destroyed, including (part of) the subcutaneous tissue (Figure 3). Full-thickness burns heal only from the edges, and therefore, unless very small (approximately 2 cm^2), always require surgical skin grafting. In fact, most burn wounds are heterogeneous in depth, i.e. a combination of partial-thickness and full-thickness burns.

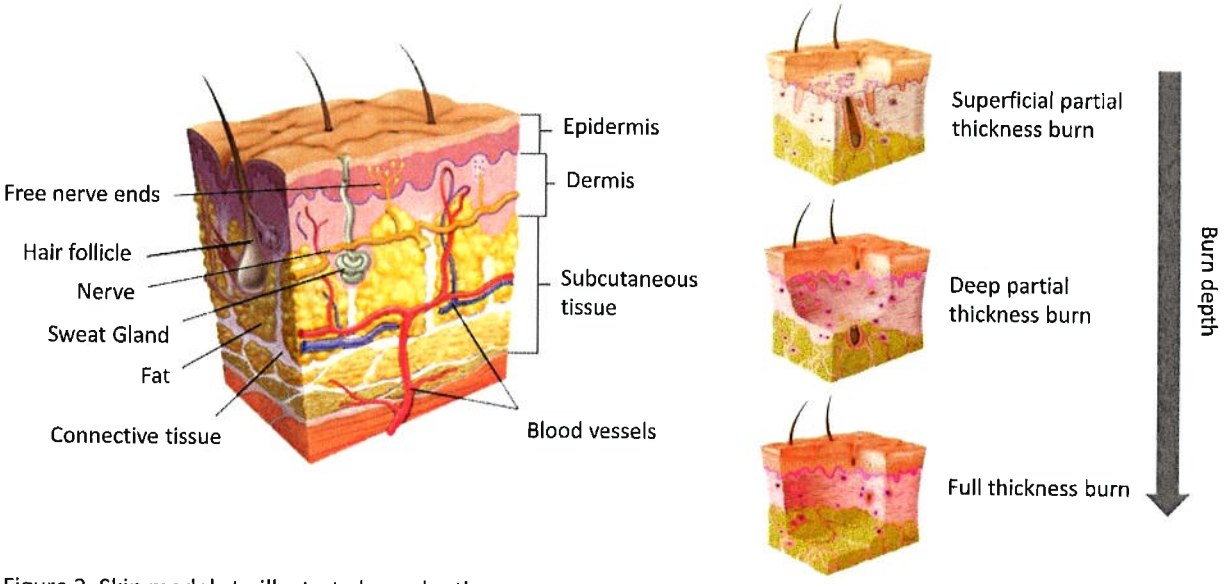

Figure 3. Skin models to illustrate burn depth.

Not every pediatric burn injury requires admission to a specialized burn center. Referral criteria for specialized burn care include, amongst others, the presence of full-thickness burns, partial-thickness burns affecting >5% TBSA (in children), electrical or chemical burns, inhalation injury, burns in particular areas like the face, hands, joints or genitals, and doubts regarding the circumstances of the injury (i.e. child abuse) [6]. In case admission is required, the length of hospital stay is relatively long compared to other pediatric injuries.

Physical consequences of pediatric burns

As this thesis focuses primarily on physical functioning, only physical consequences of pediatric burns are described here, predominantly based on findings in children and adolescents aged 6-18 years with deep partial-thickness and/or full-thickness burns. Next to these physical consequences, it is important to realize that burns can also have substantial psychological and social impact, which likely impact physical functioning as well.

Physical consequences during wound healing

Directly after the burn injury, there is an acute release of inflammatory mediators and stress hormones, resulting in a systemic inflammatory response and a profound and sustained **stress response** [7]. This also occurs in other forms of trauma and critical illness, but the extent and duration of the stress response and its debilitating nature, are unique to burn injury [8,9].

An important hallmark of the stress response to burns is **hypermetabolism**, i.e. an increased basal metabolic rate [10,11]. On the fifth day post burn, resting energy expenditure starts to rise, characterized by an increase in heart rate, body temperature, oxygen and glucose consumption, glycogenolysis, proteolysis, lipolysis, and futile substrate cycling [11,12], causing, amongst others, loss of bone density, loss of lean body mass, and muscle weakness [12-14]. The extent of the hypermetabolic response depends on the extensiveness of the burn [11].

Another serious physical consequence of burns is **muscle wasting** [9,10,13,15]. The sustained increase in inflammatory mediators and stress hormones exerts catabolism, especially of muscle mass [13]. Moreover, it has been postulated that skeletal muscles act as the body's protein depot [10,16]. That is, proteins and amino acids from the skeletal muscles are redistributed in order to facilitate recovery processes like wound healing [8-10]. Skeletal muscle catabolism and depletion of muscle protein stores result in a loss of muscle mass and strength [8,9,13,15].

Extensive pediatric burns (>30% TBSA) can also cause **impaired glucose tolerance** (i.e. stress-induced diabetes) [10,17], which is associated with impaired wound healing, loss of skin grafts [18], and higher rates of skeletal muscle catabolism [19].

Realizing the serious impact of these pathophysiological responses to burn injury, it is clear that burns affect much more than just the layers of the skin. A certain **loss of physical fitness** after pediatric burns seems inevitable, which is further exacerbated by the relatively long periods of bed rest and inactivity during hospital stay [20-23]. Wound healing, associated with painful treatment procedures, daily therapy

sessions, and possibly one or multiple surgeries, require a lot of energy from the pediatric burn patient. This, in combination with the elevated levels of resting energy expenditure and muscle wasting, often leads to pronounced feelings of **fatigue**, at least during hospital stay [24].

Physical consequences beyond wound healing

When most wounds are healed, patients are discharged from the burn center. But also beyond wound healing, intensive treatment is often required. Pediatric burn patients have to visit the burn center regularly after discharge, varying from three times a week in the first weeks after discharge to once in every few years till they become 18 years old.

Full-thickness burns and part of the deep partial-thickness burns heal by **scarring**, which is often accompanied by **itch** and **pain** [25]. To prevent or reduce excessive scarring, many patients have to wear pressure garments, i.e. tight-fitting clothes to be worn over burned areas ≥20 hours per day for many months [26,27]. With scarring, there is a risk of scar contraction causing a tight skin feeling and **limited flexibility** [25]. When contracting scar tissue is across or adjacent to a joint this may result in joint contractures, i.e. loss of range of motion in one or more movement directions of that joint [28], which is a major cause of functional impairments beyond pediatric burns [29-32].
Full scar maturation may take as long as two years [27], but also after full scar maturation, pediatric burn patients are at risk for scar contractures, as their body will grow and their scars do not. Multiple reconstructive surgeries may be required in order to release scar contractures and therewith improve function and/or cosmetic appearance [33].

The **metabolic alterations** associated with the pathophysiological stress response also persist long after wound healing, varying from on average six months in the general pediatric burn population to two years or even longer after extensive pediatric burns (>40% TBSA) [34,35]. In this latter group, lean body mass was shown to remain significantly lower compared to healthy peers for more than three years post burn, with typically higher percentages of total body fat [36]. Furthermore, exercise capacity was shown to be reduced up to five years post burn, which might be due to, amongst others, persisting **impairments in cardiovascular function** [37-39], **pulmonary function** [40], and/or **muscle strength** [36]. Finally, preliminary evidence suggests that extensive burns can alter energy metabolism of skeletal muscles, which leads to an earlier onset of muscle fatigue and longer recovery periods following exercise [41,42].

In children with less extensive burns, cardiovascular function was shown to be affected for three months or longer [43] and at least part of this population had reduced levels of exercise capacity and/or muscle strength one to five years post burn [44]. Remarkably, despite the fact that less extensive burns are much more common, the physiological impact of smaller burns is far less comprehensively documented.

Lifelong physical consequences

The most obvious lifelong physical consequences of pediatric burns are **altered appearance** and **limited skin and joint flexibility** due to permanent scars.

However, a recent long-term follow-up study showed that adults who sustained a burn injury during childhood had significantly **higher rates of physical** (i.e. arthritis, fractures, respiratory morbidity) **and mental** (i.e. major depression, anxiety disorder, substance abuse) **health issues** compared to matched controls, independent of burn size [45]. Other recent follow-up studies showed **increased hospital admission rates** for respiratory infections [46], gastrointestinal diseases [47], cardiovascular diseases [37], and musculoskeletal conditions [48] in the long-term, and even an **increased risk of premature death** [49]. The exact causes for these long-term health risks have yet to be identified, but it is assumed to be related to the long-term systemic impact of the pathophysiological stress response, even after minor burns [37]. Lack of physical activity, and therewith physical fitness, is also a potential cause of many chronic health conditions [50]. Whether this plays a role in (pediatric) burn patients, needs further exploration.

Functioning beyond pediatric burns

The physical consequences described above and the associated long-term health risks highlight the importance of monitoring and optimizing functioning beyond pediatric burns. A conceptual framework that can be used to help our understanding of the impact of pediatric burns on functioning is the International Classification of Functioning, Disability and Health: Children and Youth version (ICF-CY) (Figure 4) [51]. Within the ICF-CY, functioning is described as an umbrella term that involves three domains: body functions and structures (**functioning of the body**), activity (**functioning of the child**), and participation (**functioning of the child as a member of society**). Post burn functioning is considered to arise from the complex interaction between the impact of the burns on the one hand, and the influence of personal and (physical and social) environmental factors on the other hand. Moreover, reciprocal interactions are assumed between the three domains of functioning [51].

Dutch burn rehabilitation

The ultimate goal of pediatric burn rehabilitation is to **optimize the child's functioning** and therewith (long-term) outcomes of health and quality of life [3].

To achieve this, the Dutch burn centers provide high quality care, combined with a continuous program of rehabilitation during hospital stay. Therapy starts as early as possible, generally on admission, and includes positioning and/or splinting, range of motion exercises, balance training, strength training, and aerobic exercises. Moreover, children are encouraged to perform self-care and other activities of daily living (ADL) independently if possible [52].

After discharge from the burn center, the focus of care continues on minimizing excessive scar formation and joint contractures, ensuring proper scar management techniques, and promoting the return to daily life. Structured exercise rehabilitation is only prescribed if this is considered necessary based on clinical evaluation by the therapists, for instance in case of functional impairments in joint range of motion, or in case a child avoids to use affected body parts.

Recently, global practice guidelines for exercise prescription after burn injury were published, stating that muscle strength and exercise capacity should be evaluated in all burn patients aged ≥7 years [53]. Those who score 'below normal' should be prescribed a 6- to 12-week structured exercise program after discharge from the acute care setting [54]. However, with respect to the pediatric population, these practice guidelines were based on findings in children and adolescents with extensive burns (>30% TBSA or >40% TBSA). The question is, do all pediatric burn patients require such an evaluation and, if scores are suboptimal, such an extensive rehabilitation program after discharge to achieve optimal functioning?

Context of this thesis

Dutch burn research is mostly allied to the Association of Dutch Burn Centers (ADBC). The ADBC was founded in 2003 as an initiative to improve the cooperation between the three Dutch burn centers in the field of burn care, education, and research [55].

About a decade ago, a unique multidimensional line of research was established with regard to functioning beyond pediatric burns. This research has been conducted in close collaboration with the Center for Human Movement Sciences of University Medical Center Groningen and University of Groningen, the research group on Healthy Ageing, Allied Health Care and Nursing of the Hanze University of Applied Sciences, and the Child Development & Exercise Center of the Wilhelmina Children's Hospital

of University Medical Center Utrecht. The research line started with a cross-sectional study on physical fitness, habitual physical activity, fatigue, and health-related quality of life in children and adolescents 1-5 years post burn [56], followed by a longitudinal prospective cohort study investigating the course of these parameters during the initial six months after discharge from the burn center. The first results of the cross-sectional study (body composition, muscle strength, and exercise capacity) were brought together in the thesis of Dr. L.M. Disseldorp: *On physical functioning after pediatric burns: physical fitness and functional independence*. The current thesis provides subsequent results of the cross-sectional study (habitual physical activity and fatigue) and the first results of the longitudinal prospective cohort study (the course of exercise capacity) (Figure 4). Both research projects were funded by the Dutch Burns Foundation.

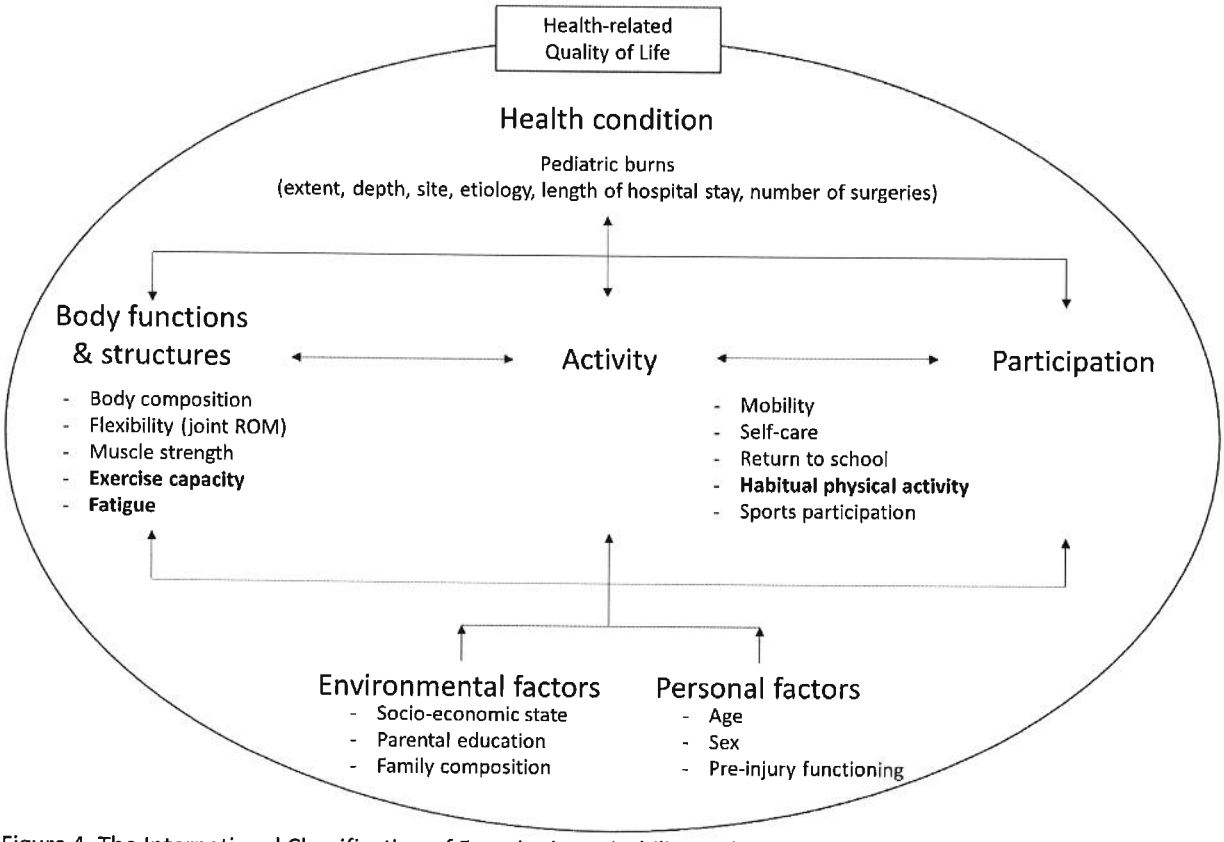

Figure 4. The International Classification of Functioning, Disability and Health: Children and Youth version [51] adapted by McDougall et al. [57], and including the parameters that were addressed within the multidimensional line of research on functioning beyond pediatric burns. Parameters in bold are the central focus of the studies in the current thesis.

Aims and outline of this thesis

The general aim of this thesis is to further our knowledge on functioning beyond pediatric burns. More specifically, it aims to assess outcomes of functioning in the general Dutch pediatric burn population, which is essential to determine and predict their rehabilitation needs beyond the acute care setting.

CHAPTER 2 describes objectively measured levels of physical activity and sedentary behavior in pediatric burn patients 1-5 years post burn, compared to non-burned peers. Furthermore, post burn physical activity levels are compared to the global physical activity recommendation of the World Health Organization, in order to identify whether their health and well-being are at risk due to inactivity. **CHAPTER 3** presents the prevalence of perceived fatigue in children and adolescents 1-5 years post burn, as reported by themselves and their parents. **CHAPTER 4** comprises a narrative review exploring the possibilities of the Oxygen Uptake Efficiency Slope (OUES) as a submaximal measure of exercise capacity that could be used in pediatric populations. **CHAPTER 5** describes the characteristics of the submaximal OUES in a healthy child population. **CHAPTER 6** describes the course of exercise capacity in pediatric burn patients, measured with the Steep Ramp Test, during the initial six months after discharge, and discusses whether adverse outcome can be predicted from burn characteristics, sociodemographic characteristics, or prior assessment of exercise capacity.

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CHAPTER 2:

Physical activity and sedentary behavior following pediatric burns: a preliminary investigation using objective activity monitoring

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Physical activity and sedentary behavior following pediatric burns – a preliminary investigation using objective activity monitoring

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Abstract

Background: Adequate levels of regular physical activity (PA) are crucial for health and well-being. Pediatric burn injuries can have major physiological consequences in both the short and long term. The question is whether these consequences affect post burn PA levels. This study therefore aimed to describe PA and sedentary behavior (SB) in children and adolescents 1–5 years after burn injury.

Methods: Daily PA and SB were monitored in 20 children and adolescents (12 boys and 8 girls, aged 6–17 years, with burns covering 10–37% of total body surface area, 1–5 years post burn) for 1 week using the ActiGraph GTX3+ accelerometer. Activity counts were categorized into SB, light PA, moderate PA, vigorous PA, moderate-to-vigorous PA (MVPA), and total PA. Outcomes were compared with non-burned reference values and PA levels recommended by the World Health Organization (WHO).

Results: The participants spent about 5.1 h per day on total PA and 7.4 h on SB. Most of the active time (~ 83%) was categorized as light PA. Thirty-five percent of the group, especially the young boys, spent on average ≥ 60 min on MVPA per day. The boys, although with large interindividual differences, spent more time on MVPA than the girls ($p < .005$). Older age was associated with less PA time, while more time was spent sedentary. No trends were found indicating an effect of burn characteristics, time post burn, or length of hospital stay, and no differences were found with non-burned peers.

Conclusion: Duration and intensity of PA and SB in children and adolescents 1–5 years after burn injury were similar to non-burned peers. However, only 35% of the group met the WHO physical activity recommendation. Given the increased long term risk for physical conditions following pediatric burns, physical activity should be encouraged in this vulnerable population.

Trial registration: The study is registered in the National Academic Research and Collaborations Information System of the Netherlands (OND1348800).

Keywords: Exercise, Outcome assessment, Accelerometry, Rehabilitation, Burns

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Background

Physical activity in children and adolescents is a widely publicized topic due to the increasing awareness of its significance for health and well-being [1]. Adequate levels of regular physical activity can improve muscular strength and cardiopulmonary endurance, help to prevent a number of chronic diseases throughout life, and are also essential for the social, emotional, and cognitive development of children and adolescents [1, 2]. In contrast, sustained sedentary behavior has been associated with negative health outcomes like cardiovascular diseases, type 2 diabetes, and metabolic syndrome [3].

Children with physical disabilities or chronic diseases tend to be more restricted in performing physical activity than their healthy peers [4]. This might also apply for children who have been hospitalized with burns, as a burn injury can have major physical and physiological consequences in both the short and long term that are expected to affect the time spent on physical activity and to encourage sedentary behavior. First, burns are associated with substantial loss of skeletal muscle mass and strength, due to amino acid depletion from the muscles for the formation of new skin [5], and prolonged periods of bed rest and immobilization. Secondly, burns covering > 30% of total body surface area can lead to hypermetabolism, which is frequently associated with cachexia [6]. In addition, there is preliminary evidence that burns can alter muscle energy metabolism, leading to an earlier onset of muscle fatigue and longer recovery periods following exercise [7]. In children and adolescents with severe burns, these burn induced metabolic and inflammatory changes have been shown to persist for 3 years after the injury [6]. Following less extensive burns, it is yet unknown whether pathophysiological alterations affect physical functioning after 1 year. Besides these physiological issues, it is feasible that children with burns experience additional barriers to physical activity, like fatigue [8], anxiety, pain, limited flexibility due to scar contractures, or psychosocial problems like difficulties with accepting their altered appearance [9].

Recently evidence emerged about long term physical health outcomes in the pediatric burn population [10–14]. A long term follow-up study showed that burn injured children had an increased risk of arthritis, fractures, and pulmonary conditions compared to their non-burned peers, even following non-severe burns [10]. Accordingly, pediatric burn patients had increased hospital admission rates for respiratory infection [11], cardiovascular diseases [12], and musculoskeletal diseases [13], and even an increased risk of mortality in the long-term [14]. Although the specific causes of those physical and physiological consequences years beyond the burn injury have yet to be identified, lack of physical activity might play a role.

To identify whether health and well-being of children and adolescents after burn injury are at risk due too inadequate daily physical activity and/or too much sedentary behavior, it is important to become aware of their daily time spent in both types of behavior. Although physical fitness after pediatric burns received more attention during the last decades [15–17], habitual physical activity (which is intrinsically associated with physical fitness) has not been assessed before. Therefore, the current study aimed to describe daily time spent in various intensities of physical activity and sedentary behavior in children and adolescents with a wide range of burn characteristics, using objective activity monitoring, and to compare these results with non-burned reference values.

Methods

The data described in this study were obtained as part of a cross-sectional descriptive study, performed by our study group, regarding physical activity and fitness following pediatric burns [18]. The entire study involved not only the assessment of physical activity and sedentary behavior, but also assessment of physical fitness, fatigue, and health-related quality of life. Study procedures were described previously in detail [18].

Study population

Eligibility criteria were 6–18 years of age, involvement in a burn accident 0.5–5 years ago, admission to one of the three Dutch Burn Centers with burns covering > 10% of their total body surface area and/or a length of hospital stay of more than 6 weeks. The national Dutch Burn Repository was used to identify potentially eligible patients. Children with extensive (pre-existing) comorbidity, insufficient Dutch language proficiency, or (mental) disabilities were excluded. In case participants had reconstructive surgery less than 2 months before the time of planned assessment, the assessment was postponed.

Accelerometry: Data collection and analysis

Daily physical activity and sedentary behavior were monitored using the triaxial ActiGraph GTX3+ accelerometer (ActiGraph, Pensacola, Florida, U.S.A.). This wearable activity monitor converts acceleration signals into samples that are summed over a user-specified time sampling interval, called *epoch*. At the end of each epoch, the summed value is stored in the monitor memory as activity counts. The Actigraph GT3X+ has been shown to be a valid and reliable instrument to assess frequency, intensity, and duration of physical activity and sedentary behavior in children and adolescents [19].

Monitors were initialized using the Actilife software (Actilife software, version 6.7.3, ActiGraph, Pensacola,

Florida, U.S.A.) to collect activity counts at 100 Hz. To enable comparison with European non-burned reference values [20, 21], only accelerometer measurements in the vertical plane were used. The previously published non-burned reference groups consisted of 4936 European children (2411 boys and 2525 girls, aged 6–11 years) [21] and 2200 European adolescents (1016 boys and 1184 girls, aged 12.5–17.5 years) [20]. Reference values were available for light physical activity, moderate-to-vigorous physical activity and sedentary behavior in children [21], and for moderate-to-vigorous physical activity and sedentary behavior in adolescents [20]. For optimal transparency of our data handling methods, the 7-step algorithm of Heil et al. [22] was used for collecting, processing, and summarizing the accelerometer data into physical activity and sedentary behavior outcome variables, according to best practice (Fig. 1). To be able to compare our activity data to those of the reference studies, the measurements needed to be comparable. Therefore, we chose to adopt the decisions in data reduction and analysis (epoch length, wear time criteria, non-wear time criteria, spurious data, cutpoints) from our reference studies. Data reduction and analysis were performed using MATLAB software (release 2015a, The MathWorks, Inc., Natick, Massachusetts, U.S.A.).

Statistical analyses

Subject characteristics and descriptors of physical activity and sedentary behavior were presented as mean, standard deviation, and range, for boys and girls separately. Influence of sex was assessed using independent t-tests. To identify potential predictors of total physical activity, moderate-to-vigorous physical activity and sedentary behavior, exploratory multiple regression analyses (hierarchical, blockwise entry) were performed. As both age and sex are known predictors of physical activity and sedentary behavior [20, 21], these variables were entered simultaneously into the model first. Subsequently, burn characteristics (%total body surface area burned, full thickness burns yes(1)/no(0), legs involved yes(1)/no(0)), time post burn (years), and length of hospital stay (days) were entered separately, one by one, in order to identify whether the regression model could be improved by one or more of these potential predictors. For each regression model, the standard error of the estimate (SEE) was provided as an indication for the accuracy of the prediction by the model. The smaller the SEE, the more accurate the prediction.

To assess achievement of physical activity levels as recommended by the World Health Organization (WHO) (Table 1), average daily time spent in moderate-to-vigorous physical activity was calculated for each subject, and results were plotted together with a line representing the recommended daily minimum of 60 min.

For comparison with non-burned reference values, individual data were plotted together with age- and sex-matched European reference values (mean ± 2 SD). Subjects that deviated more than two standard deviations from the non-burned mean were assumed different from their non-burned peers.

IBM SPSS Statistics for Windows (version 20.0, IBM Corp, Armonk, New York, U.S.A.) was used for the statistical analyses. A two-sided p-value <.05 was considered statistically significant.

Results

Data from 20 children and adolescents with burns (12 boys and 8 girls, aged 6–17 years, with burns covering 10–37% of total body surface area) were included in the current study (Fig. 2, Table 2). Inhalation injury was not present in our study population and none of the burns were caused by chemical substances or electricity. No significant differences in subject characteristics were found between boys and girls (Table 2).

Physical activity and sedentary behavior

The accelerometer was worn 4–7 days (Fig. 2), on average close to 750 min per day (Table 3). Most subjects with less than 7 valid days forgot to wear the accelerometer at one or more full days. Others attached it too late or removed it too early during the day, resulting in less than 480 min of monitoring.

Approximately 40% of the daily wear time was classified as physical activity (5.1 ± 0.8 h) and 60% was classified as sedentary behavior (7.4 ± 1.4 h) (Table 3). Most of the active time by far, 80% in boys and 88% in girls, was categorized as light physical activity and less than 10% as vigorous physical activity (7% in boys and 3% in girls). Although with large interindividual differences (Fig. 3), boys spent more time in moderate-to-vigorous physical activity than girls ($p < .005$, Table 3).

Exploratory linear regression analyses indicated that age was significantly associated with time spent in total physical activity. According to the regression line, time spent in total physical activity decreased by 6.7 min when age increased with 1 year (β − 6.7; 95% CI: -12.7 − − 0.7; $p = .031$). Time spent in sedentary behavior increased with 13.1 min by each year of age (β 13.1; 95% CI: 3.0–23.2; $p = .014$) (Fig. 3). Age explained 23.4% of the variance in time spent in total physical activity. The SEE was 41.6 (model $p < .04$) which indicates small error, given the range of 247–412 min of time spent in total physical activity (Table 3). In sedentary behavior, age explained 29.2% of the variance (SEE = 70.1, model $p < .02$). For time spent in moderate-to-vigorous physical activity, only sex was a significant predictor, explaining 39% of the variance (SEE = 19.0, model $p < .01$). The girls spent on average 29.5 min less time in moderate-to-vigorous physical activity than the boys in this study (β

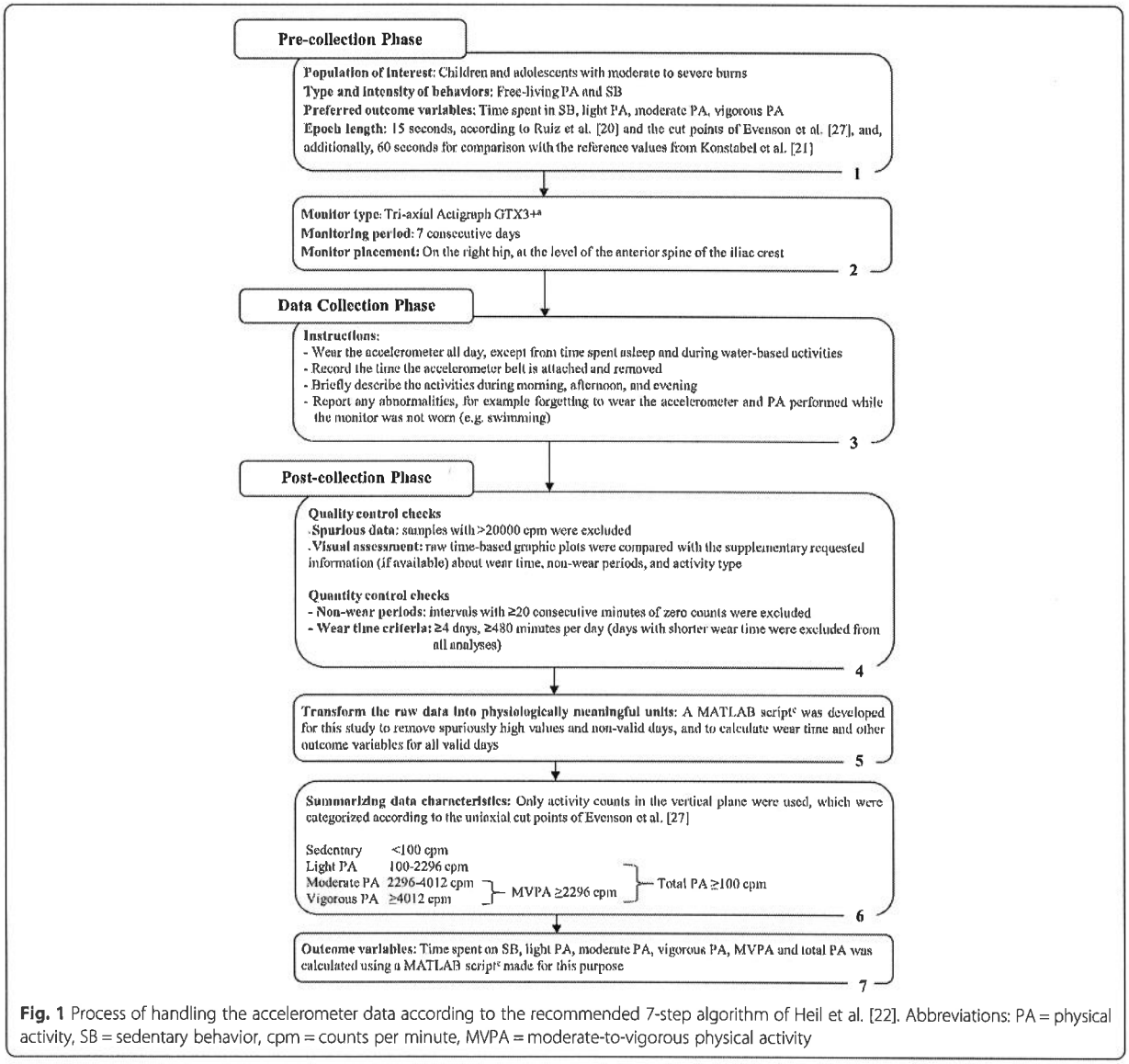

Fig. 1 Process of handling the accelerometer data according to the recommended 7-step algorithm of Heil et al. [22]. Abbreviations: PA = physical activity, SB = sedentary behavior, cpm = counts per minute, MVPA = moderate-to-vigorous physical activity

– 29.5; 95% CI: -47.7 – – 11.2; $p = .003$). None of the burn characteristics (%total body surface area burned, full thickness burns, leg involvement), time post burn, or length of hospital stay, were predictive for time spent in total physical activity, moderate-to-vigorous physical activity, or sedentary behavior.

Comparison of individual scores with the WHO physical activity recommendation (Table 1) showed that 6 of the 8 boys aged < 12 years and 1 of the 4 boys aged ≥12 years achieved the recommended 60 min of daily moderate-to-vigorous physical activity (Fig. 4). None of the girls spent on average ≥ 60 min on moderate-to-vigorous physical activity per day.

Comparison with non-burned peers

Reference values were only available for light physical activity, moderate-to-vigorous physical activity and sedentary behavior in children aged 6–11 years, and for moderate-to-vigorous physical activity and sedentary behavior in adolescents aged 12.5–17.5 years. On time spent in moderate-to-vigorous physical activity, most girls (6 out of 8) and adolescent boys (3 out of 4) scored below average, while most young boys (7 out of 8) scored on or above average. None of them, however, scored more than two SD from the non-burned reference mean (Fig. 3). Sedentary time of both boys and girls after burn injury was comparable with non-burned peers

Table 1 Outline of international definitions and recommendations of physical activity and sedentary behavior in children and adolescents

	Definition	Recommendations
Physical activity	Any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits [25].	Children and adolescents aged 5–17 should accumulate at least 60 min of moderate-to-vigorous physical activity daily. Most of the daily physical activity should be aerobic. Vigorous activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week [25].
Sedentary behavior	Any waking behavior, characterized by an energy expenditure ≤1.5 metabolic equivalents (MET's), while in a sitting or reclining posture [47].	Children (aged 5–11 years) and adolescents (aged 12–17 years) should minimize the time they spend being sedentary each day. To achieve this: - Limit use of electronic media for entertainment (e.g. television, seated electronic games and computer use) to no more than 2 h per day [48, 49] - Limit sedentary (motorized) transport, extended sitting time, and time spent indoors throughout the day [48] - Break up long periods of sitting as often as possible [49]

(Fig. 3), which was also true for time spent in light physical activity (Fig. 3b).

Discussion

This preliminary investigation was the first study that objectively assessed intensity and duration of physical activity and sedentary behavior following pediatric burns and compared those with non-burned reference values. Accelerometer data showed that children and adolescents 1–5 years after moderate to severe burns were physically active about 5.1 h and sedentary for 7.4 h per day. The boys, although with large interindividual differences, spent more time on moderate and vigorous physical activity than the girls. Similar to the findings in non-burned pediatric populations [20, 21, 23, 24], older age was associated with less time spent in physical activity, while more time was spent in sedentary behavior. No trends were found indicating an effect of burn characteristics, time post burn, or length of hospital stay, although this might be a consequence of the cross-sectional design of this study and the limited sample size. No differences were found with non-burned reference values.

Time spent in moderate-to-vigorous physical activity in children and adolescents 1–5 years after burn injury was similar to that of non-burned peers. This is consistent with the results of Disseldorp et al. [17], who indicated that both physical fitness and muscle strength were not significantly different from non-burned peers in this population. In contrast, only 35% of the group, especially the boys aged < 12 years, spent on average ≥ 60 min of moderate-to-vigorous physical activity per day, which, according to the WHO, is crucial to reduce the risk of cardiovascular and metabolic diseases throughout life [25]. Seven subjects did not reach 60 min of moderate-to-vigorous physical activity on any of the monitoring days. In non-burned references, the percentage of children achieving the recommended amount of daily moderate-to-vigorous physical activity is low as well, ranging from 2.0 to 56.8% [20, 21]. These findings suggest that long-term health and well-being might be at risk in both groups. However, pediatric burn patients already are at increased risk of several physical and physiological diseases, e.g. pulmonary, musculoskeletal, and cardiovascular diseases, in the long term [10–13]. Adequate levels of physical activity generally can help to prevent the development of such conditions [1] and this might also be true for pediatric burn patients. Therefore, it is deemed important to encourage physical activity and sports in this vulnerable population.

It is important to note, however, that there is no consensus yet on the best cut points for the classification of moderate-to-vigorous physical activity in children and adolescents [26]. According to the cut points of Evenson et al. [27], which are recommended for children and youth [28] and therefore applied in the current study, intensities of > 2296 counts per minute (cpm) are considered moderate-to-vigorous physical activity. In the literature, however, thresholds ranging from 1000 to 4000 have been used. The WHO states that an intensity of ≥3 MET (metabolic equivalent) is considered moderate-to-vigorous physical activity, however it is unclear which accelerometer counts are associated with that intensity. The height of this threshold of course has major consequences for the total number of subjects that is classified as meeting the WHO physical activity recommendation (Table 1). If our threshold for moderate-to-vigorous physical activity is higher than the threshold intended by the WHO, this would explain the low proportion of subjects that achieved the recommended amount of daily moderate-to-vigorous physical activity. When it comes to patients, it is also important to realize that the cut points recommended for healthy children might result in misclassification of activity intensity in children with a chronic condition [29]. Physiological or biomechanical limitations might require them to work at a higher energy level to complete the same task and thus reach similar accelerometer counts [29–31]. Therefore, before generalized conclusions can be made regarding the appropriateness of physical activity levels after pediatric burns, consensus is needed concerning the best cut point used to classify moderate-to-vigorous physical activity, for both healthy children and children with a (chronic) condition.

Most of the evidence linking sedentary behavior to health outcomes in children and adolescents has focused

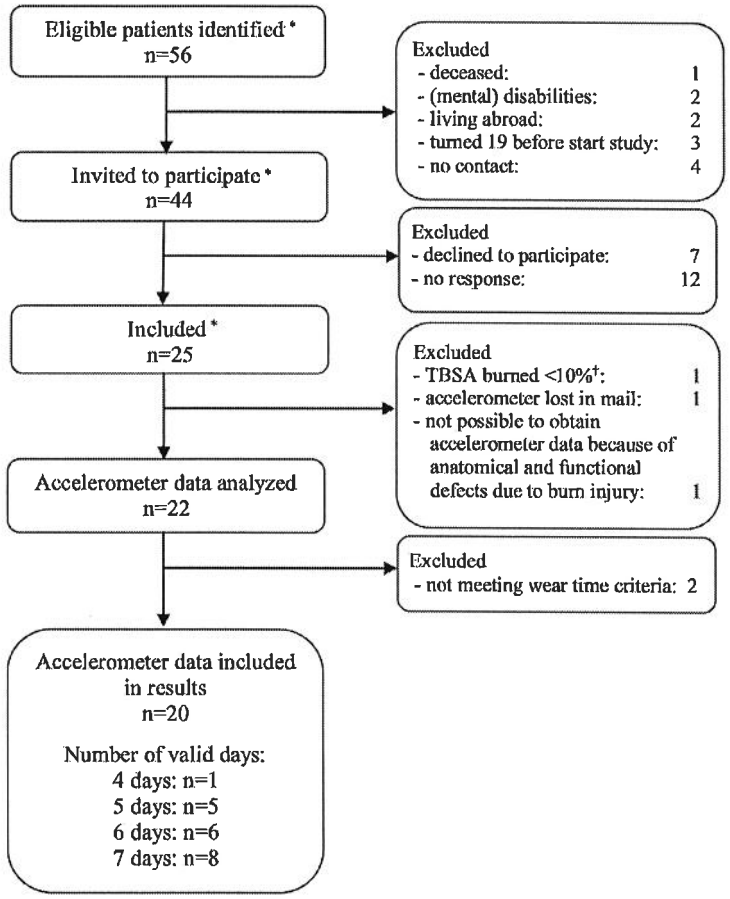

Fig. 2 Flow of patients. * Study of Disseldorp et al. [17]. † This child was registered as having burns covering > 15% of total body surface area (TBSA). It emerged however that its burns had in fact affected < 5% of TBSA. Therefore, this child was excluded

Table 2 Characteristics of the study population

Parameter	Boys ($n = 12$)			Girls ($n = 8$)			p-value[b]
	Mean	SD	Range	Mean	SD	Range	(Boys vs Girls)
Age (years)	10.8	3.7	6–17	9.6	2.7	6–14	.4424
%TBSA burned	18.3	8.4	10–37	13.5	2.8	10–17	.1391
full thickness burns	(8/12)			(5/8)			
lower extremity involved	(11/12)			(5/8)			
inhalation injury	(0/12)			(0/8)			
Surgeries (#)[a]	1		0–7	1		0–2	
Time post burn (years)	3.0	1.4	1–5	3.0	0.7	1–4	> .99
Length of stay (days)	25.8	7.9	18–42	27.3	11.8	16–55	.7362

Abbreviations: *%TBSA* percentage of total body surface area, # number, [a]mode instead of mean ± SD. [b] Independent sample *T*-tests

Table 3 Descriptors for daily physical activity and sedentary behavior

Parameter[a] (min·day^{-1})	Boys ($n = 12$)			Girls ($n = 8$)			p-value[b] (Boys vs Girls)	
	Mean	SD	Range	Mean	SD	Range		
Wear time	756	69	649–897	741	64	676–841	.6302	
Total PA	317	54	247–412	284	19	255–310	.1165	
- Light PA	255	39	201–323	251	16	229–279	.7878	
- Moderate PA	41	13	22–63	24	7	15–35	.0034	*
- Vigorous PA	22	10	4–40	9	4	5–18	.0027	*
MVPA	63	23	28–99	33	10	24–53	.0028	*
SB	439	92	345–651	457	66	389–552	.6399	

Abbreviations: *PA* physical activity, *MVPA* moderate-to-vigorous physical activity, *SB* sedentary behavior, vs versus. *$p < .005$. [a] Obtained from accelerometry with epoch length 15 s (minutes per day: mean ± SD, range). [b] Independent samples *T*-tests

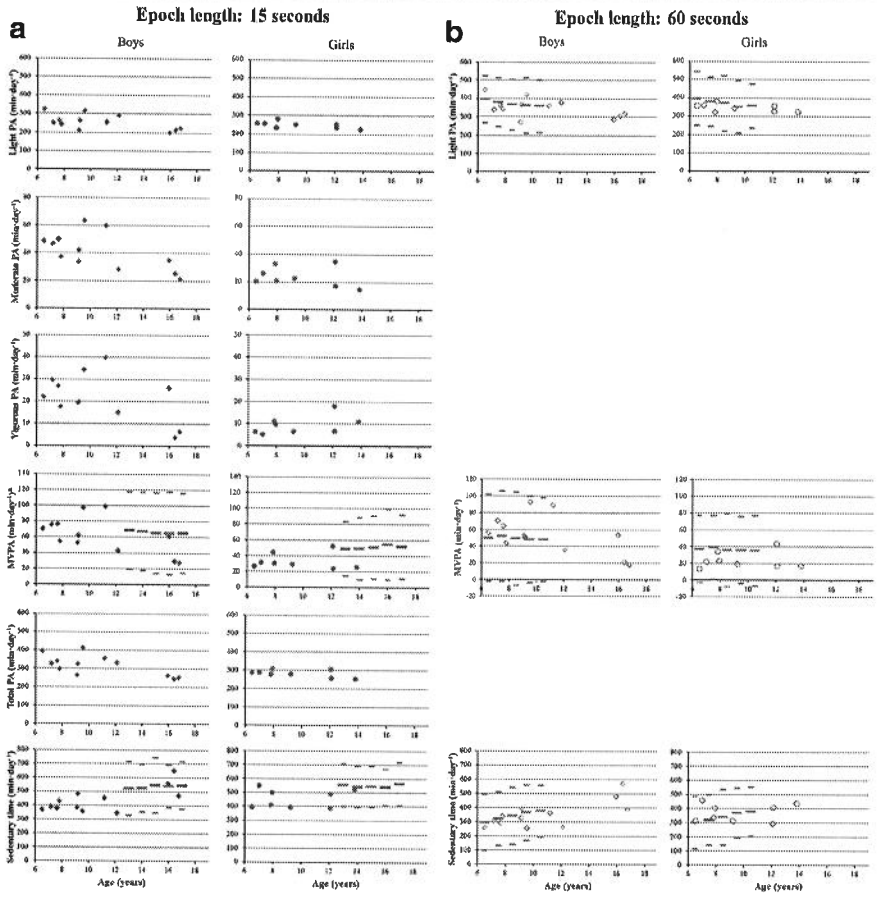

Fig. 3 **a** and **b** Individual levels of daily physical activity and sedentary behavior, compared to non-burned peers. Time spent in various physical activity intensities and sedentary behavior, relative to age for both boys (left) and girls (right) after burn injury, calculated with an epoch length of (**a**) 15 s and (**b**) 60 s. Non-burned reference values (mean ± 2 SD) for adolescents aged 12.5–17.5 years are presented in (**a**) [20], and reference values for children aged 6–11 years are presented in (**b**) [21], because of the differences in epoch length. *Please note that the cut point for moderate-to-vigorous physical activity in the study of Ruiz et al. [20] was 2000 counts per minute (cpm) compared to the 2296 cpm of Evenson et al. [27] which was used in the current study. Abbreviations: PA = physical activity; MVPA = moderate-to-vigorous physical activity; min = minutes

on screen time [3]. Watching television for more than 2 hours per day has been associated with negative health outcomes like obesity, decreased physical fitness, increased blood pressure, lower self-esteem, social behavioral problems, and decreased academic achievement in school-aged children and youth (5–17 years) [3, 32]. As accelerometry does not distinguish between screen time and other types of sedentary behavior (school, motorized transport, leisure time), it was not possible to determine whether our pediatric burn patients spent too much time watching television or playing computer games. Surprisingly, the current literature provides limited evidence for adverse effects of total time spent in sedentary behavior on health and well-being in children and adolescents [32]. Nevertheless, given the adverse effects among adults, and some evidence of tracking of sedentary behavior across the life course, encouraging children and adolescents to limit their time spent in sedentary behavior for now seems prudent [32].

Although body composition and body weight might also influence physical activity and sedentary behavior, we chose not to include these variables in our regression analyses for several reasons. First, the relationship between body weight / body composition and physical activity and sedentary behavior is probably mutual. Overweight can affect physical activity and encourage sedentary behavior, but, on the other hand, overweight can be the result of poor activity levels and abundant sedentary time. Second, both body weight and body composition are directly related to age and sex in pediatric populations. Healthy body mass index (BMI) increases with age and is different for boys and girls. Adding body weight or BMI to the regression model could therefore lead to over adjustment and create an

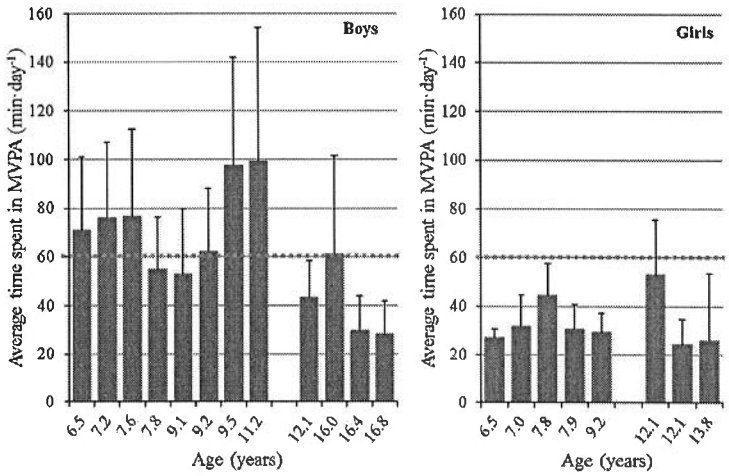

Fig. 4 Attained versus recommended levels of moderate-to-vigorous physical activity (MVPA). Average daily time (mean ± SD) spent in MVPA, relative to age (child, adolescent), for both boys (left) and girls (right) after burn injury, compared to the World Health Organization physical activity recommendation of ≥60 min of MVPA per day (dotted line) [25]. Epoch length: 15 s

apparent effect when none exists [33]. We did assess whether our subjects were classified, with regard to age and sex, as being overweight, underweight, or having healthy weight. All subjects were classified as having healthy weight, except for two girls who were classified as being severely overweight, and one girl was classified as being underweight. Activity levels and sedentary behavior of those three subjects did not deviate from the others, so it was concluded that further analysis would not be of additional value.

Accelerometry is one of the most valid methods to gain insight in habitual activity levels [34, 35], and has frequently been used to assess time spent in physical activity and sedentary behavior in children and adolescents, also in special populations [36–43]. However, comparability among studies is limited, due to the variety in epoch lengths, cut points, and outcome variables. For accurate comparison, accelerometer data should be processed and summarized similarly and in a transparent manner. For those reasons, we chose to adopt the decisions in data reduction and analysis from our reference studies, and to apply the algorithm of Heil et al. [22] for transparency of our methods. To compare our patients data with the results of Konstabel et al. [21], we needed to analyze our accelerometer data with the less favorable epoch length of 60 s, resulting in significantly different outcomes compared to the 15 s–epoch analysis [see Additional file 1]. Time spent in total physical activity and light physical activity calculated from 60s–epochs was significantly higher ($p < .0001$) compared to similar calculations based on 15 s–epochs. Time spent in both vigorous physical activity (and consequently moderate-to-vigorous physical activity) and sedentary behavior, on the other hand, was significantly lower ($p < .0001$) when 60s–epochs were used [see Additional file 1]. Individual level analyses showed that this was a systematic effect of the data processing method [see Additional file 2]. As the physical activity patterns of children and adolescents are typically characterized by frequent, short duration bursts of vigorous physical activity, this effect of epoch length is understandable. Using a 60 s epoch, short bursts of vigorous physical activity will be averaged over the minute and remain undetected. A minute of sedentary behavior, on the other hand, can be incorrectly classified as light physical activity when it contains only one short burst of vigorous physical activity [44, 45]. To obtain a 'real' picture of physical activity and sedentary behavior in children and adolescents, short epoch lengths are thus essential. A study by Edwardson and Gorely [45] suggests that a 5 s epoch would be most appropriate to detect the typical short bursts of vigorous physical activity in children and adolescents. Bland-Altman plots showed however reasonable agreement between the results obtained with 5 and 15 s epochs, which suggests that the results of studies using those epoch lengths could be compared. Studies using 60s–epochs, on the other hand, should not be compared with studies applying epochs ≤15 s [45]. This implies that new accelerometry reference values are needed for children aged 6–11 years, obtained with an epoch length of ≤15 s.

Some limitations of this study need to be discussed. First of all, participation in this study was on a voluntary basis. It is conceivable that this resulted in selection bias. It is unclear, however, how this has affected our results. It could be that those who were already interested or involved in regular physical activity were most willing to participate. On the other hand, those who still

experienced restrictions with activities and participation may have been eager to volunteer for this study.

Secondly, the cross-sectional design of this study and the small number of subjects, make it difficult to explain variance with multiple regression modeling. Nevertheless, the decline in time spent in physical activity and increase in time in sedentary behavior with age in children and adolescents observed in this study is a well-known phenomenon that is also reported in larger, longitudinal studies [23, 24]. As physical activity is known to be affected by social environment, i.e. socioeconomic state, it would have also been interesting to find out whether socioeconomic state could explain some variance in physical activity or sedentary behavior in our study population. Unfortunately, we did not obtain this information from our subjects and could therefore not control for this factor in our analyses.

This preliminary investigation is a first and important start to gain insight in daily time spent in physical activity and sedentary behavior in children and adolescents following moderate-to-severe burns. However, further research is required to obtain a full picture of post burn physical activity levels and to identify those patients who are at greatest risk of inactivity. It would be interesting to examine activity patterns in children who are closer to their burn and to assess how our subjects will do in several years, when they become adults. It has been shown that physical fitness is low in a large proportion of adult patients even decades post-burn [46]. It would therefore be interesting to examine activity patterns of adult burn patients as well.

Conclusions

Duration and intensity of physical activity and sedentary behavior in children and adolescents 1–5 years after burn injury were similar to non-burned peers. However, only 35% of the group met the WHO physical activity recommendation. Given the increased risk for physical conditions following pediatric burns, physical activity should be encouraged in this vulnerable population.

Additional files

Additional file 1: Accelerometry outcomes calculated from 15 s–epochs and 60s–epochs. As the physical activity patterns of children are typically characterized by frequent, short duration bursts of vigorous physical activity, short epoch lengths are essential to obtain a 'real' picture of their physical activity and sedentary behavior. The significant differences in accelerometry outcomes calculated from 15 s–epochs and 60s–epochs indicate that the use of 60s–epochs should be discouraged in pediatric populations. (DOCX 28 kb)

Additional file 2: The systematic effect of epoch length. This figure shows the systematic overestimation of time spent in light physical activity and the systematic underestimation of both time in vigorous physical activity and sedentary behavior, when 60s–epochs are used rather than 15 s–epochs. Abbreviations: SB = sedentary behavior; PA = physical activity; min = minutes, sec = second. (TIFF 969 kb)

Abbreviations

SD: Standard deviation; SEE: Standard error of the estimate; WHO: World Health Organization

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Availability of data and materials

Data are from the cross-sectional descriptive study as described by Disseldorp et al. [18] whose authors may be contacted at m.akkerman@mzh.nl. The datasets used and analyzed for the current study are available on reasonable request.

Authors' contributions

LJM, LMD, MVB, LHVVDW, and MKN developed the study design. LMD was responsible for the acquisition of the accelerometer data and MA was responsible for collecting, processing, and summarizing these data into physical activity and sedentary behavior outcome variables. ASN and MA performed the statistical analysis and interpretation of the data. MA, LJM, and MKN were responsible for drafting the manuscript and LMD, ASN, MVB, and LHVVDW critically revised it. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Medical Ethical Committee of the University Medical Center Groningen approved this study (NL40183.042.12). All parents (or legal representatives) and participants aged ≥12 years provided written informed consent before enrolment; only for subjects aged 18 parental informed consent was not required.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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CHAPTER 3:

Perceived fatigue following pediatric burn injuries

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Perceived fatigue following pediatric burns

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ABSTRACT

Purpose: Fatigue is a common consequence of numerous pediatric health conditions. In adult burn survivors, fatigue was found to be a major problem. The current cross-sectional study is aimed at determining the levels of perceived fatigue in pediatric burn survivors.

Methods: Perceived fatigue was assessed in 23 children and adolescents (15 boys and 8 girls, aged 6–18 years, with burns covering 10–46% of the total body surface area, 1–5 years post burn) using both child self- and parent proxy reports of the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale. Outcomes were compared with reference values of non-burned peers.

Results: At group level, pediatric burn survivors did not report significantly more symptoms of fatigue than their non-burned peers. Individual assessments showed, however, that four children experienced substantial symptoms of fatigue according to the child self-reports, compared to ten children according to the parent proxy reports. Furthermore, parents reported significantly more symptoms of fatigue than the children themselves. Age, gender, extent of burn, length of hospital stay, and number of surgeries could not predict the level of perceived fatigue post-burn.

Conclusions: Our results suggest that fatigue is prevalent in at least part of the pediatric burn population after 1–5 years. However, the fact that parents reported significantly more symptoms of fatigue then the children themselves, hampers evident conclusions. It is essential for clinicians and therapists to consider both perspectives when evaluating pediatric fatigue after burn and to determine who needs special attention, the pediatric burn patient or its parent.

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Abbreviations: TBSA, total body surface area; HRQOL, health-related quality of life; PedsQL MFS, Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.

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1. Introduction

In the Netherlands, every year 700–800 patients are admitted to one of the three designated burn centres. Approximately 35% of this group is younger than 18 years of age [Dutch Burn Repository R3, 2015]. Burns suddenly disrupt daily life and are generally followed by extensive periods of hospital stay, dominated by painful wound treatments, and often accompanied by (multiple) surgical procedures. As survival rates have increased substantially over the past decades [1,2], it becomes more and more relevant to focus on long-term outcomes of health and quality of life of burn survivors. The ultimate goal of pediatric burn rehabilitation is to assist children in returning to their pre-injury functional status as soon as possible, while maximizing their emotional and cosmetic outcomes [3].

Fatigue is a commonly experienced consequence in numerous pediatric health conditions and has been associated with poorer functional outcome and diminished quality of life [4]. Fatigue can be defined as a *'persistent, overwhelming sense of tiredness, weakness or exhaustion, resulting in a decreased capacity for physical and/or mental work, which is unrelieved by sleep or rest'* [5,6]. In adult burn survivors, fatigue has been described as a major problem [7–9], even decades post burn [9]. An extreme sense of tiredness was reported to restrict their adjustment to daily life after burn [8,10]. Post burn fatigue might also limit children and adolescents in engaging in physical and cognitive daily activities, affecting their functional independence, school performance, peer relationships, sports participation, and social life. Additionally, restrictions in daily (physical) activities can have significant implications for cardiovascular health and associated diseases in the long term [11]. For these reasons, it is deemed important to evaluate functional outcome and health as well as perceived fatigue after pediatric burns. Surprisingly, fatigue has not been studied in this pediatric population thus far.

As the definition implies that fatigue is a subjective experience, it is preferably assessed using self-report. In pediatric populations, however, parents are also generally asked to report on their child's experience. The question is, how do parent proxy reports compare to those of their children? In the assessment of fatigue, imperfect agreement between child self- and parent proxy report has been frequently reported [12–19]. Previous studies in the pediatric burn population showed that parents tended to rate their child's health-related quality of life (HRQOL) [20,21] and psychological adjustment [22] worse than the children themselves. These findings highlight the importance in obtaining both perspectives when evaluating post burn fatigue.

The aim of the current cross-sectional study was therefore to determine the levels of perceived fatigue in pediatric burn survivors .5–5 years post burn, as reported by both the children and their parents.

2. Methods

2.1. Study population

Potentially eligible subjects were identified based on the Dutch Burn Repository R3. In the period from August till December 2012, children and adolescents aged 6–18 years were invited to participate if they had been admitted to one of the Dutch burn centres .5–5 years ago, with burns covering ≥10% of their total body surface area (TBSA), and/or a length of stay of more than six weeks. Furthermore, discharge and/or reconstructive surgeries had to be at least 2 months before the time of the assessment. Extensive (pre-existing) co morbidity, (mental) disabilities, and insufficient Dutch language proficiency, were criteria for exclusion. Written informed consent was obtained from all parents (or legal representatives) as well as from the subjects aged ≥12 years, before enrolment in the study. For subjects aged 18, parental informed consent was not required. The Medical Ethical Committee of the University Medical Centre Groningen approved this study (NL40183.042.12).

This study was part of a cross-sectional descriptive study on physical fitness and physical activity in children and adolescents after burn, as described by Disseldorp et al. [23]. The total study involved the assessment of physical fitness, physical activity, fatigue, and HRQOL; study procedures were described previously in detail [23]. For all subjects, age, gender, extent of burn, location of burns, presence of inhalation injury, number of surgeries and dates of the burn incident, admission and discharge were obtained from the Dutch Burn Repository R3.

2.2. Data collection and analysis

Perceived fatigue was assessed using the Dutch version [12] of the 18-item Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) [14], according to best evidence [24]. The PedsQL MFS was specifically designed to measure child and parent perceptions of fatigue in pediatric patients [14] and has been used in a variety of pediatric health conditions, including cancer [19,25], sickle cell disease [18], obesity [17], diabetes [16], arthritis [15,26], and hearing loss [27]. The Dutch version was shown to be valid and reliable, and Dutch reference values are available [12]. These fairly recent reference values (2011) were attained from 366 child reports and 393 parent reports of Dutch children and adolescents aged 5–18 years. Both child self- and parent proxy reports were obtained and scores were presented separately for three age categories: 5–7 (young child), 8–12 (child), and 13–18 (adolescent) years old [12].

The PedsQL MFS covers three subdomains: (1) General Fatigue (6 items, e.g., 'I feel tired', 'I feel too tired to do things that I like to do'), (2) Sleep/Rest fatigue (6 items, e.g., 'I feel tired when I wake up in the morning', 'I rest a lot') and (3) Cognitive Fatigue (6 items, e.g., 'It is hard for me to keep my attention on things', 'It is hard for me to remember what people just told me') [14].

The PedsQL MFS comprises parallel child self-report and parent proxy report forms [14]. Three versions of the child self-report forms were used corresponding to the three age categories: 5–7 (young child), 8–12 (child), and 13–18 (adolescent) years old. The parent proxy report form, designed to assess the parent's perceptions of their child's fatigue, was taken parallel to the child self-report forms. Items for each of the forms were essentially identical, differing only in developmentally appropriate language, or first or third person [15].

For each item, subjects were asked to rate how often a particular problem had occurred in the past month, using a 5-point Likert scale (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). For the young child self-report (ages 5–7), the Likert scale was simplified to a 3-point scale (0=not at all a problem; 2=sometimes a problem; 4=a big problem), represented by happy to sad faces [15].

In accordance with the PedsQL MFS instructions, each item was reverse-scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0). Higher PedsQL MFS scores thus indicate better outcome, i.e. fewer symptoms of fatigue. Domain scores were calculated as the sum score of the domain items divided by the number of domain items answered. Total fatigue was calculated as the sum score of all items divided by the number of items answered in all domains [15].

2.3. *Statistical analyses*

PedsQL MFS scores of both children and parents were calculated as means with standard deviations and ranges [14]. Range of measurement was assessed by calculating the number and percentage of lowest possible scores (floor effect) and highest possible scores (ceiling effect) for each age group. Floor and ceiling effects were assumed evident if more than 25% of the subjects reported respectively the lowest or highest possible score on total fatigue or one of the PedsQL MFS subdomains [28]. Multivariate analysis of variance was performed to examine differences in scores between the three subdomains of the PedsQL. Differences between child self-report and parent proxy reports were described and tested using paired samples t-tests.

To assess whether children and adolescents after burn reported significantly higher levels of perceived fatigue compared to non-burned references, one-tailed independent samples t-tests were used. The unequal distribution of subjects across age groups in our study sample was controlled for by calculating weighted means and SDs for the non-burned reference group.

Additionally, individual PedsQL MFS scores of our patients and their parents were plotted in figures together with age-group matched Dutch reference values (mean and 1 SD below the mean). In line with the interpretation of PedsQL HRQOL scale scores in other pediatric health conditions [29,30], subjects who scored more than one SD below the non-burned reference mean on the PedsQL MFS were assumed *at risk* for fatigue-related difficulties. In a typically developing population, assuming normal distribution, approximately 16% of the children will score more than one, and 2.5% will score more than two SD below the population mean.

Exploratory multiple regression analyses were performed to identify potential predictors of total fatigue and its subdomains. First, both age and gender were entered simultaneously in the model, as Gordijn et al. [12] showed that these factors are associated with fatigue in healthy children; e.g. older children and boys experience more fatigue. Subsequently, the extent of burn (% of TBSA involved), time post burn (years), age at burn (years), length of hospital stay (days), and number of surgeries were entered separately, one by one, to examine whether the regression model could be improved by one or more of these potential predictors.

IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp.) was used for the statistical analyses. An alpha-level of 5% was adopted, so p-values below .05 were considered statistically significant.

3. Results

Data from 23 children and adolescents with burns (15 boys and 8 girls, aged 6–18 years, with burns covering 10–46% of their TBSA) were included in the current study (Fig. 1 and Table 1). Of one subject only a child self-report, and of two subjects only a parent proxy report was obtained. For 20 subjects, both self- and parent proxy reports were available. All obtained questionnaires were filled in completely.

3.1. *PedsQL Multidimensional Fatigue Scale outcomes*

3.1.1. *Total fatigue*

PedsQL MFS child report scores on total fatigue ranged from 58.3 to 100, with similar scores across the three age groups (Table 2). PedsQL MFS parent proxy scores on total fatigue ranged from 48.6 to 100, with again similar scores across the age groups (Table 2).

3.1.2. *General fatigue*

Child report scores for the total group ranged from 75 to 100, while parent proxy scores ranged from 37.5 to 100. Although statistically non-significant, most symptoms of general fatigue were reported by the children aged 8–12 years and the parents of the adolescent group (Table 2).

3.1.3. *Sleep/rest fatigue*

Child report scores for the total group ranged from 50 to 100, while parent proxy scores ranged from 37.5 to 100. Although statistically non-significant, most symptoms of sleep/rest fatigue were observed in the adolescent group according to both child self- and parent proxy reports (Table 2).

3.1.4. *Cognitive fatigue*

Child report scores for the total group ranged from 50 to 100, while parent proxy scores ranged from 37.5 to 100. Although statistically non-significant, most symptoms of cognitive fatigue, were observed in the youngest group according to both child self- and parent proxy reports (even though three of these young children (37.5%) reported no cognitive fatigue at all) (Table 2).

Of all three PedsQL MFS domains, the children and adolescents reported the least amount of symptoms on general fatigue ($F=11.3$; $p=.001$). Their parents also reported this domain to be least affected ($F=2.95$; $p=.078$).

None of the subjects reported extreme symptoms of fatigue (score 0) on any of the PedsQL MFS domains. One child and one parent reported no perceived fatigue at all (score 100 on all PedsQL MFS domains). Evident ceiling effects were found on

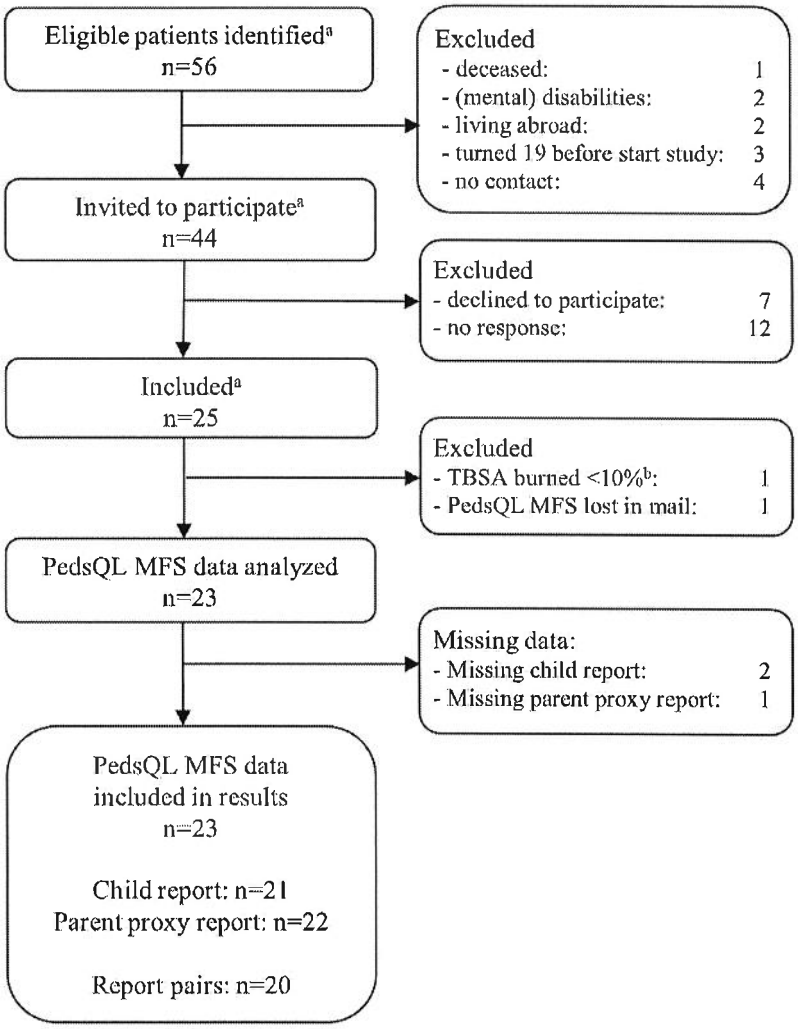

Fig. 1 – Flow of patients.
[a]Study of Disseldorp et al. [44]. [b]This child was registered as having burns covering >15% of total body surface area (TBSA). It emerged however that its burns had in fact affected <5% of TBSA. Therefore, this child was excluded.

the general fatigue domain in the child reports of both the youngest group (6–7 years; 50%) and the adolescent group (13–18 years; 50%), and in the parent proxy reports of the child group (8–12 years; 44.4%) (Table 2). On the cognitive fatigue domain, an evident ceiling effect was found in the child reports of the youngest group (37.5%) (Table 2).

Table 1 – Characteristics of the study sample.

	Young child group (6–7 years) n=9 (5 boys, 4 girls)			Child group (8–12 years) n=9 (6 boys, 3 girls)			Adolescent group (13–18 years) n=5 (4 boys, 1 girl)			Total sample n=23 (15 boys, 8 girls)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age (years)	7.3	.6	6.4–7.9	10.6	1.3	9.1–12.2	16.3	1.7	13.7–18.6	10.5	3.6	6–18
TBSA burned (%)	19.0	13.0	10–46	17.6	4.6	10–24	18.6	8.7	11–31	18.4	9.1	10–46
Surgeries (#)[a]	1		0–7	2		0–3	1		1–2	1		0–7
Time post burn (years)	3.3	1.2	1–5	2.8	1.4	1–5	3.0	1.5	1–5	3.0	1.3	1–5
Length of stay (days)	31.7	21.3	16–78	26.3	4.3	23–37	30.0	9.7	20–42	29.2	14.0	16–78

Abbreviations: TBSA=total body surface area.
[a] Number of surgeries, mode instead of mean.

Table 2 – Outcomes of the PedsQL Multidimensional Fatigue Scale after paediatric burns per age group.

	Young child group (6–7 years)					Child group (8–12 years)					Adolescent group (13–18 years)				
	N	Mean	SD	Range	Ceiling#[a]	N	Mean	SD	Range	Ceiling#[a]	N	Mean	SD	Range	Ceiling#[a]
Child report															
Total fatigue	8	84.0	13.8	58–100	1 (12.5%)	9	84.6	9.4	68–98	0 (0%)	4	86.8	7.6	76–95	0 (0%)
General fatigue	8	92.7	9.4	75–100	4 (50%)[b]	9	88.4	9.7	75–100	2 (22.2%)	4	96.9	4.0	91–100	2 (50%)[b]
Sleep/rest fatigue	8	83.3	16.1	50–100	2 (25%)	9	80.6	14.6	58–100	1 (11.1%)	4	75.0	8.3	70–88	0 (0%)
Cognitive fatigue	8	76.0	22.0	50–100	3 (37.5%)[b]	9	84.7	16.3	58–100	2 (22.2%)	4	88.5	15.0	66–100	1 (25%)
Parent proxy report															
Total fatigue	9	77.3	9.3	59–89	0 (0%)	9	78.9	16.0	48–100	1 (11.1%)	4	75.4	9.5	66–89	0 (0%)
General fatigue	9	84.3	9.7	70–100	1 (11.1%)	9	82.9	22.5	37–100	4 (44.4%)[b]	4	79.2	14.0	70–100	1 (25%)
Sleep/rest fatigue	9	82.9	15.9	54–100	1 (11.1%)	9	78.2	19.5	37–100	1 (11.1%)	4	72.9	11.0	62–88	0 (0%)
Cognitive fatigue	9	64.8	20.8	37–96	0 (0%)	9	75.5	15.4	58–100	2 (22.2%)	4	74.0	6.3	66–80	0 (0%)

Higher scores reflect better outcome, i.e. fewer symptoms of fatigue.
[a] Number (and %) of subjects with the highest possible domain score of 100 (no symptoms of fatigue).
[b] Evident ceiling effect: >25% of subjects reported the highest possible domain score.

3.2. *Parent–child agreement*

Mean child report PedsQL MFS scores were higher compared to the mean parent proxy report scores, indicating that children and adolescents following burn generally reported less perceived fatigue in comparison to their parents (Fig. 2). These differences were statistically significant for total fatigue ($t_{(19)}$ =2.906, p=.009), general fatigue ($t_{(19)}$=2.442, p=.025), and cognitive fatigue ($t_{(19)}$=2.714, p=.014), but not for sleep-rest fatigue ($t_{(19)}$=1.211, p=.241).

3.3. *Comparison with non-burned peers*

At group level, both child self- and parent proxy report scores of the burn sample were not significantly lower than non-burned reference scores for total fatigue, general fatigue, and cognitive fatigue (Table 3). For sleep/rest fatigue, parent proxy scores of the burn sample were significantly lower than the parent proxy scores of the non-burned reference group ($t_{(413)}$ =−2.1557, p=.016), indicating that pediatric burn survivors experience more symptoms of sleep/rest fatigue than non-

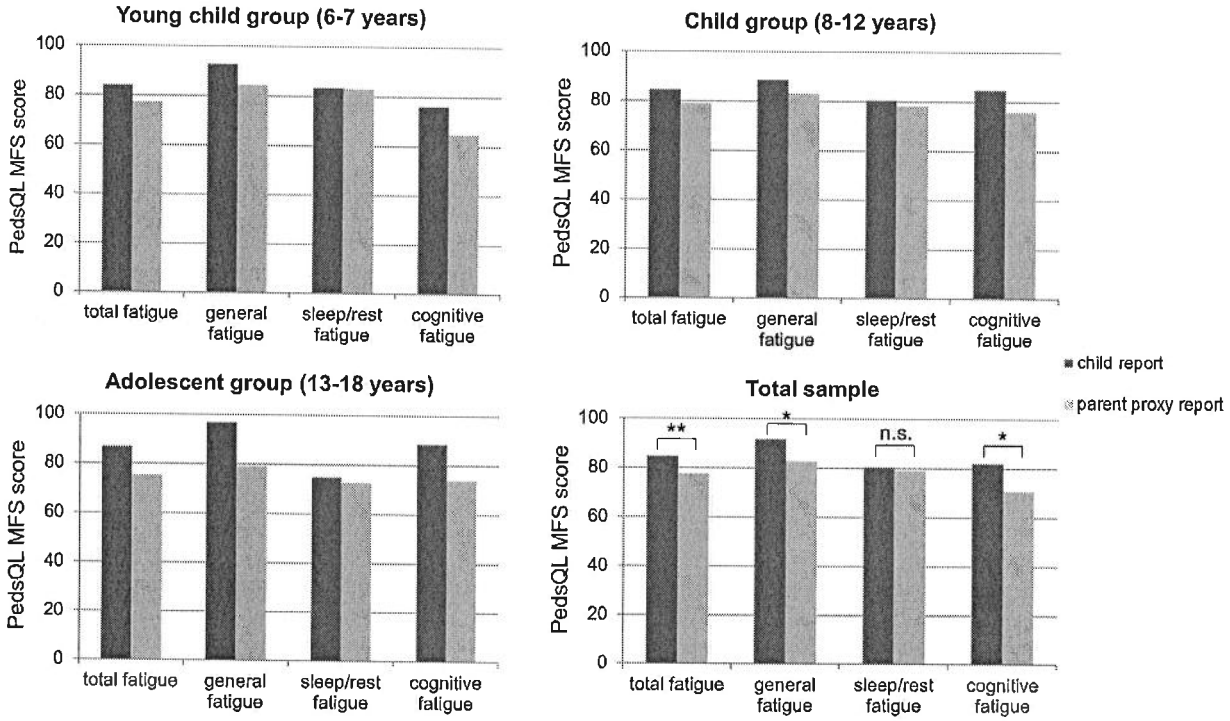

Fig. 2 – Child report (n=21) versus parent proxy report (n=22) scores on the PedsQL Multidimensional Fatigue Scale. Higher scores reflect better outcome, i.e. fewer symptoms of fatigue. *p<.05; **p<.01.

Table 3 – PedsQL Multidimensional Fatigue Scale outcomes in paediatric burn survivors compared to non-burned peers.

Child report	Burn survivors			Non-burned peers[a]				>1SD below non-burned mean# (%)[c]	>2SD below non-burned mean# (%)[d]
	N	Mean	SD	N	Mean	SD	*p*-Value[b]		
Total fatigue	21	84.8	10.6	366	77.2	13.0	.995	1 (4.8%)	0 (0%)
General fatigue		91.7	9.0		81.8	14.3	.999	0 (0%)	0 (0%)
Sleep/rest fatigue		80.6	14.0		75.1	16.3	.933	3 (14.3%)	0 (0%)
Cognitive fatigue		82.1	18.3		74.7	19.4	.957	2 (9.5%)	0 (0%)
Parent proxy report									
Total fatigue	22	77.6	12.0	393	81.5	12.4	.075	4 (18.2%)†	2 (9.1%)‡
General fatigue		82.8	16.0		82.2	13.7	.569	3 (13.6%)	1 (4.5%)‡
Sleep/rest fatigue		79.2	16.5		85.5	13.2	.016*	6 (27.3%)†	4 (18.2%)†
Cognitive fatigue		70.8	17.0		76.8	18.4	.068	4 (18.2%)†	2 (9.1%)‡

Higher scores reflect better outcome, i.e. fewer symptoms of fatigue.
* $p<.05$.
† >16%.
‡ >2.5%.
[a] Gordijn et al. [12], weighted means and SDs.
[b] Independent samples t-tests, one-tailed.
[c] Number (and %) of subjects scoring more than 1 SD below the mean of non-burned peers (assessed per age group). This includes 16% in a typically developing population, assuming normal distribution.
[d] Number (and %) of subjects scoring more than 2 SD below the mean of non-burned peers (assessed per age group). This includes 2.5% in a typically developing population, assuming normal distribution.

burned peers according to their parents. Child report scores on this domain were not significantly lower than those of their non-burned peers (Table 3).

Individual analyses revealed that, according to the 21 child reports, none of the subjects was at risk for general fatigue, three (14%) were at risk for sleep/rest fatigue, and two (10%), both from the youngest group (6–7 years), were at risk for cognitive fatigue (Table 3 and Fig. 3). According to the 22 parent proxy reports, three subjects (14%) were at risk for general fatigue, six (27%) were at risk for sleep/rest fatigue, and four (18%), all from the youngest group (6–7 years), were at risk for cognitive fatigue (Table 3 and Fig. 3).

Overall, ten subjects were found to be at risk on at least one PedsQL MFS domain according to their parents. Four of them, the ones whose parents scored them 'at risk' on two or more PedsQL MFS domains, had also a self-reported score >1 SD below their non-burned peers on at least one domain.

3.4. *Predictors of fatigue*

Exploratory linear regression analyses showed that time post burn was significantly associated with child report scores of total fatigue (β −4.4; 95% CI: −.7.9 to −1.0; $p=.013$) and cognitive fatigue (β −7.9; 95% CI: −13.7 to −2.0; $p=.011$). These cross-sectional associations suggest that perceived fatigue, especially on the cognitive domain, may be worse with longer time post burn. Age at burn was also significantly associated with child report scores of cognitive fatigue (β 2.2; 95% CI: .05–4.4; $p=.046$). This cross-sectional association suggests that children who have a burn at a younger age, experience more symptoms of cognitive fatigue on the long term. Time post burn alone explained 28.2% of the variance in total fatigue (SEE=9.17, model $p=.01$) and 29.2% of the variance in cognitive fatigue (SEE=15.81, model $p=.01$). Adding age at burn to the regression model explaining cognitive fatigue, resulted in a significantly higher percentage explained variance: R-square improved from 29.2 to 39.4% (SEE=15.03, model $p=.01$). Age, gender, %TBSA burned, length of hospital stay, and number of surgeries could not predict the level of perceived fatigue post burn. Regression analyses on parent proxy reports did not reveal significant predictive value of any of the selected variables for the level of perceived fatigue.

4. Discussion

The current study describes perceived fatigue, expressed as PedsQL MFS scores, in 23 children and adolescents aged 6–18 years with a wide range of burn characteristics, 1–5 years post burn. Of all three PedsQL MFS domains, the least amount of symptoms were reported on general fatigue. At group level, pediatric burn survivors did not report significantly more symptoms of fatigue than their non-burned peers. Their parents reported significantly more symptoms on sleep/rest fatigue than the parents of the non-burned reference group. Individual self-reports revealed that four subjects (19%) perceived substantial symptoms of sleep/rest and/or cognitive fatigue (score more than one SD below the non-burned reference mean). According to the parent proxy reports, ten subjects (45%) were at risk on at least one PedsQL MFS domain.

Parents reported significantly more symptoms of fatigue compared to the children themselves. This finding is in line with previous findings in other pediatric burn samples, where parents tended to underestimate their child's HRQOL [20,21] and psychological adjustment [22] post burn. In the non-burned reference group, children and adolescents reported significantly more symptoms of fatigue than reported by their parents [12]. Possible reasons for these findings might be that

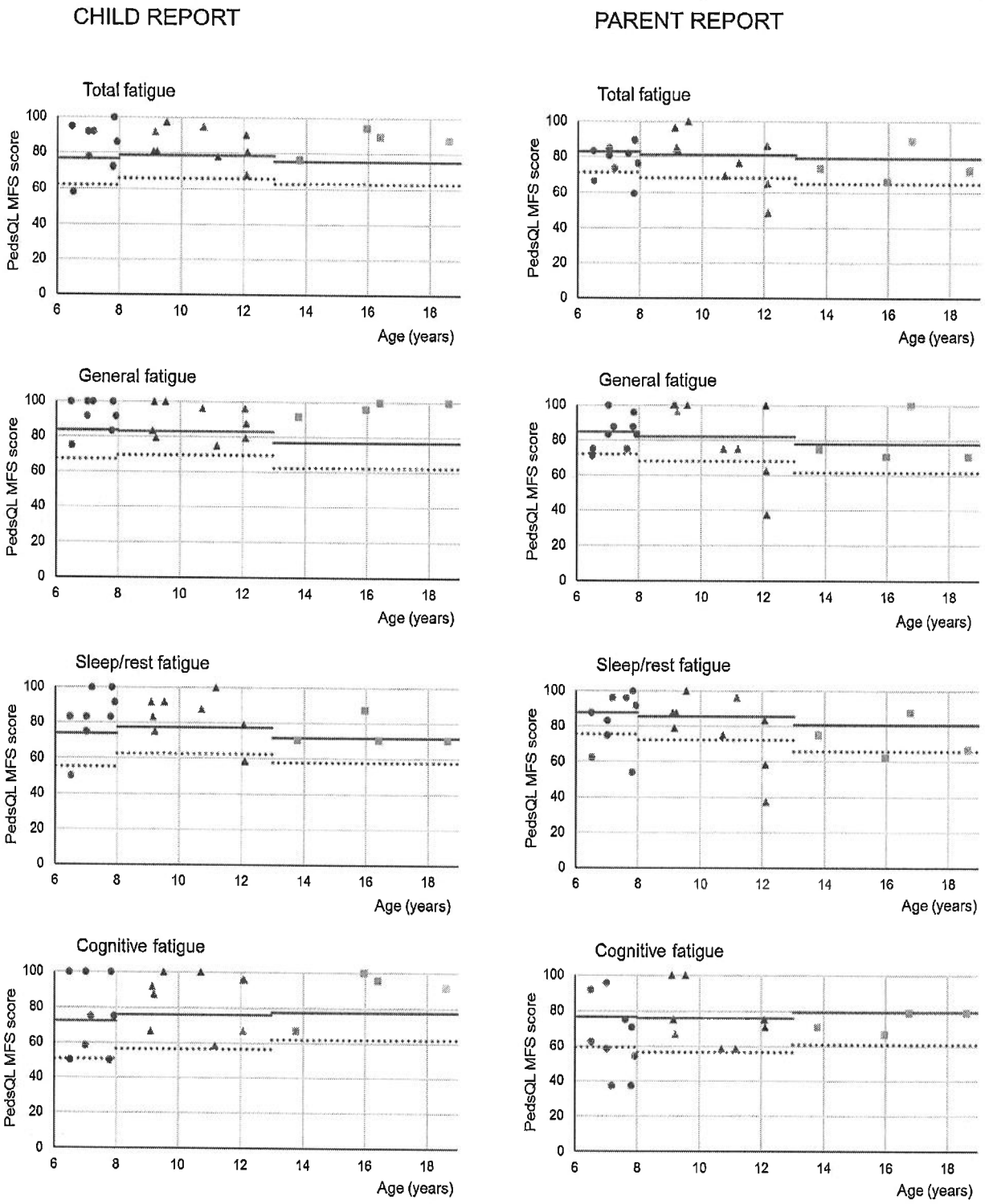

Fig. 3 – Individual PedsQL Multidimensional Fatigue Scale outcomes of paediatric burn survivors compared to non-burned age-group matched reference values.
Higher scores reflect better outcome, i.e. fewer symptoms of fatigue.
Legend: dots—young child group (aged 6–7 years); triangles—child group (aged 8–12 years); squares—adolescent group (aged 13–18 years); solid lines—age group-specific reference mean; dotted lines—1 SD below age group-specific reference mean.

pediatric burn survivors underestimate or deny their feelings of fatigue, or that their positive ratings are a consequence of a shift in internalized standards of fatigue [13,31]. Their parents could, on the other hand, overrate symptoms of fatigue due to exaggerated concerns or, in some cases, their own post-traumatic stress symptoms. Unfortunately, none of these issues has been studied thus far.

Previous research has demonstrated higher discrepancies for internalizing or less readily observable measures, like fatigue, pain, and emotional distress, in comparison with externalizing or more easily observed measures of physical functioning [32,33]. The differences found between child self- and parent proxy reports in the assessment of fatigue are therefore not surprising. The question is, whose perceptions tell us most about how the child is really doing and should lead the treatment by clinicians and therapists? On the one hand, one could argue that the child's perspective should be leading, as the child knows best if he/she experiences fatigue. On the other hand, however, it is not exactly known how adequately children can score subjective feelings of fatigue on a rating scale. Davis et al. [34] examined the discordance between child self-report and parent proxy reports of HRQOL and found that children tended to have different response styles and different ways of reasoning compared to their parents. For example, some dyads provided the same reasoning for a particular item, but rated the item differently. Children and parents might thus interpret or use rating scales differently. Furthermore, they found that children tended to base their response on one single example. Parents, on the other hand, tended to cite several examples or might even base their responses on the child's usual disposition, rather than the child's functioning throughout the previous week [34]. The perception of the parents at variance from the child absolutely supports the importance of measuring both perspectives in evaluating pediatric fatigue [13]. For clinicians and therapists it is essential to consider both perspectives when evaluating post burn fatigue and to determine who needs special attention, the pediatric burn patient or its parent. Previous research has indicated that it was often the parent's perception of their child's health, even more than actual symptoms, that influenced health care utilization [35]. Moreover, a recent study showed that discrepancies between child self- and parent proxy reports of fatigue were associated with negative mood and increased activity limitations, at least in children with juvenile idiopathic arthritis [36]. For these reasons, it is certainly worthwhile exploring the complex psychological factors that may be involved with these differences.

As the ultimate goal of pediatric burn rehabilitation is to help children return to their pre-injury functional status [3], it is important to identify which children are at risk for post burn fatigue. In contrast to recent findings in adults [37], neither extent of the burn, nor length of hospital stay were predictive for perceived fatigue in our study sample. Time post burn predicted 29.2% of the variance in child self-reported symptoms of cognitive fatigue, and consequently total fatigue (28.2%). Contrary to prior expectations, however, symptoms of cognitive fatigue tended to *increase* with time post burn. Children for whom the burn was longer ago at the time of assessment reported more symptoms of cognitive fatigue. The model explaining cognitive fatigue was improved by adding age at burn (39.4% of variance explained). This finding indicates that age at burn also plays a role in predicting perceived cognitive fatigue in pediatric burn survivors. Burns at younger age would lead to higher levels of perceived cognitive fatigue in the long term. Another notable finding was that all 'at risk'-scores for cognitive fatigue were found in the youngest group (6–7 years), in the age range at which children learn to read and write in the Netherlands. Unfortunately, no evidence is available yet on cognitive difficulties after pediatric burns in the current literature. Nonetheless, concentration problems manifesting a few years post burn are a clinically common conveyed complaint from children and/or their parents during the regular follow-up visits in our burn center [personal communications]. These findings emphasize the need for consequent longitudinal monitoring of post burn fatigue. Although children and their parents can always contact staff at the burn centres in case of problems, they might not realize that symptoms of fatigue even years after the injury, can still be a consequence of their burns. Therefore, it can be helpful to inform parents and their children about this possible long-term consequence of burn. Once the problem of (cognitive) fatigue is identified, and other possible causes rejected, physical exercise [38,39] or cognitive behavioral therapy [40,41] might help to reduce perceived levels of fatigue and improve HRQOL.

According to the definition [5,6], disease-associated fatigue is unrelieved by sleep and rest. It is feasible, however, that disturbed sleeping patterns worsen the symptoms of fatigue. Sleep problems after pediatric burns are common in the acute pediatric burn population, and have also been reported several years post burn [42,43]. Mayes et al. [42] found a marked reduction in the restorative phases of sleep and diminished sleep efficiency in children and adolescents with burns who exhibited sleep problems during hospital stay or whose parents reported disturbed sleep at home. In our study sample, only three of the 23 subjects or their parents reported sleep problems. However, those subjects were not the ones who were assumed at risk for fatigue-related difficulties according to their PedsQL MFS scores.

Evidently, our sample size and ceiling effects hampered the interpretation of the multiple regression analyses. Therefore, caution is warranted when interpreting our results. However, the finding that burn severity does not predict outcome in pediatric burn patients is not uncommon. Earlier findings of our research group indicated that burn severity was also not associated with muscle strength [44], aerobic capacity [44], or levels of physical activity [Akkerman et al., submitted] in this study sample. These findings are also in line with other studies indicating that the extent of burn does not explain variance in activity and participation [45] or psychological outcome [46] in children and adolescents after burn. In adults, on the other hand, burn severity does seem to influence outcome, e.g. return to work [47], muscle strength [48], and fatigue [7,37]. These differences point out the importance of (longitudinal) pediatric burn outcome studies, as children can and may not be seen as "little adults".

Some limitations of the current study need to be discussed. First, participation in this study was – of course – on a voluntary basis. It is conceivable that this resulted in selection bias, with the children who were fatigued not willing to participate in this cross-sectional study comprising extensive

physical fitness and activity measures [23]. Accordingly, it is reasonable that a larger part of the pediatric burn population is at risk for fatigue-related difficulties than presented in the current study. Therefore, incorporation of the PedsQL MFS during regular follow-up visits is warranted.

Secondly, evident ceiling effects were found in both the general and cognitive domain of the PedsQL MFS. In the non-burned reference group, these ceiling effects were not observed [12]. Generally, questionnaires with evident floor and/or ceiling effects are considered less precise in measuring latent constructs (e.g. fatigue) at the extremes of the scaling range [18]. The ceiling effects, in combination with the cross-sectional design of this study and the number of subjects, made it difficult to explain variance with multiple regression modeling. However, the fact that no effect was found for burn severity is in line with previous findings on pediatric post burn outcome studies. Furthermore, the fact that more symptoms of cognitive fatigue were reported with longer time post burn, on the other hand, matches the clinical experiences of our burn care staff [personal communications]. In general, ceiling effects underline the importance of examining individual scores rather than group means and pay special attention to the subjects with suboptimal outcomes, especially in small (patient) samples.

Lastly, we do realize that the PedsQL MFS evaluates only *subjective* perceptions of the complex multidimensional construct called fatigue [49]. Moreover, these child- and parent proxy report scales primarily focus on psychosocial and cognitive aspects of fatigue. Physical problems, like earlier onset of fatigue during exercise and longer time needed for recovery, are not assessed by the PedsQL MFS. To expand our understanding of fatigue after pediatric burns, it would be interesting to examine *objective* performance fatigability as well, during both motor and cognitive tasks [49]. Furthermore, it would be interesting to longitudinally assess both subjective perceptions of fatigue and objective performance fatigability at discharge from the burn center and during the following months/years.

5. Conclusions

This study is a first and important start to gain insight in symptoms of fatigue in children and adolescents after burn. Although our results suggest that fatigue is prevalent in at least part of the pediatric burn population, the remarkable differences between child self- and parent proxy reports (19% and 45% respectively) hamper evident conclusions. The perception of the parents at variance from the child with regard to perceived fatigue after burn is certainly worth exploring the complex psychological factors that may be involved with these differences. For clinicians and therapists, it is essential to consider both perspectives when evaluating pediatric fatigue after burn and to determine who needs special attention, the pediatric burn patient or its parent.

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Conflicts of interest

The authors declare no conflicts of interest.

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CHAPTER 4:

The Oxygen Uptake Efficiency Slope: what do we know?

Akkerman M, Van Brussel M, Hulzebos HJ, Vanhees L, Helders PJM, Takken T (2010). The Oxygen Uptake Efficiency Slope: what do we know? JCRP, 2010, 30, 357-373

The Oxygen Uptake Efficiency Slope

WHAT DO WE KNOW?

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- **PURPOSE:** To summarize what is currently known about the oxygen uptake efficiency slope (OUES) as an objective and independent submaximal measure of cardiorespiratory fitness in health and disease.
- **METHODS:** A literature search was performed within the following electronic databases—PubMed, Cochrane Library, Embase, Web of Science, CINAHL, PsycINFO, Scopus, and MEDLINE—using the search terms "OUES," "oxygen uptake efficiency slope," and "ventilatory efficiency." The search identified 51 articles. Selection, evaluation, and data extraction were accomplished independently by 2 authors.
- **RESULTS:** Twenty-four studies satisfied all inclusion criteria: 17 cross-sectional studies and 7 intervention studies. The results indicated that the OUES is relatively independent of exercise intensity, correlates highly with other exercise parameters, appears to have discriminative value, and is sensitive to the effects of physical training in patients with cardiac disease. Oxygen uptake efficiency slope values are considerably influenced by anthropometric variables and show large interindividual variation.
- **CONCLUSION:** Oxygen uptake efficiency slope is an independent and reproducible measure of cardiorespiratory function that does not require maximal exercise. It greatly reduces test variability because of motivational and subjective factors and is reliable and easily determinable in all subjects. Although OUES appears not interchangeable with maximal parameters of cardiopulmonary function, it seems to be a useful submaximal alternative in subjects unable to perform maximal exercise.

K E Y W O R D S

exercise parameter

OUES

oxygen uptake efficiency slope

ventilatory efficiency

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Exercise testing is widely used in clinical practice to assess the response of both patients and healthy people to exercise. Maximal oxygen uptake ($\dot{V}O_{2max}$), the highest rate at which an individual can utilize oxygen during exercise, is widely recognized as the single best measure of aerobic fitness.[1] Theoretically, it is defined as the point at which oxygen uptake ($\dot{V}O_2$) reaches a plateau despite further increases in work rate; however, a true plateau is not always attained during standard incremental exercise testing.[2,3] Therefore, this objective measure is regularly replaced by the rate of oxygen uptake that occurs at peak exercise ($\dot{V}O_{2peak}$),[4-7] even though $\dot{V}O_{2peak}$ measurement is influenced by patient characteristics and motivation, the selected exercise protocol, and the experience of the tester to determine the peak during exercise.[4,8-10]

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A number of indices that do not require maximal exercise have been introduced, including the oxygen uptake at the ventilatory anaerobic threshold (VAT), the slope of the regression line between minute ventilation ($\dot{V}_E$) and carbon dioxide production ($\dot{V}_{CO2}$) ($\dot{V}_E/\dot{V}_{CO2}$ slope), and the extrapolated maximal oxygen uptake (EMOC).[7,11-13] However, several limitations have been reported in the literature with regard to these measures.[7] Ventilatory anaerobic threshold, for example, is not identifiable in all subjects,[8,14] and controversy remains with regard to the reproducibility of this measurement, since seldom a distinct point of change in ventilation can be identified.[15-17] Moreover, VAT appears to be protocol dependent and its value is considerably influenced by the nutritional state of the subject (eg, carbohydrate loaded or depleted).[8,16] Although the prognostic value of the $\dot{V}_E/\dot{V}_{CO2}$ slope is robust in patients with heart failure (HF)[18] and it has the advantage of being derived from multiple data points throughout the exercise, the linearity of this slope appears to be lost beyond the so-called second anaerobic threshold, leading to dependency on exercise duration.[17,19] Furthermore, weak inverse correlations with $\dot{V}O_{2max}$ were reported for this slope.[15,20,21] Finally, extrapolating the "true" $\dot{V}O_{2max}$ by using a quadratic function (EMOC) appears to be intensity dependent and has not proved useful enough to be widely adopted.[13,21,22]

In an attempt to develop an objective and independent submaximal measure of cardiorespiratory reserve, Baba et al[21] introduced the oxygen uptake efficiency slope (OUES) in 1996. The OUES represents the rate of increase of $\dot{V}O_2$ in response to a given $\dot{V}_E$ during incremental exercise, indicating how effectively oxygen is extracted and taken into the body.[21] Physiologically, the OUES is based on the development of metabolic acidosis (which depends on the distribution of blood to the working skeletal muscles), muscle mass, oxygen extraction and utilization, and the physiologic pulmonary dead space,[21] which is affected by the perfusion in the lungs and their structural integrity. Cardiovascular, musculoskeletal, and respiratory functions are thus incorporated into a single index.[7]

Oxygen uptake efficiency slope is calculated from the linear relation of $\dot{V}O_2$ versus the logarithm of $\dot{V}_E$ during exercise; that is, $\dot{V}O_2 = \log_{10} \dot{V}_E + b$. The slope a in this formula represents the rate of increase in $\dot{V}O_2$ in response to $\dot{V}_E$ and is defined as the OUES, whereas b is the intercept.[21] The index can be graphically presented if $\dot{V}O_2$ is plotted on the y-axis and the logarithm of $\dot{V}_E$ is plotted on the x-axis. As such, OUES provides an estimation of the efficiency of ventilation with respect to $\dot{V}O_2$, with greater slopes indicating greater ventilatory efficiency. In fact, the OUES reflects the absolute rate of increase in $\dot{V}O_2$ per 10-fold increase in ventilation and thereby indicates how effectively oxygen is transferred by the lungs and used in the periphery. The logarithmic transformation of $\dot{V}_E$ is aimed at linearizing the otherwise curvilinear relation of $\dot{V}O_2$ versus $\dot{V}_E$, thus making the OUES theoretically independent of the patient-achieved effort level.

To our knowledge, the only known review article pertaining to the OUES was written by Baba.[23] The author concluded that OUES appears to provide an objective, effort-independent estimation of cardiorespiratory reserve, even in pediatric populations and adults with HF.[23] Since these first results were promising, OUES has been used and suggested in the literature.[7] Thorough understanding and examination of the OUES are required to assess its usefulness and justify its use in both clinical practice and scientific research. Therefore, the aim of this review is to summarize what is currently known about the OUES.

METHODOLOGY

A systematic literature search was conducted for eligible articles (published up to January 2009) within the following electronic databases: PubMed, Cochrane Library, Embase, Web of Science, CINAHL, PsycINFO, Scopus, and MEDLINE. Each database has its own indexing term, and thus search terms included were developed for each database. The primary search terms included "OUES," "oxygen uptake efficiency slope," and "ventilatory efficiency." Furthermore, reference tracking of all the identified articles was performed.

Inclusion Criteria

Articles were included if they fulfilled the following criteria: (1) the original study assessed OUES characteristics (eg, reliability, reproducibility, determinants, usefulness, interprotocol agreement, and clinical/prognostic/discriminative value), compared OUES values to other cardiorespiratory variables, or investigated the effects of a specific intervention on the OUES; (2) the study was published in a peer-reviewed journal up to January 2009; and (3) the full-text article was available in the English, German, French, or Dutch language.

Exclusion Criteria

Case studies, letters, theses, and meeting abstracts and all other studies that did not fulfill the inclusion criteria were excluded.

Validity Assessment

The systematic search strategy identified 51 potentially relevant references. Two independent researchers

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screened the search results for potentially eligible studies. When titles and abstracts suggested that a study was potentially eligible for inclusion, a full-text article of the study was obtained. Disagreements between the 2 authors regarding study eligibility were resolved by discussion until consensus was reached or, where necessary, a third independent researcher acted as adjudicator. Twenty-four articles matched all inclusion criteria. A flowchart of the selection procedure and reasons for the exclusion of articles are depicted in Figure 1.

RESULTS

Overall, a total of 24 articles (of which 17 cross-sectional studies and 7 intervention studies) were considered appropriate for this review. Among these studies, the OUES has been investigated in healthy adults (n = 7),[4,24-29] in adult patients with a chronic condition (n = 15),[4,8,14,18,21,22,28,30-36] and in children (n = 5).[19,21,37-39] The results of aforementioned studies are described below. The effects of specific interventions on the OUES are considered thereafter. All included studies are presented in Table 1.

OUES in Healthy Adults

The OUES has been studied in a total of 1187 healthy adults between 19 and 96 years of age. Health was defined as the absence of cardiac, respiratory, or other diseases, as confirmed by physical examination.[4,24-29] In addition, 4 studies performed electrocardiographic assessment[4,25,28,29] and 1 study also performed spirometric and echocardiographic assessment.[28] The participants in the study by Pogliaghi et al[27] underwent an exercise stress test to evaluate possible exclusion criteria and pathological response to exercise.

Correlations With Other Measures of Cardiorespiratory Function

Pichon et al[25] assessed correlations with $\dot{V}O_{2max}$ and showed significant correlations ($P < .001$) for both maximal ($r = 0.79$) and submaximal ($r = 0.77$ and $r = 0.65$ for OUES at 85% and 75% of the maximal aerobic running speed, respectively) OUES. Moreover, $\dot{V}O_{2max}$ predicted by OUES did not significantly differ from measured $\dot{V}O_{2max}$.[25] Correlations between OUES and $\dot{V}O_{2peak}$ were highly significant as well ($r = 0.72$-0.96 [0.83, 0.88, 0.91, 0.94, 0.96, 0.83, 0.89, 0.82, 0.89]; $P < .001$),[4,24-29] even if only the first half of exercise duration was used for OUES calculation ($r = 0.92$).[28] The relationship with the VAT appeared to be moderately high to strong ($r = 0.66$, $r = 0.76$, $r = 0.78$ for maximal OUES; $r = 0.59$, $r = 0.75$, $r = 0.80$, $r = 0.83$, $r = 0.70$ for submaximal OUES).[26,27,29]

Influence of Exercise Duration and Intensity

No significant differences were found between OUES at submaximal and maximal exercises.[4,27,29] One study[28] even demonstrated that OUES values calculated from the first half of exercise did not significantly differ from values calculated from the second half or the entire exercise test data. However, another study reported significantly higher values of OUES calculated from data up to 75% and 85% of maximal running speed than those obtained from the entire test data.[25] Since several authors discussed the issue of limited prospective utility of a time-based approach to the calculation of submaximal OUES values,[14,38] Pogliaghi et al[27] calculated the OUES from data obtained up to 60% and 80% of the heart rate reserve. No significant

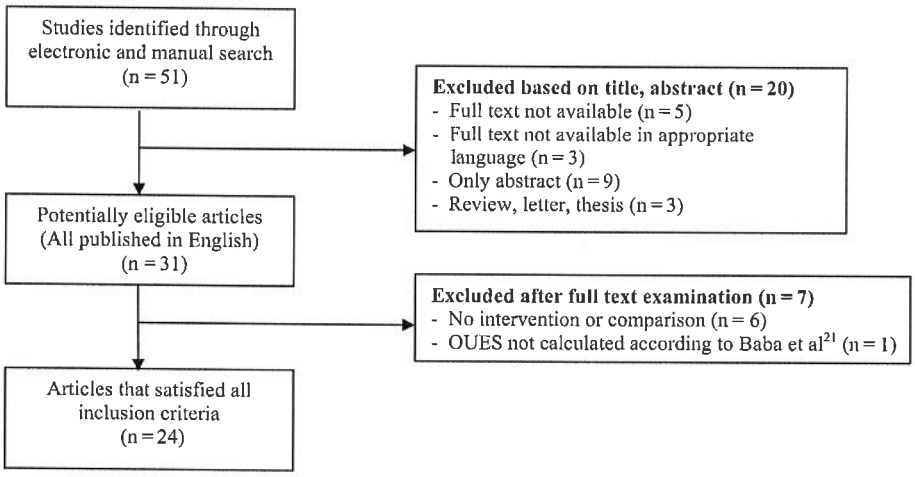

Figure 1. Flowchart of study selection and exclusion criteria. Abbreviation: OUES, oxygen uptake efficiency slope.

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Adults						
Healthy	Baba, et al[24]	19 (11 M/8 F)	21 ± 1 Range: 19-40	Cycle ergometer exercise tests (maximal), 2 times within 7 d. Initial workload 0 W (2 min), increment 20 or 30 or 40 W/min. Intertest reproducibility with Bland-Altman COR.	OUES, VAT, $\dot{V}O_{2peak}$, HR_{max}	Correlations between OUES and $\dot{V}O_{2peak}$ (r = 0.91-.94). Excellent reproducibility of $\dot{V}O_{2peak}$ and OUES (COR 16% and 20%, respectively), VAT less reproducible (COR 31%).
	Pichon et al[25]	50 M	24 ± 9.9	Treadmill exercise tests (maximal), using a standardized protocol. Warm-up (5 min) between 7 and 10 km/h, increment 1 km/h/min. Bland-Altman for agreement.	OUES (at 75%, 85%, and 100% of MAS), VAT, $\dot{V}O_{2max}$, RER, HRmax, MAS	Correlations with $\dot{V}O_{2max}$: OUES-100 (r = 0.79), OUES-85 (r = 0.77), OUES-75 (r = 0.65), and VAT (r = 0.71). OUES at 75% and 85% of MAS significantly greater than OUES at 100%. $\dot{V}O_{2max}$ predicted by OUES not significantly different from measured $\dot{V}O_{2max}$. Limits of agreement (Bland-Altman) ±10.5 mL O_2/min/kg.
	Mourot et al[26]	15 F (8 E/7 C)	E: 21.8 ± 3.3 C: 21.7 ± 1.9	Cycle ergometer exercise tests (maximal), both before and after the intervention period. Initial workload 0 W (3 min), increment 30 W/3 min. Intertest reproducibility with Bland-Altman COR. Intervention: 6 wk, 3 times/wk intermittent SWEET (cycling).	OUES (at 75%, 90%, and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2peak}$, Vd/VAT, RER	Correlations with $\dot{V}O_{2peak}$: OUES at 75%, 90%, and 100% (r = 0.65, r = 0.71, r = 0.72) and VAT (r = 0.83). Correlations between OUES at 75%, 90%, and 100% and VAT (r = 0.59, r = 0.69, r = 0.66). Strong correlations between OUES at 75%, 90%, and 100% of ET (r = 0.80-0.95). No significant differences in OUES, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}_E/\dot{V}O_2$, and Vd/VAT after training, despite increased $\dot{V}O_{2peak}$ and delayed VAT.
	Pogliaghi et al[27]	29 (18 M/11 F)	M: 68.6 ± 5.8 F: 67.1 ± 3.8 Age > 60	Cycle ergometry exercise tests (maximal). Initial workload 50 W (3 min), increment 10 W/min.	OUES (at 75%, 90%, and 100% of ET, and 60% and 80% of HRreserve), $\dot{V}O_{2peak}$	No significant differences between OUES at 75%, 90%, and 100% of ET or between OUES at 100% and HRreserve-based measures of OUES (OUES 80% HRreserve and OUES 60% HRreserve).
	Mollard et al[29]	24 M (10 T/14 UT)	T: 29 ± 5 UT: 27 ± 5	Cycle ergometer exercise tests (maximal). Initial workload 60 W (3 min), increment 30 W/2 min. Intervention: Each subject measured on 4 simulated altitudes (0, 1000, 2500, and 4500 m).	OUES (at 80% and 100% of ET), VAT, $\dot{V}O_{2peak}$	Correlations for OUES at 80% and 100% with $\dot{V}O_{2peak}$ (r = 0.83-0.89) and VAT (r = 0.70-0.83). OUES at 80% similar to OUES at 100% in all conditions. No reduction in OUES at 1000 m. OUES declined faster in T subjects than in UT subjects during exercise in hypoxia.

(*continues*)

Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Patients	Baba et al[8]	50 with HF: NYHA I (12 M/7 F) NYHA II (14 M/6 F) NYHA III (4 M/7 F)	I: 61.1 ± 7.9 II: 65.9 ± 8.3 III: 67.7 ± 10.2	Treadmill exercise tests (maximal), using the symptom-limited original or modified Bruce protocol.	OUES (at 75%, 90%, and 100% of ET), VAT, $\dot{V}O_{2peak}$	Correlation between OUES and $\dot{V}O_{2peak}$ ($r = 0.78$). No significant differences and excellent agreement between OUES at 75%, 90%, and 100% (ICC = 0.99) Significant differences in OUES, $\dot{V}O_{2peak}$, and VAT between NYHA functional classes (I-III).
	Van Laethem et al[32]	80 with HF: 45 with and 35 without LVD	With LVD: 64 ± 6 Without LVD: 58 ± 10	Cycle ergometer exercise test (maximal), using a ramp protocol. Initial workload 20 W, increment 10 W/min.	OUES (at 50%, 75%, and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2peak}$	Correlations with $\dot{V}O_{2peak}$: VAT ($r = 0.81$), OUES/kg ($r = 0.78$), OUES ($r = 0.68$), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.49$). Values obtained from data up to 50%, 75%, and 100% of ET did significantly differ for $\dot{V}O_{2peak}$ and $\dot{V}_E/\dot{V}CO_2$ slope, whereas OUES/kg remained stable. OUES at 75% differed <3.0% from OUES at 100%. OUES and other submaximal parameters significantly lower in patients with LVD.
	Davies et al[22]	243 with HF (212 M/31 F): NYHA I-IV	59 ± 12	Treadmill exercise tests (maximal), following a modification of the Bruce protocol	OUES (at 50% and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}_E/\dot{V}O_2$ slope, RER	Correlations for OUES with $\dot{V}O_{2peak}$ ($r = 0.81$), VAT (0.62), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.62$). Values obtained from the first 50% of exercise and those obtained with full data differed 1% for OUES vs 25% for $\dot{V}O_{2peak}$. OUES values were significantly lower than predicted on the base of age, sex, and BSA. OUES values fell with worsening symptoms. In a multivariable prediction model, OUES was the only significant independent prognostic variable.
	Defoor et al[14]	590 with CAD (512 M/78 F)	55.1 ± 9.7	Cycle ergometer exercise tests (maximal), initial workload 20 W, increment 30 W/3 min. Intervention: 3-mo supervised exercise training program, mean frequency 2.21 ± 0.49 times/wk, mean intensity 80.9 ± 10.3% of HR_{peak}.	OUES (at RER = 1.0 and at 90% and 100% of ET), VAT, $\dot{V}_E/\dot{V}CO_2$ slope	Correlations with $\dot{V}O_{2peak}$: OUES at the various ETs ($r = 0.84$-0.89) and VATs ($r = 0.86$). No differences between OUES values at 90% and 100%, but significantly higher values at RER = 1.0. OUES, $\dot{V}O_{2peak}$, and VAT increased significantly after training, whereas the $\dot{V}_E/\dot{V}CO_2$ slope mildly decreased. Multiple regression analysis revealed training frequency as the strongest determinant for the change in OUES. Changes in $\dot{V}O_{2peak}$ correlated better with changes in OUES ($r = 0.61$) and VAT ($r = 0.55$) than with changes in $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.17$).

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Trenell et al[30]	10 with MM (3 M/7 F)	42 ± 14	Cycle ergometer exercise tests (submaximal: 80% HR_{max}), individually tailored work rates, increment every 2 min. Intervention: 3-mo aerobic exercise therapy (cycling), 3 times/wk.	OUES, HRR-$\dot{V}O_2$	Significant improvement in OUES, but no significant increase in HRR-$\dot{V}O_2$ after exercise therapy in patients with MM.
Van de Veire et al[31]	214 with CAD (182 M/ 32 F): NYHA I-III	67 ± 8	Cycle ergometer exercise tests (maximal).	OUES, $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope, $\dot{V}O_{2max}$, RER	Correlations with $\dot{V}O_{2peak}$: OUES/kg ($r = 0.79$) and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.29$). Significant differences between patients with intermediate $\dot{V}O_{2peak}$ values differing from each other in terms of indices of progressive LV remodeling, systolic dysfunction, and neurohormonal activation.
Van Laethem et al[40]	160 with CAD (132 M/28 F)	68 ± 5 Age > 60	Cycle ergometer exercise tests (maximal), using a ramp or gradual protocol. Initial workload 50 W, increment 25 W/min. Bland-Altman for agreement.	OUES, $\dot{V}O_{2peak}$, VAT, $\dot{V}_E/\dot{V}CO_2$ slope	Correlations with $\dot{V}O_{2peak}$: OUES ($r = 0.73$), OUES/kg ($r = 0.84$), VAT ($r = 0.85$), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.44$). OUES/kg and VAT best submaximal predictors of $\dot{V}O_{2peak}$. Significant differences between measured $\dot{V}O_{2peak}$ and estimated $\dot{V}O_{2peak}$ predicted by OUES/kg in patients with severely decreased or preserved exercise capacity, but not in patients with intermediate exercise capacity. Significant differences between measured $\dot{V}O_{2peak}$ and estimated $\dot{V}O_{2peak}$ predicted by VAT within all subgroups.
Arena et al[18]	341 with HF (283 M/58 F)	56.3 ± 14.2	Treadmill exercise tests (maximal), following a ramping protocol.	OUES and $\dot{V}_E/\dot{V}CO_2$ slope (both at 50% and 100% of ET), $\dot{V}O_{2peak}$	Correlations for OUES (at 50% and 100%) with $\dot{V}O_{2peak}$ ($r = 0.65$, $r = 0.73$) and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.61$, $r = -0.65$). ROC curve analysis demonstrated statistically significant classification schemes for both $\dot{V}_E/\dot{V}CO_2$ slope and OUES calculations as well as $\dot{V}O_{2peak}$ (all areas under the ROC curve ≥0.74). Area under the ROC curve for the $\dot{V}_E/\dot{V}CO_2$ slope at 100% was significantly greater than for $\dot{V}O_{2peak}$ and OUES at 50% and 100%.

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
	Van Laethem et al[35]	35 with HF (26 M/9 F): NYHA II-III	54 ± 9	Cycle ergometer tests (maximal) at the start, the middle, and the end of the intervention, using a gradual protocol. Initial workload 25 W, increment 10 W/min. Intervention: 6-mo cardiac rehabilitation program, 2 times/wk.	OUES (at 90% and 100% of ET), $\dot{V}O_{2peak}$, VAT, $\dot{V}_E/\dot{V}CO_2$ slope, RER	Excellent correlation between OUES at 90% and 100% of ET ($r = 0.97$). OUES, $\dot{V}O_{2peak}$, VAT, and $\dot{V}_E/\dot{V}CO_2$ slope improved during the first part of the ET period; only VAT continued to improve in the second part. Improvement in OUES correlated significantly better with improvements in $\dot{V}O_{2peak}$ ($r = 0.64$-0.77) than in any other included exercise parameter.
	Van Laethem et al[34]	30 HTx patients	59.9 ± 9.1	Cycle ergometer exercise tests (maximal), using a stepwise incremental protocol. Initial workload 25 W, increment 10 or 25 W/min. Intervention: HTx.	OUES, $\dot{V}O_{2peak}$, VAT, $\dot{V}_E/\dot{V}CO_2$ slope, RER	Correlations for OUES/kg with $\dot{V}O_{2peak}$ ($r = 0.63$), VAT ($r = 0.92$), and $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.49$) before HTx. Changes in OUES/kg after HTx significantly correlated with changes in $\dot{V}O_{2peak}$ and VAT (both $r = 0.63$), but not with changes in $\dot{V}_E/\dot{V}CO_2$ slope or marked improvements in central hemodynamics or resting lung function.
	Arena et al[33]	337 with HF (280 M/57 F) (normal weight, overweight, and obese)	56.5 ± 14.1	Treadmill exercise tests, using a conservative ramping protocol.	OUES, BMI	Significant correlation between OUES and BMI ($r = 0.32$). OUES differ significantly among all 3 BMI groups, with the most favorable value found in the obese subgroup. OUES prognostically significant in normal weight (optimal threshold: ≤/>1.2, hazard ratio: 3.7, 95% CI: 1.4-9.9, $P = .01$), overweight (optimal threshold: ≤/>1.5, hazard ratio: 3.9, 95% CI: 1.3-11.1, $P = .01$), and obese (optimal threshold: ≤/>1.7, hazard ratio: 4.1, 95% CI: 1.4-12.8, $P = .01$) subgroups.
	Gademan et al[36]	34 with HF E: 19 M/1 F C: 13 M/1 F NYHA II-III	E: 60 ± 9 C: 63 ± 10	Cycle ergometer exercise tests (maximal) at baseline and after 4 wk (C) or after the exercise training program (E). Initial workload 5 W, increment 5 W/30 s. Intervention: 30 sessions exercise training, 2-3 times/wk.	OUES (at 75%, 90%, and 100% of ET), $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope	No significant differences between OUES at 75%, 90%, and 100% of ET. Experimental group showed a significant increase in $\dot{V}O_{2peak}$ (14%), OUES (19%), OUES/kg (17%), OUES 75 (21%), and OUES 90 (22%) and a decrease in $\dot{V}_E/\dot{V}CO_2$ slope (14%) after training. Control group showed slight improvements in OUES but significantly higher increases in the experimental group.
Healthy vs patients	Hollenberg et al[4]	1010 998 healthy (419 M/579 F) 12 M with HF	Median: 68 Range: 53-96	Treadmill exercise tests (maximal), following the Cornell modification of the Bruce protocol. 725 healthy subjects were tested again after 2 y.	OUES (at 75%, 90%, and 100% of ET), $\dot{V}O_{2peak}$, RER	OUES correlated with $\dot{V}O_{2peak}$ in both men ($r = 0.88$) and women ($r = 0.83$). OUES at 75% differed only 1.9% from OUES at 100%. On serial tests, OUES less variable than exercise duration or $\dot{V}O_{2peak}$. OUES declined linearly with age. Strong correlation with FEV_1 and smoking history. OUES values in patients with HF much lower than those of healthy elderly.

(*continues*)

Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
	Giardini et al[28]	88 35 healthy (18 M/17 F), 53 with heart disease: Fontan (10 M/13 F) M/S (18 M/12 F)	Healthy: 25 ± 9 Fontan: 20 ± 6 M/S: 27 ± 10	Cycle ergometer tests (maximal). Initial workload 10 W, increment 10 W/min.	OUES (from the first 50%, the last 50%, and 100% of the exercise data), $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope	No significant differences between OUES, OUES 0-50, and OUES 50-100, and no differences between measured and predicted values of OUES in healthy subjects, patients with M/S and Fontan who were not cyanotic at rest. In patients with Fontan who were cyanotic at rest, OUES 0-50 differed significantly from OUES and OUES 50-100 and measured and predicted values of both OUES and OUES 50-100 differed significantly as well.
Children						
Healthy	Baba et al[37]	16 (10 M/6 F)	12.7 ± 2.8	Treadmill exercise tests (maximal), using both the Bruce protocol and the RIS protocol. Bland-Altman for agreement.	OUES, VAT, $\dot{V}O_{2max}$, RER	No between-protocol differences in mean values of OUES, VAT, and $\dot{V}O_{2max}$. Interprotocol variability lower for OUES (+17% to −18%) than for $\dot{V}O_{2max}$ (+24 to −20%) and VAT (+31% to −31%).
	Marinov et al[38]	60 (30 M/30 F) 30 normal weight, 30 obese	11 ± 1.1	Treadmill exercise tests (maximal), using a modification of the Balke protocol. Initial elevation 6%, increment 2%/min, constant velocity 5.4 km/h.	OUES (at VAT and 100%), $\dot{V}O_{2peak}$, RER	High correlations for OUES with $\dot{V}O_{2peak}$ (r = 0.91), oxygen pulse = $\dot{V}O_2$/HR (r = 0.80), and anthropometric variables (height, BSA, FFM, age, weight; r = 0.78-0.88). Strong correlation between OUES at VAT and at 100% (r = 0.98); difference only 1.1%. No significant differences between OUES in obese and OUES in nonobese children; slightly higher OUES in obese group.
	Drinkard et al[39]	150 (22 M/21 F normal weight, 42 M/65 F obese)	Normal weight: 14.8 ± 1.7 Obese: 14.4 ± 1.5	Cycle ergometer tests (maximal). Initial workload 0 W (4 min), increment 15 or 20 W/min. Bland-Altman for agreement.	OUES (at LI, 150% of LI, and 100% of ET), LI, $\dot{V}O_{2peak}$, RER	OUES significant predictors of $\dot{V}O_{2peak}$ for both groups at all exercise intensities, despite limits of agreement as high as 30% to 34%. Significant increase in OUES with increasing exercise intensity in both groups. When adjusted for lean body mass, $\dot{V}O_{2peak}$ and OUES at all exercise intensities lower in overweight subjects.
	Marinov et al[19]	114 (58 M/56 F)	Range: 7-18	Treadmill exercise tests (maximal), using a modification of the Balke protocol. Initial elevation 6%, increment 2%/min, constant velocity 5.4 km/h.	OUES (at VAT and 100%), $\dot{V}O_{2max}$, $\dot{V}O_{2peak}$, RER	Correlation between OUES and $\dot{V}O_{2peak}$ (r = 0.92). No significant difference between OUES at VAT and at 100%. Steady trend for $\dot{V}O_{2peak}$, V_E, and OUES to increase in the age span of 7 to 14 y. Rise more strongly correlated with height than with age. $\dot{V}O_{2peak}$ and OUES significantly higher in boys than in girls. Very high linear correlations between OUES and anthropometric variables (BSA, weight, FFM, height, age; r = 0.76-0.86).

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Table 1 • Overview of Included Studies Investigating the Oxygen Uptake Efficiency Slope (*Continued*)

	First Author	n	Age, y (Mean ± SD)	Methods	Outcome Measures	Results
Healthy vs patients	Baba et al[21]	144 (83 M/61 F) 36 healthy, 108 with heart disease	11.7 ± 4.4	Treadmill exercise tests (maximal), using the standardized Bruce protocol.	OUES (at 75%, 90%, 100%), VAT, $\dot{V}_E/\dot{V}CO_2$ slope, EMOC, $\dot{V}O_{2max}$	Correlation with $\dot{V}O_{2max}$ stronger for OUES ($r = 0.94$) than for other submaximal measures (VAT: $r = 0.86$, $\dot{V}_E/\dot{V}CO_2$ slope: $r = 0.15$, EMOC: $r = 0.23$). Deviation of the estimated $\dot{V}O_{2max}$ from the measured $\dot{V}O_{2max}$ smallest for the $\dot{V}O_{2max}$ predicted by OUES. No differences in OUES between 90% and 100% of exercise; at 75% of exercise slightly lower OUES.

Abbreviations: BMI, body mass index; BSA, body surface area; C, control group; CAD, coronary artery disease; COR, coefficient of repeatability; E, experimental group; EMOC, extrapolated maximal oxygen uptake; ET, exercise time; FEV_1, forced expired volume in 1 second; FFM, fat-free mass; HF, heart failure; HRreserve, heart rate reserve; HRR-$\dot{V}O_2$, heart rate restricted oxygen uptake; HTx, orthotropic heart transplantation; ICC, intraclass correlation coefficient; LI, lactate inflection point. LVD, left ventricular dysfunction; MAS, maximal aerobic speed; MM, mitochondrial myopathy; M/S, Mustard/Senning operation; NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; RER, respiratory exchange ratio; RIS, rapidly increasing staged; ROC, receiver operating characteristic; SWEET, square-wave endurance exercise training; T, trained subjects; UT, untrained subjects; VAT, ventilatory threshold; $\dot{V}CO_2$, CO_2 elimination; Vd/VAT, dead space to tidal volume ratio; $\dot{V}_E$, minute ventilation; $\dot{V}O_2$, oxygen uptake.

differences were found between these heart rate reserve–based OUES calculations and OUES obtained from the entire exercise test data. The study of Hollenberg and Tager[4] adopted another alternative by comparing the OUES in individuals who achieved different exercise intensities. The authors divided their subjects into 3 groups according to the peak respiratory exchange ratio (RER_{peak}) achieved. Results of this study indicated that OUES values were similar in subjects with an RER_{peak} of either 1.00 to 1.09 or ≥1.10, whereas significantly lower values were obtained in subjects with RER_{peak} <1.0. However, these subjects were older, had shorter exercise durations, and reached lower values of $\dot{V}O_{2peak}$ and FEV_1 (forced expired volume in 1 second) than those who reached RER_{peak} >1.0.

Reproducibility

Only 1 study assessed the reproducibility of the maximal OUES, $\dot{V}O_{2peak}$, and VAT.[24] Agreement between 2 exercise tests separated by a time interval of maximal 7 days was better for $\dot{V}O_{2peak}$ and OUES (coefficients of repeatability 16% and 20%, respectively) than for VAT (coefficient of repeatability 31%), indicating that VAT is less reproducible compared with OUES and $\dot{V}O_{2peak}$. It seems that $\dot{V}O_{2peak}$ was less reproducible in this study than is often reported in the literature (Coefficient of variation <10%).

Influence of sex and basic anthropometric variables

Oxygen uptake efficiency slope values appeared to be significantly higher in males than in females (2492 ± 471 vs 1741 ± 418, with $P < .05$),[27] and the results of a large cross-sectional study (n = 998) suggest that OUES declines linearly with age in healthy elderly.[4] This latter article examined which variables contributed significantly to the prediction of OUES. They introduced the following prediction equations—1 for men and 1 for women—on the basis of age and body surface area (BSA in m^2):

Men: OUES = 1320 − (26.7 × age) + (1394 × BSA)
Women: OUES = 1175 − (15.8 × age) + (841 × BSA)

OUES in Adults With Chronic Conditions

Oxygen uptake efficiency slope characteristics have been investigated in 2179 patients, aged between 16 and 89 years, with various conditions of the heart, including HF,[4,8,18,22,32-36] coronary artery disease (CAD)[14,31,40] and congenital heart disease.[28] One study included patients with mitochondrial myopathy,[30] in which OUES was used as an outcome measure to assess the effects of exercise therapy on exercise capacity.

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Correlations with other measures of cardiorespiratory function

The study of Baba et al[24] provided moderately high to strong correlations (r = 0.78 for 18 subjects who reached maximal exercise intensity; r = 0.68 when all subjects were included) between maximal OUES and $\dot{V}O_{2max}$ in patients with HF. Correlations with $\dot{V}O_{2peak}$ values ranged from moderately high to strong (r = 0.68, r = 0.73, r = 0.81; $P < .001$) as well.[4,18,22,32] Similar correlation coefficients between OUES and $\dot{V}O_{2peak}$ were reported in patients with CAD (r = 0.73, r = 0.84, r = 0.89; $P < .001$).[14,40] Oxygen uptake efficiency slope standardized for body mass (OUES/kg) also correlated strongly with $\dot{V}O_{2peak}$ (r = 0.79, r = 0.84; $P < .001$) in these patients.[1,31,35] One of the intervention studies[14] demonstrated that training-induced changes in $\dot{V}O_{2peak}$ correlated better with changes in OUES (r = 0.61; $P < .001$) and VAT (r = 0.55; $P < .001$) than with changes in the $\dot{V}_E/\dot{V}CO_2$ slope (r = −.13 to −0.17; $P < .001$) in patients with CAD. Another exercise training study in patients with HF[34] showed that improvements in $\dot{V}O_{2peak}$ correlated significantly better ($P < .01$) with the training-induced changes in OUES (r = 0.64-0.77) than with those of any other included exercise parameter (VAT, $\dot{V}_E/\dot{V}CO_2$ slope, W_{peak}, RER_{peak}) ($r < 0.55$).

Influence of exercise duration/intensity

Various studies suggested that the OUES remains relatively stable over the entire exercise duration,[8,32,36] whereas others found that OUES at 50% and OUES up to RER = 1.0 differed significantly from OUES obtained from the full data.[14,22] In terms of percentages, these differences between submaximal and maximal values were very small for OUES (1%-2%),[4,22] whereas more profound differences were found for $\dot{V}O_{2peak}$ (25%).[22] In line with these findings, Van Laethem et al[32] showed that shortened exercise duration affected both $\dot{V}O_{2peak}$ and $\dot{V}_E/\dot{V}CO_2$ slope, whereas OUES remained stable.

Influence of sex and basic anthropometric variables

The only study primarily examining the influence of anthropometric variables[33] found that OUES differed significantly ($P < .05$) between 3 subgroups of patients with HF differing in body mass index (BMI): normal weight, overweight, and obese. Interestingly, the most favorable values were found in the obese subgroup.

Discriminative ability and prognostic value

Several studies examining exercise capacity in patients with HF[8,32] or CAD[31,40] reported significant differences in OUES values between New York Heart Association functional classes (I-III) or subgroups based on other variables, such as left ventricular dysfunction, neurohormonal activation, exercise capacity, and BMI. Two studies[4,22] demonstrated that OUES values in patients with HF were significantly lower than the values predicted by the prediction equations for healthy adults as introduced by Hollenberg and Tager.[4] Furthermore, Davies et al[22] identified OUES as the only significant independent prognostic variable in a multivariable prediction model and found that OUES values were lower with worsening symptoms.

OUES in Healthy Children

Five studies examined the OUES in 415 healthy children between 6 and 18 years of age. Physical examinations revealed that the children were in good health and took no medication that might affect exercise performance.[19,24,37-39] All subjects were moderately active, but not engaged in regular training activities. The overweight adolescents in the study by Drinkard et al[39] were in good general health but were required to have a BMI greater than 95th percentile for age, sex, and race and at least 1 obesity-related comorbid condition (primarily hyperinsulinemia and/or dyslipidemia). All subjects in this latter study underwent a 12-lead electrocardiogram to ensure the absence of cardiac diseases. One study[21] included children with heart disease as well, but in the results no distinction was made between healthy children and patients.

Correlations with other measures of cardiorespiratory function

Baba et al[21] found significantly stronger correlations with $\dot{V}O_{2max}$ for OUES (r = 0.94) than for other submaximal measures of cardiorespiratory function, including VAT (r = 0.86), $\dot{V}_E/\dot{V}CO_2$ slope (r = 0.15), and EMOC (r = 0.28). The deviation of the estimated $\dot{V}O_{2peak}$ from the measured $\dot{V}O_{2peak}$ appeared to be smallest for the estimated $\dot{V}O_{2max}$ predicted by OUES[21] and strong correlations were found with $\dot{V}O_{2peak}$ (r = 0.91 − 0.92) and oxygen pulse (r = 0.80).[19,38] The study of Drinkard et al[39] demonstrated a significant relationship between OUES and $\dot{V}O_{2peak}$ at several exercise intensities for both obese and nonobese adolescents. Bland-Altman plots comparing measured $\dot{V}O_{2peak}$ with estimated $\dot{V}O_{2peak}$ predicted from OUES, however, showed large limits of agreement (30%-34% of average $\dot{V}O_{2peak}$).[39]

Influence of exercise duration

Two studies[21,39] found that the submaximal OUES was slightly, however significantly, lower than the maximal OUES calculated from the entire exercise test data. Conversely, another study[38] found higher submaximal OUES values, whereas a fourth study[19] did not find any effects of exercise duration on the OUES.

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Protocol dependency

The only study[37] examining protocol dependency of the maximal OUES did not find significant differences in OUES, VAT, or $\dot{V}O_{2max}$ values obtained with 2 different protocols for treadmill exercise testing. Interprotocol variability was found to be smallest for the OUES (limits of agreement −18% to 17%).

Influence of sex and basic anthropometric variables

In a cross-sectional study by Marinov et al,[19] a steady trend was observed for $\dot{V}O_{2peak}$, $\dot{V}_E$, and OUES to increase in the age span of 7 to 14 years. Both OUES and $\dot{V}O_{2peak}$ appeared to be significantly higher in boys than in girls.[19,38] Dividing these variables by lean body mass removed the sex differences almost completely; however, it did not remove the differences in the individual age and height groups. The increases in $\dot{V}O_{2peak}$ and OUES appeared to be more strongly correlated with height than with age.[19] Studies examining the relationship between OUES and anthropometric variables found that OUES was strongly correlated with BSA, height, weight, lean body mass, and age.[19,38] Absolute values of OUES at VAT and over the entire exercise testing data appeared to be significantly higher in severely overweight adolescents (mean BMI 40.0 ± 8.0 kg/m^2) compared with their nonoverweight peers.[38] These findings are in line with the results of Arena et al,[33] who also found the most favorable OUES values in the obese subgroup of adult patients with HF. Conversely, when expressed relative to lean body mass, exercise parameters were significantly lower in overweight than in nonoverweight adolescents.[19,38]

To assess which factors influence OUES in the pediatric population, Marinov and Kostianev[38] applied stepwise regression analysis and introduced the following equation to predict OUES from height (cm) and BSA (m^2) (r^2 = 0.793; standard error of estimate = 369; n = 60):

$$OUES = -3346.9 + 28.08 \times height + 794.2 \times BSA$$

More recently, Marinov et al[19] introduced another equation to predict OUES in healthy children, including BSA and gender as the main determinants (R^2 = 0.765; standard error of estimate = 316; n = 114):

$$OUES = -398 + 1958.1 \times BSA - 199.5 \times gender$$

OUES in Children with Chronic Conditions

Only 1 study[21] examined the OUES in 108 children with heart disease. However, in this study, no distinction was made between the healthy participants and those suffering from heart disease. The results of this study are discussed earlier.

Intervention Studies

Seven studies examined the effects of a particular intervention on the OUES; however, none applied a randomized controlled design. The interventions included exercise training,[14,26,30,34,36] orthotropic heart transplantation,[35] and hypoxia.[29]

Exercise training induced significant improvements in $\dot{V}O_{2peak}$, OUES, and VAT in a large number of patients with cardiac disease.[14,34,36] The study of Defoor et al[14] showed that the training-induced changes in $\dot{V}O_{2peak}$ correlated with changes in OUES (r = 0.61; $P < .001$) and in VAT (r = 0.55; $P < .001$). These relations remained significant after adjusting for age, gender, body height and weight, and training intensity and frequency (r = 0.57 and r = 0.52; $P < .001$, respectively). Stepwise multiple regression analysis revealed training frequency (r = 0.249; $P < .001$) as the strongest determinant for the change in OUES with physical training and that the change in VAT was the largest contributor to the change in OUES.[14]

Patients with mitochondrial myopathy also showed significantly higher OUES values following aerobic exercise therapy, whereas no significant increases were demonstrated in heart rate–restricted $\dot{V}O_2$.[30] One study,[27] however, did not find significant changes in the OUES and $\dot{V}_E/\dot{V}CO_2$ slope after intermittent endurance training in healthy young women, despite significant increases in $\dot{V}O_{2peak}$ and VAT.

The study of Van Laethem et al[35] investigated the OUES in patients before and after heart transplantation. Significant improvements ($P < .05$) in OUES were found during the first year after surgery, but similar to other exercise parameters, OUES remained considerably impaired when compared with age- and gender-normalized values. The changes in OUES after heart transplantation highly correlated with the changes in other exercise variables ($\dot{V}O_{2peak}$ and VAT), but not with marked improvements in central hemodynamics or resting lung function. The latter might suggest that the increase in OUES is elicited by beneficial alterations in the skeletal musculature after heart transplantation rather than by improvements in central hemodynamics or resting lung function.

In a study concerning the responsiveness of the OUES to hypoxia in healthy subjects with a broad range of cardiorespiratory fitness,[29] both maximal and submaximal OUES values were influenced by oxygen availability and utilization by active tissues. Mild hypoxia did not significantly alter OUES values, but more severe hypoxia at higher simulated altitudes caused significant reductions in OUES. An interesting finding was that the OUES declined faster in trained than in untrained subjects.

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DISCUSSION

The results of this review indicate that OUES is an objective and reproducible measure with broad applicability. Oxygen uptake efficiency slope is relatively independent of exercise intensity/duration, correlates highly with other exercise parameters, appears to have discriminative value, and is sensitive to the effects of physical training in adult cardiac populations. However, OUES values are considerably influenced by anthropometric variables and show large interindividual variation.

Correlation Between OUES and Other Exercise Parameters

Strong correlations were found between OUES (submaximal and maximal) and $\dot{V}O_{2peak}$. Using correlation and regression analysis, several authors concluded that the assessment of OUES was accurate enough as a substitute of $\dot{V}O_{2max}$.[4,8,22,24,29,32,34,37] However, a strong statistical correlation between 2 parameters is not necessarily a proof for the interchangeability of these parameters.[40] Bland-Altman analysis assessing interindividual variability showed wide 95% confidence intervals.[25,39,40] These findings indicate that although OUES and $\dot{V}O_{2peak}$ are highly correlated, interindividual variation exists in OUES values, which might limit the clinical utility of this parameter. Since OUES was not able to reliably predict $\dot{V}O_{2max}$, it appears not interchangeable with this "golden standard."[25,39,40] Nonetheless, Pichon et al[25] compared the submaximal OUES with the VAT, which is widely used in clinical practice, and showed that the submaximal OUES provided a better approximation of measured $\dot{V}O_{2max}$ compared with the VAT. Various studies revealed that compared with other submaximal parameters, OUES is strongly correlated with the VAT[21,26,27,29] and with the submaximal $\dot{V}_E/\dot{V}CO_2$ slope.[18] However, relationship differences of OUES and VAT between studies are not fully understood and identified; different approaches for determining the VAT and even different exercise protocols (Table 1) might contribute to these differences in relationships.

Influence of Exercise Duration/Intensity on OUES

The logarithmic transformation of $\dot{V}_E$ is aimed at linearizing the otherwise curvilinear relation of $\dot{V}O_2$ versus $\dot{V}_E$, thus making the OUES theoretically independent of the patient-achieved maximal effort level. Many studies confirmed that submaximal and maximal OUES values were highly correlated.[8,26,34,38] The use of submaximal exercise data did not alter OUES values in most studies,[8,19,27-29,32,36] and in those where shortened exercise duration did affect the OUES,[4,14,21,22,25,38,39] only small differences were reported. However, controversy exists with regard to the submaximal OUES values. Some studies[14,25,38] found significantly higher submaximal OUES values as compared with maximal OUES values, whereas others did not find differences[8,19,27-29,32,36] or suggested a tendency toward lower submaximal values.[4,21,39] We could not identify explanatory factors for these inconsistent findings; however, it might be related to the underlying disease. The validity of the OUES might be different across patient groups.

Despite the fact that the submaximal OUES values are calculated in numerous studies, important characteristics (such as interprotocol agreement, reproducibility, discriminative ability, and prognostic value) are examined only for the maximal OUES in the majority of studies. Since the original purpose of the OUES was to provide a submaximal measure of cardiorespiratory function, which could be used as a substitute for $\dot{V}O_{2peak}$ in (clinical) populations unable to perform maximal exercise, it would be more appropriate to examine these characteristics for the submaximal OUES. Three studies[14,26,36] examined the responsiveness to exercise training for the submaximal OUES and 2 of these showed a significant increase in submaximal OUES values following exercise training in patients with HF[36] or CAD.[14] A study by Mollard et al[29] indicated that the submaximal OUES was sensitive to the effects of hypoxia during exercise. Only 1 study[18] assessed the prognostic value of the submaximal OUES and demonstrated that it, like the maximal OUES, was a significant predictor of mortality in patients with HF.

Sensitivity of OUES

Results of the intervention studies suggest that OUES is sensitive to change after exercise training in patients with CAD, HF, or mitochondrial myopathy and, thus, can be used to evaluate the progression of exercise capacity in the aforementioned populations following rehabilitation or training programs in these patient groups. Several authors have concluded that OUES is a more consistent parameter than $\dot{V}O_{2peak}$, since $\dot{V}O_{2peak}$ is effort, protocol, and observer dependent.[4,32,36] In populations with cardiac conditions, exercise capacity appears to be primarily restricted by underperfusion of both the lungs and the skeletal muscles. An increase in OUES suggests that a similar $\dot{V}O_2$ is achieved with lower ventilatory cost.[14,35,36] This might be due to direct training-induced improvements in pulmonary function (eg, increased alveolar capillary membrane perfusion and capillary blood flow) and/or muscular function (eg, increased capillary

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density, blood flow, and mitochondrial density) in these patient populations. In subjects without cardiopulmonary limitations, however, measures of ventilatory efficiency, and consequently OUES, might not be the most appropriate to assess the effects of training. This has been observed in the healthy young women who participated in the study of Mourot et al.[26]

It is striking that the responsiveness of OUES to exercise training or other interventions has never been investigated in pediatric populations and, moreover, that none of the intervention studies on OUES involved randomized controlled trials. Further, more research is required to determine whether an increase in OUES in patients is associated with an improved prognosis.

OUES in Patients

The study of Davies et al[22] was the first study that examined the prognostic value of the OUES in patients with HF. They found that its prognostic value was stronger compared to the best available existing measures of exercise physiology, including $\dot{V}O_{2peak}$, VAT, and $\dot{V}_E/\dot{V}CO_2$ slope. Other studies, similar to this finding, suggested strong discriminative value of the OUES in patients with HF or CAD.[4,8,31,32] Hence, OUES appears to be useful for the quantification of exercise performance in these patients.[40] In patients with CAD, OUES is significantly reduced.[14,32,34] Patients who have undergone percutaneous transluminal coronary angioplasty with or without prior myocardial infarction have significantly higher OUES values compared with patients after coronary artery bypass grafting.[14] This may be explained by a higher disease severity, preoperative and postoperative deconditioning, and the impact of chest surgery on lung perfusion and structural integrity in the latter group. Furthermore, OUES is impaired in CAD patients with arterial fibrillation as compared with those with normal sinus rhythm;[14] this is likely because of the impact of decreased oxygen delivery on the working muscles in patients with arterial fibrillation owing to lower stroke volume and CO response during exercise.[41] The study of Arena et al[18] showed that OUES was a significant predictor of mortality in patients with HF, though they also concluded that the $\dot{V}_E/\dot{V}CO_2$ slope maintained an optimal prognostic value. However, the $\dot{V}_E/\dot{V}CO_2$ slope was calculated from maximal exercise in their study. When only submaximal data were used for OUES determination, this superiority of the $\dot{V}_E/\dot{V}CO_2$ slope compared with the OUES was no longer significant. Although OUES appears to have good discriminative ability in these populations, further investigation is required for exploring the prognostic power of OUES in the risk stratification of patient with other (chronic) conditions. In addition, future studies should examine the relationship between OUES and other markers of physiologic function reflecting disease severity (eg, Doppler echo, cardiac magnetic resonance imaging, brain natriuretic peptide concentrations in blood, or pulmonary pressure).

Both the $\dot{V}_E/\dot{V}CO_2$ slope and OUES could potentially be used to identify a subgroup within CAD patients with intermediate $\dot{V}O_{2peak}$, who might have a worse outcome. Arena et al[18] reported that although OUES is a significant prognostic marker in patients with HF, the $\dot{V}_E/\dot{V}CO_2$ slope calculated with all exercise data remained prognostically superior. Davies et al[22] performed a similar analysis, though they concluded that OUES was the best predictor of mortality. In this latter study, patients were tested between 1992 and 1996, while only 2.6% of the participants of Arena et al[18] underwent testing before 1997. Given the changes in HF management since the 1990s, the findings of Arena et al[18] may be more reflective of present-day clinical practice.

OUES in Children

Mean submaximal OUES values in healthy children are significantly lower than those in healthy adult populations (1900-2200 vs 2910-4300, respectively).[19,24,25,28,29,38,39] An interesting finding is that the OUES increases linearly with age during childhood,[19] whereas it was found to decrease linearly with age in healthy elderly.[4] Correlation coefficients with other exercise parameters in children are similar to those found in healthy adults. However, caution is recommended when interpreting OUES as an exercise parameter in the development course of childhood, since OUES is considerably influenced by anthropometric variables.[19,38]

To our knowledge, only 1 study examined OUES in children with chronic conditions. Baba et al[21] included both healthy children and children with various conditions of the heart. However, the study population was very heterogeneous, and furthermore, no distinction was made between the patients and healthy children in their results. Thus, as far as we know, no studies are published that compare OUES values in children with various (chronic) diseases with those in healthy peers. As a consequence, it is currently not known whether the OUES is able to discriminate between healthy children and children with various (chronic) diseases or disabilities. Moreover, none of the included studies investigated the effects of pubertal stages on OUES, despite the fact that exercise capacity is known to be influenced by this developmental milestone. Future research should address this interesting issue.

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OUES Versus VAT

Oxygen uptake efficiency slope determination involves calculating the slope of the relationship between $\dot{V}_E$ and $\dot{V}O_2$ rather than a single cross-sectional determination with substantial inter- and intraobserver variability during exercise, like the VAT. As a consequence, OUES is objectively identifiable in all subjects and seems to be sufficiently reproducible.[24] Moreover, the slope is derived from multiple data points throughout the exercise test and, therefore, provides more profound physiological information. Oxygen uptake efficiency slope includes both metabolic acidosis and physiologic pulmonary dead space and hence displays the status of both systemic and pulmonary perfusion, whereas VAT primarily represents the status of blood distribution to the working muscles rather than perfusion to the lungs.[21] Also, caution has to be taken when reporting about data measured at different anaerobic thresholds to avoid mixing up methods;[17] this is not applicable for OUES, because it concerns a single fixed and simple mathematical formula. Furthermore, VAT values can be considerably influenced by the nutritional state of the subject (eg, carbohydrate loaded or depleted). Baba et al[24] have stated that this is not the case for OUES values.

OUES Versus $\dot{V}_E/\dot{V}CO_2$ Slope

Both the OUES and $\dot{V}_E/\dot{V}CO_2$ slope reflect ventilatory efficiency and have the advantage of being derived from multiple data points throughout the exercise. Contrary to the $\dot{V}_E/\dot{V}CO_2$ slope, OUES appears to be relatively independent of patient-achieved effort level.

OUES differs in theory from the $\dot{V}_E/\dot{V}CO_2$ slope in that it considers changes in ventilation in terms of scale factor, that is, in multiples of the baseline value. Consequently, any abnormalities that increase ventilation by a constant proportion, both at rest and during exercise, will not directly influence OUES. Only abnormalities that increase ventilation during exercise by a greater proportion than at rest will cause a decline in OUES values. Oxygen uptake efficiency slope may therefore quantify the specific pattern of ventilatory response to exercise having automatically "controlled" for abnormalities present at rest.[22]

Correlation coefficients with traditional measures of cardiopulmonary function, including $\dot{V}O_{2max}$, $\dot{V}O_{2peak}$, and VAT, reported for OUES were much stronger than for the $\dot{V}_E/\dot{V}CO_2$ slope.[15,20,21] The latter, which is related to physiologic pulmonary dead space, is affected mainly by perfusion to the lungs. Oxygen uptake efficiency slope, affected both by metabolic acidosis and by physiologic pulmonary dead space, reflects the status of both systemic and pulmonary perfusion, which seems to account for the superiority of OUES concerning the correlation with traditional parameters.[42]

The prognostic value of both slopes in predicting morbidity and mortality is confirmed in patients with HF or CAD.[18,22,31] Defoor et al,[14] however, reported that the $\dot{V}_E/\dot{V}CO_2$ slope might be less suitable than OUES to evaluate the effects of physical training in CAD patients without an increased $\dot{V}_E/\dot{V}CO_2$ slope at baseline measurement. They found that changes in VAT contributed most to the changes in OUES than in the $\dot{V}_E/\dot{V}CO_2$ slope. In addition, Van Laethem et al[35] found that the training-induced changes in OUES correlated better with the changes in $\dot{V}O_{2peak}$ in patients with HF than the changes in the $\dot{V}_E/\dot{V}CO_2$ slope.

Several studies examined the relationship between underlying pathophysiology and an abnormally elevated $\dot{V}_E/\dot{V}CO_2$ slope in patients with HF. The mechanisms appear to be multifaceted with both central and peripheral contributions.[18] Such studies are lacking for OUES thus far. Additional research is required to examine the mechanism behind the abnormally low OUES observed in patients with HF.[18] Furthermore, future research should reveal which submaximal efficiency slope appears most useful in clinical practice with various patient populations.

Interpretation of OUES

During the analysis of the different studies it became clear that OUES was expressed in various entities, which can be confusing. In fact, OUES represents the slope of a regression line and forms the quotient of $\dot{V}O_2$ (mL/min) and log $\dot{V}_E$ (L/min). As a result, OUES formally has no entity.

Drinkard et al[39] attempted to predict $\dot{V}O_{2peak}$ from OUES values in a pediatric population and did not find significant differences between the actual $\dot{V}O_{2peak}$ and the $\dot{V}O_{2peak}$ predicted by the submaximal OUES. However, the authors identified a significant bias in overweight adolescents. This is in line with the results of Pichon et al,[25] who found that the $\dot{V}O_{2max}$ predicted by the OUES did not significantly differ from measured $\dot{V}O_{2max}$. Since OUES is not able to reliably predict $\dot{V}O_{2max}$, it appears not interchangeable with the "gold standard." However, we suppose that the OUES is not meant to predict maximal exercise parameters. The index itself provides an objective and independent measure of cardiorespiratory function, reflecting the efficiency of ventilation with regard to the oxygen uptake during exercise. The interpretation of its values is dependent on comparison with adequate reference values, comparisons between (groups of) subjects, or comparisons within subjects (eg, to detect individual changes in

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ventilatory efficiency over time or following a specific intervention).

Normalization of OUES

Since OUES is considerably influenced by anthropometric variables, it is recommended to normalize its values for body size, especially in children. Maximal indices such as $\dot{V}O_{2peak}$ are also known to be strongly influenced by changes in body size. Therefore, $\dot{V}O_{2peak}$ is often normalized by body weight;[43] however, the influence of body mass is not entirely compensated by this method.[44] The study of Marinov and Kostianev[38] showed that normalizing $\dot{V}O_{2peak}$ for BSA (depends on both weight and height) compensates for the differences between different weight groups. Since height, weight, lean body mass, and BSA are strongly correlated with OUES,[19] normalizing its values for one of these parameters seems appropriate, especially in pediatric populations. Previous studies have normalized OUES by body weight, lean body mass (a surrogate for muscle mass), or BSA. From a physiological perspective, we presume that BSA provides the best indication of total pulmonary volume, taking both height and weight into account. However, which adjustment is most useful in normalizing the OUES has to be further investigated.

Applications to Practice and Implications for Further Research

There is a need for adequate reference values for the OUES in (healthy) adults and children. Appropriate reference values should be generated with respect to age, gender, race, and other factors such as maturation and anthropometrics. To our knowledge, influences of puberty on the OUES have not been investigated. Since puberty causes significant changes in body composition, muscle strength, $\dot{V}_{Emax}$, ventilatory equivalent, and physical activity patterns,[45] it might also influence ventilatory efficiency (OUES). Future studies should address the aforementioned variables.

Also, it is currently unknown whether the submaximal OUES is able to differentiate between healthy children and children with a (chronic) disease. Previous findings suggest that OUES has discriminative value in adults;[4,8,22,31,32] however, further research is required to assess its discriminative ability in different pediatric populations.

Furthermore, the responsiveness of the OUES to exercise training has never been addressed in pediatric (patient) populations. Results from adult studies suggest that the OUES increases following physical training in both patients with CAD and those with HF. The training-induced changes in OUES parallel those in $\dot{V}O_{2peak}$ in cardiorespiratory-limited populations,[14,34] showing that OUES is sensitive to improvement in exercise tolerance. Therefore, OUES would seem to be clinically useful to monitor changes in exercise performance and effects of physical training in adults, particularly in those who can perform only submaximal exercise. Several authors have stated that the OUES is more robust than the $\dot{V}O_{2peak}$, since maximal workload assessed during a symptom-limited exercise test can be influenced by multiple factors.[4,32,36] However, none of these studies involved randomized controlled trials and the responsiveness of the OUES in pediatric populations remains the subject of further research.

It is currently unknown whether the type of ergometer affects OUES determination. The included studies used both a treadmill ergometer or a cycle ergometer for OUES determination and various exercise protocols. Since $\dot{V}O_{2peak}$ values are usually higher with a treadmill protocol[46] and since OUES is highly correlated with $\dot{V}O_{2peak}$, it is likely that the OUES could be influenced by the type of ergometer. The only study assessing interprotocol agreement showed excellent intraindividual agreement between OUES obtained with 2 different treadmill protocols, unlike VAT and $\dot{V}O_{2max}$.[37] However, no additional studies are yet published to confirm these findings. Whether values of OUES are ergometer and/or protocol dependent thus remains the subject of future research.

SUMMARY

OUES appears to be a reproducible measure of cardiorespiratory function that does not require maximal exercise. It greatly reduces test variability because of motivational and subjective factors and is reliable and easily determinable in all subjects when respiratory gas analysis systems with breath-by-breath or mixing chamber are used. Despite the strong correlations with $\dot{V}O_{2peak}$ and $\dot{V}O_{2max}$, OUES appears not interchangeable with these maximal exercise parameters. Nonetheless, OUES seems to be a promising alternative submaximal exercise parameter to assess cardiorespiratory function in subjects unable to perform maximal exercise, like children and patients with progressed disease states. However, appropriate reference values for both adult and pediatric populations are required.

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Erratum

Rural and Urban Characteristics Impact Cardiovascular Risk Reduction: Erratum

In the article that appeared on page 299 of the September/October issue, the list of authors was incomplete; the complete author list is as follows:

Timothy R. McConnell, PhD; William P. Santamore, PhD; Sharon L. Larson, PhD; Carol J. Homko, PhD; Mohamed Kashem, MD, PhD; Robert C. Cross, MD; Alfred A. Bove, MD, PhD

In addition, the article should have included a note indicating that it was registered as part of ClinicalTrials.gov (Clinical Trial no. NCT00778804).

Reference:

McConnell TR, Santamore WP, Larson, SL, et al. Rural and urban characteristics impact cardiovascular risk reduction. *J Cardiopulm Rehabil Prev.* 2010;30(5):299-308.

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CHAPTER 5:

The Oxygen Uptake Efficiency Slope in healthy children

Akkerman M, Van Brussel M, Bongers B, Hulzebos HJ, Helders PJM, Takken T (2010). The Oxygen Uptake Efficiency Slope in healthy children. Ped Exerc Sci, 2010, 22, 431-441

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Oxygen Uptake Efficiency Slope in Healthy Children

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The objective of this study was to investigate the characteristics of the submaximal Oxygen Uptake Efficiency Slope (OUES) in a healthy pediatric population. Bicycle ergometry exercise tests with gas-analyses were performed in 46 healthy children aged 7–17 years. Maximal OUES, submaximal OUES, $\dot{V}O_2$peak, $V_E$peak, and ventilatory threshold (VT) were determined. The submaximal OUES correlated highly with $\dot{V}O_2$peak, $V_E$peak, and VT. Strong correlations were found with basic anthropometric variables. The submaximal OUES could provide an objective, independent measure of cardiorespiratory function in children, reflecting efficiency of ventilation. We recommend expressing OUES values relative to Body Surface Area (BSA) or Fat Free Mass (FFM).

Exercise testing is currently widely used in clinical practice to assess the response to exercise in both patients and healthy individuals. Maximal oxygen uptake ($\dot{V}O_2$max), the highest rate at which an individual can consume oxygen during exercise, is widely recognized as the single best measure of person's aerobic fitness (26). $\dot{V}O_2$max requires maximal effort and leveling-off (plateau) of oxygen uptake, despite continuing exercise and increasing workload. Therefore, its application is mainly limited to healthy adult subjects who can fulfill these requirements (18). In pediatric populations, a true plateau in oxygen uptake is seldom attained (21,25). Since several authors (2,3,25) have shown that a true plateau is not essential for defining the highest oxygen uptake in children, it gradually became more usual to use the rate of oxygen uptake occurring at peak exercise ($\dot{V}O_2$peak; 4, 18). However, the measurement of these parameters can be strongly influenced by the patients' motivation, the selected exercise protocol, and the experience of the tester (1,7,18,28). Furthermore, exhaustive incremental tests for determining the $\dot{V}O_2$peak in pediatric populations generally do not mimic activity levels of their daily life. Therefore, exercise performance at submaximal exercise might be more representative in pediatric populations, especially in children with a chronic condition.

Baba et al. (5) introduced the Oxygen Uptake Efficiency Slope (OUES) in an attempt to develop an objective and effort-independent submaximal measure

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of cardiopulmonary reserve. Their approach involves deriving the slope of the semilog plot of minute ventilation ($\dot{V}_E$) versus oxygen uptake ($\dot{V}O_2$). As such, the OUES provides an estimation of the efficiency of ventilation with respect to $\dot{V}O_2$, with steeper slopes indicating a larger ventilatory efficiency. Physiologically, the OUES is based on: (i) the development of metabolic acidosis, which is controlled by the distribution of blood to the skeletal muscles; and (ii) the physiological dead space, which is affected by the perfusion to the lungs (5,7). The OUES was initially applied in a cohort of healthy children and children with heart disease (7), however the OUES has also been frequently investigated in healthy adults, adolescents, and patient populations later on (19).

To our knowledge, merely five studies (5,6,11,22) examined the properties of the OUES in children and adolescents. All the aforementioned studies included healthy children while the study of Baba et al. (5) also included children with heart disease. To verify the assumption that the OUES is independent of exercise duration (effort), both maximal and submaximal values of OUES were calculated in four of these studies (5,11,21,22). Two studies (5,11) described that the submaximal OUES was slightly, however significantly, lower compared with the maximal OUES. One study (21) described higher submaximal OUES values, whereas a fourth study (22) did not describe any effects of exercise duration on the OUES.

In general, strong correlations were reported between the maximal OUES and $\dot{V}O_2$max (r = .94) and $\dot{V}O_2$peak (r = .77, r = .91, r = .92; 11, 21, 22). Only two studies (5,11) assessed also the aforementioned correlations for the submaximal OUES and reported a correlation with $\dot{V}O_2$max of r = .95 in healthy children and children with heart disease, and r = .59 in overweight adolescents, respectively.

The OUES appears to be significantly higher in boys compared with girls (2335 ± 875 versus 1730 ± 580; and 2254 ± 735 versus 1943 ± 497; 21, 22) and correlates significantly with basic anthropometric parameters, including age (r = .83, r = .76), height (r = .88, r = .84), body mass (r = .78, r = .85), Body Mass Index (BMI; r = .48, r = .57), Body Surface Area (BSA; r = .86), and Fat Free Mass (FFM; r = .86, r = .84); with $p < .001$ for all coefficients; 21, 22). However, these characteristics were only examined for the maximal OUES and not for the submaximal OUES.

Since the original rationale of the OUES was to provide a submaximal measure of cardiorespiratory function, which could be used as a possible substitute for or an addition to $\dot{V}O_2$peak or $\dot{V}O_2$max in populations unable to perform maximal exercise, it would be appropriate to examine submaximal OUES characteristics. Therefore, the aim of our current study was to investigate the properties of the submaximal OUES in a healthy pediatric population.

Material and Methods

Participants

Forty-six children and adolescents (27 boys and 19 girls; aged 7–17 years) participated in this study. These subjects included family members of our hospital staff and children living in the neighborhood of the hospital. All children were in good health, without chronic diseases, and were not on medications which might affect their exercise capacity. Informed consent was obtained from the parents and/or from the children themselves if they were ≥12 years of age. The study protocol

was approved by the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands.

Anthropometric Measures

The participants' body mass and height were determined using respectively an electronic scale and a stadiometer, respectively. BMI was calculated as body mass (kg)/height $(m)^2$. BSA was calculated using the equation of Haycock et al. (17): $BSA\ (m^2) = 0.024265 \cdot Ht^{0.3964} \cdot Wt^{0.5378}$, where Ht represents height in cm and Wt is body mass in kg. This equation is validated in infants, children, and adults (17). Subcutaneous fat distribution was measured from skin fold measurement (mm) using Harpender skin fold calipers. The measurements were taken at four sites (at the right side of the body); triceps, biceps, subscapular, and supra-iliacal according to Deurenberg et al. (10). The sum of the four skin folds (å4SF) was used to estimate the body density by means of the equations by Deurenberg et al. (10) derived from anthropometric data of Dutch children aged 7–20 years. Percentage body fat and subsequent FFM were estimated using a modification of the Siri equation proposed by Weststrate and Deurenberg (37).

Exercise Testing

Cardiopulmonary exercise tests were performed using an electronically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, the Netherlands). The test started with one minute of unloaded cycling before the application of resistance to the ergometer. Subsequently, workload was increased with a constant increment of 10, 15 or 20 Watts every minute according to the Godfrey protocol (16). This protocol continued until the patient stopped because of voluntary exhaustion, despite strong verbal encouragement of the test-leader. Heart rate (HR) was measured continuously during the maximal exercise test by using a heart rate monitor (Polar, Kempele, Finland).

Analysis of Expired Gas

During the exercise tests, subjects breathed through a facemask (Hans Rudolph Inc, Kansas City, MO) connected to a calibrated respiratory gas analysis system (Jaeger Oxycon Champion, Cardinal Health, Houten, the Netherlands). Expired gas passed through a flowmeter (Triple V volume transducer), oxygen (O_2) analyzer, and a carbon dioxide (CO_2) analyzer. The flowmeter and gas analyzers were connected to a computer, which calculated breath-by-breath V_E, $\dot{V}O_2$, carbon dioxide output (VCO_2), and the Respiratory Exchange Ratio (RER) from conventional equations. Output from the gas analyses was averaged at 10 s-intervals and stored in an Excel file for the off-line calculation of the OUES. Maximal effort was defined when at least one of the following criteria was met: HR > 180 beats per minute or RER > 1.0. $\dot{V}O_2$peak and peak ventilation ($V_E$peak) were determined as the average $\dot{V}O_2$ and V_E value over the last 30 s during the maximal exercise test. The ventilatory threshold (VT) was determined as the level of $\dot{V}O_2$ at which the linear relation between VCO_2 and $\dot{V}O_2$ disappeared, according to the V-slope method. The OUES was determined by plotting $\dot{V}O_2$ ($mL \cdot min^{-1}$) against the logarithm of V_E ($L \cdot min^{-1}$) and calculating the slope of this linear relation through single regression analysis.

In accordance with the original equation introduced by Baba et al. (5): ($\dot{V}O_2 = a \log V_E + b$), this slope 'a' represents the OUES. For submaximal OUES determination, only data up to VT were included in the analyses. Data from the first minute of exercise were excluded because of the often very irregular breathing pattern at the onset of exercise (36). Relative values for the exercise parameters were calculated by dividing the absolute values by body mass, FFM or BSA. Several studies reported good reproducibility of OUES in healthy participants (4,32).

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (version 15.0; SPSS Inc., Chicago, IL). Data are presented as mean values ± *SD* (*SD*) and corresponding ranges. Differences between boys and girls were examined using the independent-sample T-test for the anthropometric variables and the Mann-Whitney test for the exercise parameters. A Wilcoxon signed ranks test was used to determine whether the submaximal OUES differed significantly from the maximal OUES. Spearman correlation coefficients were calculated to examine the relationships between the different exercise parameters and between the submaximal OUES and basic anthropometric variables. Significance was set a priori at the .05 level.

Results

Participant characteristics are depicted in Table 1. No significant differences were found between boys and girls regarding age, height, BSA, and FFM; whereas body mass, BMI, the Σ4SF, body density, and BF% were significantly lower in boys compared with girls.

Table 1 Population Characteristics

	Boys (*n* = 27) Mean ± *SD*. Range		Girls (*n* = 19) Mean ± *SD*. Range		
Age (years)	11.8 ± 2.2	(7.9–16.8)	12.9 ± 2.6	(8.4–16.5)	
Height (m)	1.54 ± 0.15	(1.29–1.91)	1.59 ± 0.12	(1.39–1.79)	
Body mass (kg)	41.5 ± 12.0	(24.1–66.5)	49.4 ± 14.3	(28.2–81.7)	*
BMI ($kg \cdot m^{-2}$)	17.0 ± 2.0	(13.8–21.3)	19.0 ± 3.0	(14.6–25.5)	**
BSA (m^2)	1.32 ± 0.25	(0.92–1.86)	1.47 ± 0.27	(1.03–2.02)	
Σ4SF (mm)	28.87 ± 9.55	(19.67–65.17)	40.59 ± 14.27	(22.17–71.67)	**
Body density ($kg \cdot L^{-1}$)	1.05 ± 0.01	(1.03–1.06)	1.04 ± 0.01	(1.03–1.06)	**
BF (%)	16.04 ± 3.18	(12.01–26.43)	20.94 ± 4.21	(14.41–28.66)	***
FFM (kg)	35.02 ± 10.14	(20.78–56.31)	38.87 ± 10.22	(24.14–59.74)	

Abbreviations: BMI = body mass index; BSA = body surface area; Σ 4SF = sum of the four skin folds; BF = percentage of body fat; FFM = fat free mass; * $p<.05$, ** $p<.01$, *** $p<.001$

All maximal cardiopulmonary exercise tests were completed without adverse effects, such as dizziness, fainting, or vomiting. Results are presented in Table 2. During the interpretation of the exercise tests, the VT could not be properly be determined in one subject. The average submaximal OUES of the entire population was 2200.5 ± 693.6, with values varying over a wide range (1062.6–4120.5; Figure 1). After adjusting for the anthropometric variables height (1383.8 ± 342.9; range: 764.5–2527.9), body mass (49.5 ± 9.9; range: 34.4–82.7), BMI (122.1 ±30.2; range 66.4–219.8), FFM (60.6 ± 10.7; range 39.7–97.0), or BSA (1569.9 ± 306.7; range 974.9–2747.0), the variation within submaximal OUES values was reduced.

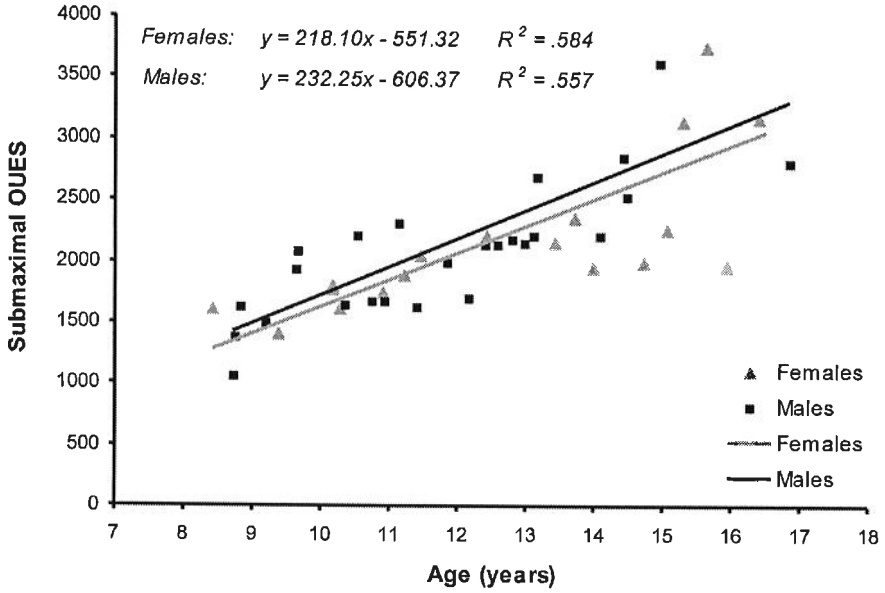

Figure 1 — Age-related changes in OUES.

The submaximal OUES did not differ significantly from the maximal OUES (p = .296), even when the OUES values were expressed relative to body mass (p = .413), BSA (p = .370), or FFM (p = .579). A Bland-Altman plot of the maximal OUES versus the submaximal OUES is shown in Figure 2. Furthermore, a strong correlation was observed between both parameters (r = .92). The submaximal OUES showed a high correlation with $\dot{V}O_2$peak (r = .88), $V_E$peak (r = .73), and VT (r = .85); with $p < .01$ for all coefficients. However, when normalized for body mass, the correlations with $\dot{V}O_2$peak and $V_E$peak declined (r = .60 and r = .51, respectively; $p < .01$). Similarly, lower correlations were found when normalized for BSA (r = .67 and r = .45, respectively) or FFM (r = .49 and r = .39, respectively); with $p < .01$ for all coefficients. No significant gender differences were found for the absolute values of all studied exercise parameters (data not shown). However, when expressed relative to body mass, BSA or FFM, both $\dot{V}O_2$peak and $V_E$peak

Table 2 Population Exercise Parameters

	Boys (n = 27) Mean ± SD Range		Girls (n = 19) Mean ± SD Range		
HR_{peak} (beats·min^{-1})	192.6 ± 7.9	(181–206)	193.7 ± 6.8	(180–212)	
RER_{peak}	1.15 ± 0.06	(1.02–1.28)	1.16 ± 0.08	(1.01–1.29)	
VT (mL·min^{-1})[a]	1533.6 ± 468.3	(830.0–2712.0)	1425.4 ± 498.5	(936.0–2767.0)	
$\dot{V}O_2$peak (mL·min^{-1})	2188.0 ± 671.4	(1150.0–3590.0)	2176.8 ± 807.8	(1230.0–4140.0)	
$\dot{V}O_2$peak/kg (mL·min^{-1}·kg^{-1})	52.9 ± 6.7	(40.3–63.3)	43.6 ± 5.5	(33.6–55.6)	***
$\dot{V}O_2$peak/BSA (mL·min^{-1}·m^{-2})	1633.0 ± 248.3	(1128.6–2086.7)	1449.3 ± 276.1	(1138.9–2102.7)	*
$\dot{V}O_2$peak/FFM (mL·min^{-1}·kg^{-1})	62.85 ± 7.26	(49.42–74.49)	55.75 ± 6.78	(46.67–71.31)	**
$V_E$peak (L·min^{-1})	77.7 ± 25.1	(45.2–149.5)	76.1 ± 28.2	(44.6–144.3)	
$V_E$peak/kg (L·min^{-1}·kg^{-1})	1.88 ± 0.28	(1.42–2.40)	1.55 ± 0.32	(0.82–2.06)	**
$V_E$peak/BSA (L·min^{-1}·m^{-2})	58.1 ± 9.6	(41.7–80.4)	51.2 ± 11.8	(28.6–78.0)	*
$V_E$peak/FFM (L·min^{-1}·kg^{-1})	2.25 ± 0.29	(1.68–2.76)	1.96 ± 0.40	(1.15–2.64)	*
Maximal OUES	2185.2 ± 676.2	(849.0–3521.5)	2237.0 ± 759.5	(1236.1–3777.1)	
Maximal OUES/kg	52.9 ± 8.6	(35.2–70.7)	45.2 ± 6.1	(37.3–59.9)	**
Maximal OUES/BSA	1632.2 ± 294.3	(922.9–2347.7)	1496.3 ± 261.3	(1144.5–1998.5)	
Maximal OUES/FFM	62.71 ± 9.67	(40.85–82.86)	57.51 ± 7.13	(47.32–71.08)	*
Submaximal OUES[a]	2156.8 ± 668.6	(1062.6–4120.5)	2260.3 ± 740.6	(1405.2–4074.5)	
Submaximal OUES/kg[a]	51.8 ± 10.3	(34.4–82.7)	46.3 ± 8.5	(36.0–62.9)	
Submaximal OUES/BSA[a]	1602.9 ± 323.8	(974.9–2747.0)	1524.6 ± 283.9	(1202.0–2202.4)	
Submaximal OUES/FFM[a]	61.70 ± 11.80	(39.71–96.95)	59.15 ± 9.14	(46.19–74.69)	

Abbreviations: BSA = body surface area; FFM = fat free mass; HR = heart rate; OUES = oxygen uptake efficiency slope; RER = respiratory exchange ratio; VT = ventilatory threshold; V_E = minute ventilation; $\dot{V}O_2$ = oxygen uptake. [a] VT was not determinable in one boy, so in this case n = 26 for the boys. * p<.05, ** p<.01, *** p<.001.

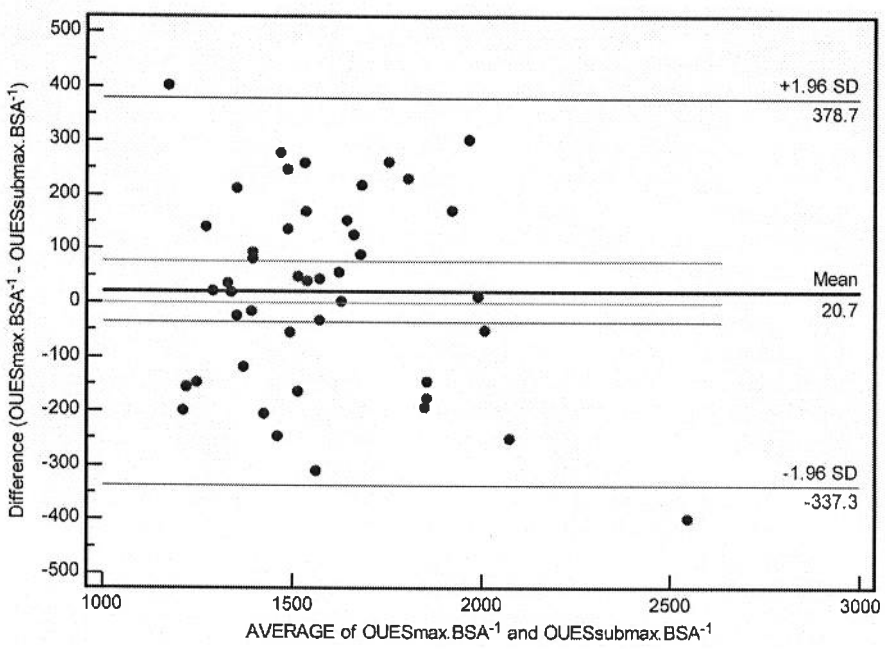

Figure 2 — Bland-Altman plot of maximal OUES·BSA^{-1} and submaximal OUES·BSA^{-1} showing the bias (difference in mean) and limits of agreement.

were significantly higher in boys compared with girls, whereas adjustment of the submaximal OUES did not result in gender differences. High correlations were found between the submaximal OUES and basic anthropometric variables, including height (r = .82), BSA (r = .77), age (r = .82), body mass (r = .75), FFM (r = .84) and BMI (r = .53); with $p < .01$ for all coefficients. The submaximal OUES appeared to linearly increase with age, as is shown in Figure 1.

Discussion

This study describes submaximal OUES characteristics in a healthy pediatric population, aged 7–17 years. The main findings indicate that the OUES in healthy children (i) is independent of exercise intensity, (ii) correlates highly with other exercise parameters (such as $\dot{V}O_2$peak, $V_E$peak, VT), and (iii) shows a linear increase with age during childhood and into adolescence. However, our results also illustrate that the OUES is considerably influenced by anthropometric variables and that its values show large interindividual variation.

The submaximal OUES values found in our population are in line with earlier studies of children with corresponding ages (11,21,22); despite the fact that those two studies used a treadmill rather than a cycle ergometer to perform the maximal exercise tests. The strong correlation between the submaximal OUES and $\dot{V}O_2$peak also is in line with the results of Baba et al. (5) who reported a very strong correlation

between the submaximal OUES and $\dot{V}O_2$max ($r = .95$). The submaximal OUES did not significantly differ from the maximal OUES in this current study, which confirms the results of Marinov et al. (22). Other studies, however, found submaximal OUES values to be slightly, but significantly, higher (21) or lower (5,11) compared with maximal OUES values. Large interindividual differences in OUES values might be responsible for these inconsistent findings among the abovementioned studies. Although previous studies reported the OUES to be significantly higher in boys compared with girls, our current study suggest that although boys generally achieve higher peak values in both $\dot{V}O_2$ and V_E, their ventilatory efficiency (OUES) does not differ significantly from girls.

The strong correlations between the submaximal OUES and various basic anthropometric variables in this study reflect changes in ventilatory efficiency during childhood and into adolescence, and are in line with to those found for the maximal OUES in earlier studies (21,22). During maturation, with the associated changes in length, body mass, and body composition, absolute peak values of both V_E and $\dot{V}O_2$ will also change making it reasonable that it will affect the OUES as well.

Maximal indices such as $\dot{V}O_2$peak are known to be strongly influenced by changes in body size. Therefore, $\dot{V}O_2$peak is often expressed in relation to body mass. Although this does not fully compensate the influence of body size on $\dot{V}O_2$peak (20). The study of Marinov & Kostianev (21) showed that normalizing $\dot{V}O_2$peak by dividing it by BSA compensates for the differences between various weight groups. Therefore, OUES during childhood should be interpreted with caution, which is in line with the current study results which indicate that the submaximal OUES in children is considerably influenced by anthropometric variables. Adjusting its values for body size seems appropriate, especially in childhood. Previous studies have expressed OUES relative to body mass, FFM, and BSA. Our current study results indicate that FFM will reduce the overall variability to the greatest extent, followed by BSA, and hence adjustment of submaximal OUES values for BSA or FFM in children seems recommended. Moreover, from a physiological perspective, FFM provides the best indication of $\dot{V}O_2$peak (as a direct relation is assumed between muscle mass and its capacity to consume oxygen for energy metabolism) (13,29,34), whereas BSA is supposed to provide a more precise indication of body volume compared with merely height or body mass (12,23).

This present study has some limitations such as the relatively small and heterogeneous population, which could be responsible for the large interindividual variation and skewed distributions. During data exploration five individuals were detected as outliers. All deviated on the top side of the box plot, indicating that they had a significantly higher aerobic capacity than the rest of the group. Profound investigation revealed that these subjects were significantly older than the other participants (15.45 ± 1.12 versus 11.83 ± 2.25 years respectively; $p < .001$), participated regularly (>3 hr·week^{-1}) in endurance sports, and showed significantly higher $\dot{V}O_2$peak values. As a result of their physical activity patterns, these subjects might be highly trained and therefore may not be representative for a normal pediatric population. Elimination of the outliers resulted in a decrease in overall distribution of OUES values. However, it might be a first indication of the responsiveness of the OUES with exercise training in children.

Furthermore, appropriate cut-off values should be used for submaximal OUES determination. However, at present it remains unclear which endpoint approach is

most useful to simulate submaximal effort (approaches based on RER, VT, heart rate reserve, or a percentage of exercise duration or $\dot{V}O_2$max; 19). In the current study, VT was used as a cut-off value for submaximal OUES determination, although VT cannot always be determined and its values depend on the method used for detection (27). Shimizu et al. showed that the V-slope method had consistently good agreement among observers (with intraclass correlations ranging from .85 to .98) and was least affected by the used exercise protocol. Furthermore, the study of Wasserman (35) identified this method as the most practical method. Since the submaximal OUES is derived from multiple data points up to VT and the OUES appears to be effort-independent (15,22,24,31), the exact endpoints will nonetheless not have influenced OUES values to a great extent.

There is a need for adequate reference values for the OUES in (healthy) children. Appropriate reference values should be generated with respect to age, gender, race, and other relevant factors such as maturation and anthropometrics. To our knowledge, influences of puberty on the OUES have not been investigated. Since puberty could lead to significant changes in body composition, muscle strength, $V_E$max, ventilatory equivalent, and physical activity patterns, it might also influence ventilatory efficiency (OUES). Future studies should address these variables.

Furthermore, it is currently unknown whether the submaximal OUES is able to differentiate between healthy children and children with a (chronic) disease. Previous findings suggest that OUES has discriminative value in adults (7,8,18,30,31), however further research is required to assess its discriminative properties in different pediatric populations.

The responsiveness of the OUES to physical training is another issue that has not been addressed in pediatric populations. Results from adult studies suggest the OUES to increase following physical training in cardiac patients (9,14,33). The OUES is useful to evaluate progression in exercise capacity, given that an increase in OUES suggests that a similar oxygen uptake is achieved with lower ventilatory cost (increase in efficiency; 9, 14, 33). Several authors even state that the OUES is more stable and robust than the maximal parameter $\dot{V}O_2$peak, since peak work load attained during a symptom-limited exercise test can be influenced by multiple factors (14,18,31). However, large interindividual variation may limit the usefulness of OUES in clinical practice. To the best of our knowledge, none of the studies in the current literature on OUES investigated the practical application of OUES by correlating OUES values in children with their running speeds or other practical test criteria. However, children with higher $\dot{V}O_2$peak values, indicating better endurance performance, show higher OUES values than children with lower values of $\dot{V}O_2$peak. The responsiveness and the practical application of the OUES in pediatric populations remains subject of further research.

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CHAPTER 6:

Predictability of exercise capacity following pediatric burns: a preliminary investigation

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ORIGINAL ARTICLE

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Predictability of exercise capacity following pediatric burns: a preliminary investigation

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ABSTRACT

Purpose: Describe the course of exercise capacity in pediatric burn patients during the initial 6 months after hospital discharge, and examine whether its recovery can be predicted from burn characteristics, sociodemographic characteristics, and/or prior assessment.

Materials and methods: Exercise capacity was assessed at discharge, and 6 weeks, 3 months, and 6 months after discharge using the Steep Ramp Test (SRT).

Results: Twenty-four pediatric patients with burns affecting 0.1–34% of total body surface area were included. At group level, exercise capacity was low at discharge and did not reach healthy reference values within 6 months, despite significant improvement over time. At individual level, the course of exercise capacity varied widely. Six months after discharge, 48% of participants scored more than one standard deviation below healthy age- and sex-specific reference values. SRT outcomes at 6 weeks and 3 months were the best predictors of exercise capacity 6 months after discharge, explaining, respectively, 76% and 93% of variance.

Conclusions: Forty-eight percent of participants did not achieve healthy reference values of exercise capacity and were therefore considered "at risk" for diminished functioning. Our preliminary conclusion that early assessment of exercise capacity with the SRT can timely identify those patients, needs to be strengthened by further research.

➤ IMPLICATIONS FOR REHABILITATION

- Pediatric burns can be considered as a chronic medical condition because of the lifelong consequences.
- Exercise capacity is reduced following- even minor -pediatric burns.
- Recovery patterns vary widely: some pediatric burn patients achieve healthy levels of exercise capacity without specific intervention, while others do not.
- The Steep Ramp Test can be used to assess exercise capacity, identifying those "at risk" for adverse outcomes at an early stage.
- Patients "at risk" should be encouraged to play sports and adopt an active lifestyle.

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Introduction

Burn injuries during childhood can have a tremendous impact. The pathophysiology of burns generally leads to muscle wasting and a decline in exercise capacity, which is exacerbated by the long periods of hospital stay with bed rest and inactivity [1–3]. The primary focus of burn care is helping children to return to the activities they were involved in before the burn injury, with minimal functional limitations, psychological consequences, and cosmetic alterations [4]. Recovery of exercise capacity is an important prerequisite to achieve optimal levels of functioning, participation, and quality of life [5–7]. Moreover, exercise capacity is an important predictor of (long-term) health outcomes [8,9]. As pediatric burn patients, even those with minor burns, already have an increased risk for secondary health conditions in the long term [10–13], it is important to ensure that every one of them achieves and maintains healthy levels of exercise capacity.

The majority of evidence regarding exercise capacity after pediatric burns originates from the Shriners Hospital for Children in Galveston, U.S.A. [6,14–27]. These studies included children and adolescents with extensive burns (>30% or >40% of total body surface area (TBSA)). In this exceptional group of patients, exercise capacity was shown to be affected up to 5 years post-burn, despite significant improvements caused by structured exercise and/or drug interventions [14–16,20,21,24–27]. Fortunately, such

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extensive pediatric burns are rare in both the Netherlands and the U.S.A. [28], and this will also be the case in other developed countries.

In patients with less extensive burns, the general pediatric burn population admitted to a burn center, a certain decline in exercise capacity is assumed as well. It is often supposed, however, that their exercise capacity will recover to healthy levels without specific intervention. Surprisingly, only two studies actually assessed exercise capacity in the general pediatric burn population. Both studies were cross-sectional and assessed exercise capacity beyond the initial 6 months after hospital discharge. Valenciano et al. [29] showed that pediatric burn patients (4–12.5%TBSA) obtained healthy values of walking distance on the 6-minute walk test, 6–24 months after discharge from the burn center. It is important to note, however, that this test reflects the capacity to perform *sub*maximal exercise. Disseldorp et al. [28] assessed maximal exercise capacity 1–5 years postburn, and showed that pediatric burn patients (10–41% TBSA) did not perform significantly worse compared to healthy peers. Individual assessment showed, however, that one third of the participants scored more than one standard deviation (SD) below age- and sex-specific healthy reference values and was therefore considered "at risk" for diminished functioning, participation, and quality of life. Additional data from these patients showed that the majority of them (65%) did not achieve the physical activity recommendation of the World Health Organization [30]. Inactivity leads to a further decrease in exercise capacity, and this downward spiral of deconditioning can cause significant health problems in the long term [5].

To identify the potential rehabilitation needs of the general pediatric burn population admitted to a burn center, it is essential to determine the course of their exercise capacity after discharge. Examining factors that can predict the recovery of exercise capacity at an early stage, enables early intervention for those who need this. Therefore, this study aimed (1) to describe the course of exercise capacity in children and adolescents with a wide range of burn characteristics during the initial 6 months after hospital discharge, and (2) to examine whether exercise capacity 6 months after discharge can be predicted from burn characteristics, sociodemographic characteristics, and/or prior assessment of exercise capacity.

Materials and methods

The data described in this study were obtained as part of a multicenter prospective cohort study. During the initial 6 months after discharge, exercise capacity was systematically assessed four times: at discharge, and at 6 weeks, 3 months, and 6 months after discharge. The total study comprised also the assessment of body composition, joint range of motion, muscular strength, physical activity and sedentary behavior, perceived fatigue, and health-related quality of life. Results of these additional variables will be presented in future publications. All assessments were conducted as described by Disseldorp et al. [31], with the exception of exercise capacity, for which the procedure is described below. Assessments were performed at the burn center where regular follow-up visits took place, usually also the center of admission. All assessments were performed by trained physical therapists and researchers from the burn centers. The Regional Committee for Patient-Oriented Research Leeuwarden (in Dutch: Regionale Toetsings-commissie Patiëntgebonden Onderzoek - RTPO) approved the study (date November 18, 2013; protocol number NL45917.099.13; chairperson Dr A. Wolthuis). The study has been registered in the National Academic Research and Collaborations Information System (trial registration number: OND1353942).

Study population

Eligible for this prospective cohort study were children and adolescents aged 6–18 years who were hospitalized in one of the three Dutch burn centers in the period from March 2014 till February 2017, with burns affecting 5% TBSA or more, or a length of hospital stay of more than 2 weeks, or both. Extensive (pre-existing) comorbidity, (mental) disabilities, insufficient Dutch language proficiency, and contra-indications for maximal exercise testing, as identified by the Exercise Pre-participation Screening form, were criteria for exclusion. Written informed consent was provided by all parents (or legal representatives) as well as by participants aged $\geq$12 years before enrollment; for participants aged 18 parental informed consent was not required.

Data collection

Exercise capacity

Exercise capacity was assessed on an electronically braked bicycle ergometer (Lode Corival, Lode, ProCare BV, Groningen) using the Steep Ramp Test (SRT). Seat height was adjusted to a comfortable leg length for each participant. To enable comparison with Dutch age- and sex-matched reference values [32], the SRT protocol as described by Bongers et al. [32] was used (realized using Lode Ergometry Manager software, version 9.4.7). According to this protocol, workload increased every two seconds with 2, 3, or 4 Watts (W), depending on the participant's body height (<1.20 m, between 1.20 and 1.50 m, and >1.50 m, respectively). The protocol applicable at discharge was used in all subsequent assessments of that child. The children were instructed to maintain a pedaling rate between 60 and 80 revolutions per minute (rpm) until they could no longer maintain a pedaling rate of $\geq$60 rpm, despite strong verbal encouragement. Peak power output (POpeak), the main outcome parameter of the SRT, was defined as the maximum workload (in W) attained before the pedaling frequency definitely dropped below 60 rpm. POpeak was expressed relative to body weight (POpeak/kg) in order to adjust for body size [32].

The SRT has shown to be feasible, valid, and reliable for evaluating exercise capacity of children and adolescents in daily clinical practice [33–35]. POpeak has been indicated as an appropriate alternative to peak oxygen uptake assessment in pediatric populations [33]. Limits of agreement varied from 9% to −13% (smallest detectable change = 11%) in healthy children and adolescents, which indicates that the SRT can be used to determine meaningful improvements within a single individual [33]. Furthermore, in healthy children and adolescents assessed twice within a period of 2 weeks, there was no evidence of a significant learning effect [33].

The investigator recorded whether subjective signs of intense effort, like unsteady cycling, sweating, facial flushing, and clear inability to continue despite strong verbal encouragement, were present at the end stage of the test. Only assessments in which the participant clearly showed subjective signs of intense effort at the end stage of the test, were included in the analyses.

Burn and sociodemographic characteristics

Data on age, sex, extent of burn, number of surgeries, location of burns, etiology, presence of inhalation injury, and date of injury, admission, and discharge, were obtained from the national Dutch Burn Repository. Data regarding sports participation were

obtained from the Standard Questionnaire for Activity [36] and data regarding parental education and behavioral problems were obtained from the Dutch version of the American Burn Association/Shriners Hospitals for Children Burn Outcome Questionnaire [37]. Low parental education was assumed if both parents had finished only elementary school or secondary school, without further education. Socio-economic state (SES) was based on postal code areas, with low SES defined as households within the lowest quintile.

Statistical analyses

Representativeness of participants

To evaluate whether the participants could be considered representative for all eligible pediatric burn patients, participants and non-participants were compared with regard to age, extent of burn, length of hospital stay, and number of surgeries, using independent samples *t*-tests. Non-participants were those patients who were invited but declined to participate ($n = 21$) and the patients who were eligible but not invited due to organizational matters ($n = 4$).

Z-scores for comparison with age- and sex-matched reference values

Absolute scores of POpeak (in W/kg) and body weight were converted to Z-scores. These standardized scores enable the comparison of individual scores to age- and sex-matched healthy reference values obtained from the literature [32]. As such, Z-scores are increasingly adopted in pediatric health care [38]. Individual Z-scores were obtained by calculating how many SDs each individual POpeak/kg score deviated from the age- and sex-specific reference value [32]. Group Z-scores were calculated as the mean of individual Z-scores at each time point. In line with previous studies, participants with a Z-score <-1.0 were considered "at risk" [39,40]. In a typically developing population, assuming normal distribution, approximately 16% of the children will score more than one, and 2.5% will score more than two SDs below the population mean.

Body weight of each participant was compared to the healthy body weight-for-height curve [41] in order to determine which participants were (severely) underweight or (severely) overweight (defined as >1 SD (or >2 SD) below or above the healthy body weight-for-height curve, respectively) [42].

Group level analysis

To gain insight in the group results on exercise capacity over time a multilevel regression model was applied, with burn center, participant, and time point as levels. Only participants with two or more valid SRT assessments were included in the multilevel regression analyses. Time points were defined as dummy variables with T1 (discharge) as reference. Additionally, analyses were performed using T2 (6 weeks after discharge) and T3 (3 months after discharge) as reference. By using multilevel regression models, it was possible to correct for potential differences between burn centers.

To enable comparison with existing literature regarding the course of exercise capacity following pediatric burns [14–16], rate of change (%) in POpeak/kg scores between assessments was calculated. The following formula was used for this purpose:

$$100 \times (\text{POpeak (W/kg)}_{\text{subsequent}} - \text{POpeak (W/kg)}_{\text{previous}}) / \text{POpeak (W/kg)}_{\text{previous}}$$

Individual level analysis

To examine the course of exercise capacity at an individual level, POpeak/kg scores of individual participants over time were plotted against individual age- and sex-matched reference values [32]. Additionally, Z-score scatter plots were used to examine for each time point how many participants scored more than one SD below the age- and sex-specific healthy reference value and were thus considered "at risk".

Predictability of exercise capacity

To evaluate whether exercise capacity 6 months after discharge could be predicted from burn characteristics, sociodemographic characteristics, and/or prior assessment, univariate multilevel regression analyses were performed. Extent of burn, length of hospital stay, number of surgeries, location of burns (legs involved), etiology, age, sex, weight status, sports participation, behavioral problems, parental education, SES, and the SRT outcome at discharge, 6 weeks, and 3 months were included as independent variables in separate univariate multilevel regression models, in order to assess the individual contribution of each variable to exercise capacity 6 months after discharge.

IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: IBM Corp.) was used for general statistical analyses, MLwin version 2.02 (Center for Multilevel Modeling, University of Bristol, UK) for multilevel analyses, and Microsoft Excel 2010 for graphing. An alpha-level of 5% was adopted, so *p*-values below 0.05 were considered statistically significant.

Results

In the period from March 2014 till February 2017, 53 pediatric burn patients were eligible, 24 of them were included (Figure 1), and 19 completed all four assessments. Comparison of participants and non-participants showed no significant differences with regard to the distribution of sex, mean age at burn injury, extent of burn, length of hospital stay, and number of surgeries (Table 1).

Participant characteristics

The participants ($n = 24$) covered the age range between 6 and 18 years, had burns affecting 0.1–34% of TBSA, and a length of hospital stay varying from 12 to 66 days (Table 1). Burns were caused by hot liquid ($n = 10$) or fire/flames ($n = 14$), with one patient from the latter group also having sustained an inhalation injury. Two participants were referred for additional physical therapy after discharge because of persisting restrictions in range of motion over one or more joints. All participants were discharged home. Two participants had one reconstructive surgery each during the study period. Most participants had a body weight matching their standing height. One participant was severely underweight, four were overweight, and five were severely overweight, throughout the entire study period.

Assessments

Of the 96 SRT assessments that could have been performed (24 children, four assessments each), eight were not obtained due to no show or loss to follow-up, and 14 were considered invalid (Figure 1).

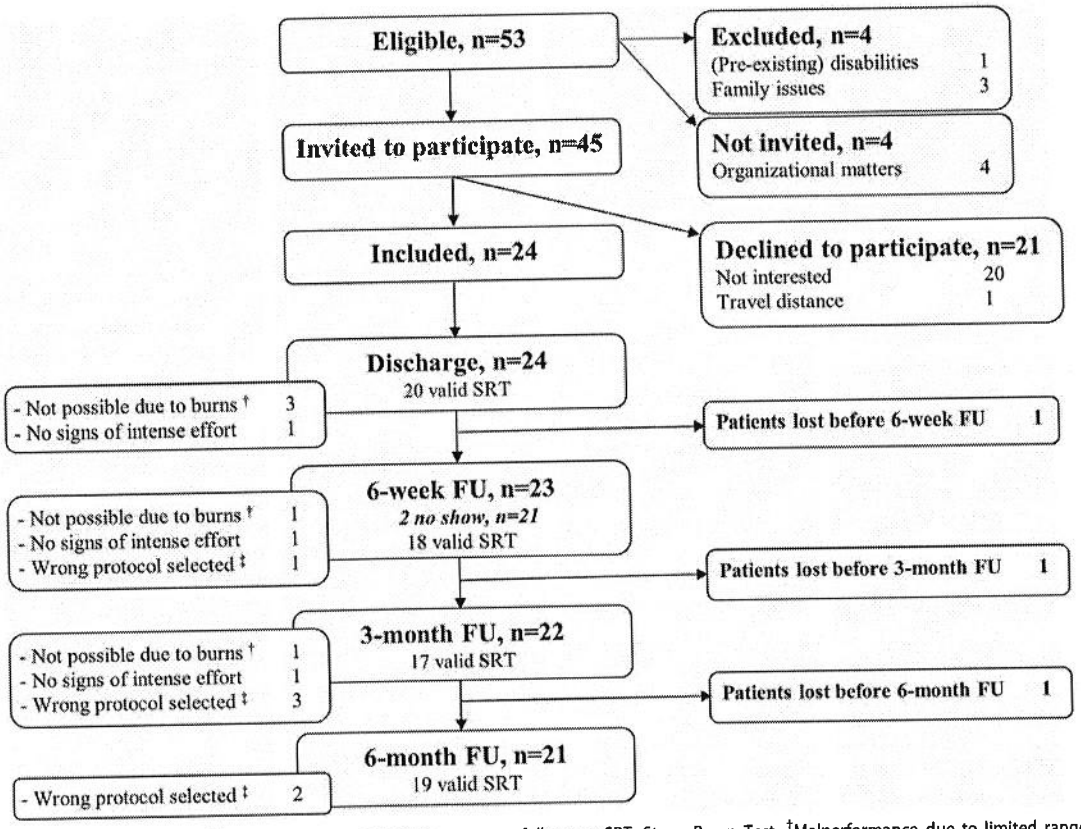

Figure 1. Flow chart and number of valid assessments at each time point. FU: follow-up; SRT: Steep Ramp Test. †Malperformance due to limited range of motion of one or both knees. ‡Another protocol than required for that participant, or using a manual instead of software-driven workload increment program.

Table 1. Characteristics of participants and non-participants.

Parameter	Participants ($n=24$)	Non-participants ($n=25$)[a]	p-value[b]
Male, *n* (%)	15 (62.5)	15 (60.0)	0.858
Age at burn injury (years)	12.6 ± 3.6 (6–18)	12.2 ± 4.4 (6–18)	0.778
%TBSA involved	11.8 ± 8.8 (0.1–34)	13.4 ± 11.7 (3–45)	0.600
<10%, *n* (%)	13 (54)	14 (56)	
>20%, *n* (%)	5 (21)	5 (20)	
Legs involved, *n* (%)	18 (75)		
Length of hospital stay (days)	22.5 ± 13.8 (12–66)	23.9 ± 23.4 (6–115)	0.803
≤2 weeks, *n* (%)	6 (25)	11 (44)	
≥4 weeks, *n* (%)	5 (21)	7 (28)	
Number of surgeries	1.4 (0–5)	1.3 (0–8)	0.907

Results are shown as mean ± SD (range), unless specified otherwise. *n*: number; %TBSA: percentage of total body surface area affected by burns.
[a]Non-participants were those patients who were invited but declined to participate ($n=21$) and the patients who were eligible but not invited due to organizational matters ($n=4$).
[b]A chi-square test was used to compare sex distribution across groups. Independent samples *t*-tests were used for all other comparisons.

The course of exercise capacity over time - group level

At discharge, group level exercise capacity was approximately two SDs below age- and sex-specific healthy reference values (Figure 2). Exercise capacity improved significantly over time, with the biggest improvements observed during the initial 6 weeks after discharge (Figure 2). Additional analyses, using T2 (6 weeks after discharge) as reference, showed that the improvement observed in the period from 6 weeks to 6 months after discharge was significant as well. Despite the significant improvement over time, group level exercise capacity remained more than one SD below age- and sex-specific healthy reference values 6 months after discharge (Figure 2).

Examination of absolute SRT scores showed that POpeak/kg had increased with 5.4 ± 13.6% after 6 weeks. In the period from 6 weeks to 3 months, less improvement was observed, that is 3.7 ± 8.5%. From 3 months to 6 months after discharge, exercise capacity improved with 5.5 ± 6.3%.

The course of exercise capacity over time - individual level

Individual data showed that the course of exercise capacity varied widely among participants. By visual inspection of the graphs in which individual POpeak/kg scores were presented with respect to age- and sex-specific healthy reference values, four patterns could be distinguished, differing from each other with regard to starting point (SRT outcome at discharge), endpoint (SRT outcome 6 months after discharge), and general course of SRT scores over time (Figure 3). Five participants already had healthy reference values of exercise capacity at discharge (Figure 3, pattern A) and seven others achieved healthy reference values within 6 months (Figure 3, pattern B). Eleven participants (48%) did not reach healthy reference values of exercise capacity within 6 months, i.e. SRT score 6 months after discharge more than one SD below the age- and sex-specific healthy reference value (Figure 3, patterns C + D), five of which showed no improvement over time (Figure 3, pattern D).

Individuals "at risk"

Analysis of individual Z-scores at different time points showed that the majority of participants scored below age- and sex-matched healthy reference values on exercise capacity at each time point (Figure 4). At discharge, 15 of the 20 participants (75%) scored more than one SD below the age- and sex-specific healthy reference value and were thus considered "at risk" for diminished functioning, participation, and quality of life. At 6 weeks, 3 months, and 6 months after discharge, these percentages were 56, 59, and 44%, respectively.

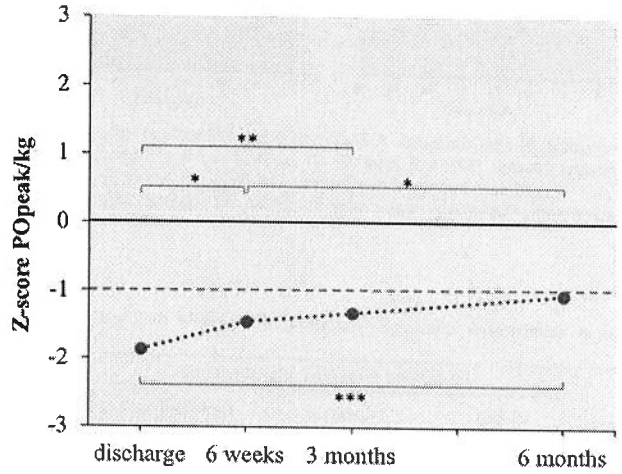

Figure 2. The course of exercise capacity in pediatric burn patients after discharge—output from multilevel regression modeling ($n = 21$). Group Z-scores represent the mean of individual Z-scores (each individual POpeak/kg score compared to an age- and sex-specific reference value). A Z-score of 0 (solid black line) indicates POpeak/kg equal to the mean score of age- and sex-matched healthy controls [32]. A Z-score of −1 (dashed red line) represents POpeak/kg one standard deviation below the age- and sex-specific healthy reference value. POpeak/kg: peak power output (in W) attained during the Steep Ramp Test relative to body weight (in kg); $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

Prediction of exercise capacity from burn characteristics

Univariate multilevel regression analyses showed that etiology and location of burns were both significant predictors of exercise capacity 6 months after discharge, whereas %TBSA affected, length of hospital stay, and number of surgeries were not (Table 2). Of the predicting factors, etiology of the burns predicted 17.9% of the variance in exercise capacity 6 months after discharge. Children with burns caused by hot liquids generally had better exercise capacity than those suffering from fire/flame burns. Leg involvement explained 23.4% of the variance and was positively associated with exercise capacity 6 months after discharge.

Prediction of exercise capacity from sociodemographic characteristics

Univariate multilevel regression analyses showed that age, weight status, behavioral problems, and SES were significant predictors of exercise capacity 6 months after discharge, whereas sex, sports participation, and low parental education were not (Table 2). Of the predicting factors, younger age, being overweight, being diagnosed with behavioral problems, and low SES were negatively associated with exercise capacity 6 months after discharge (Table 2). Being overweight independently explained 45.9% of the

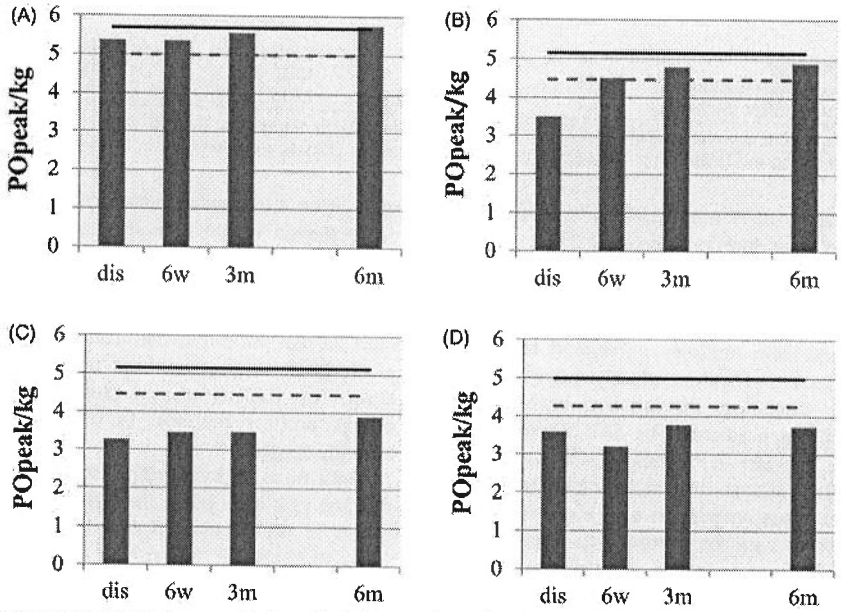

Figure 3. Different patterns in the course of exercise capacity in pediatric burn patients after discharge. The solid black line indicates the mean peak power output (POpeak/kg) of age- and sex-matched healthy individuals (reference value) [32]. The dashed red line represents one standard deviation below the age- and sex-matched reference value. Four different patterns were distinguished in the course of individual exercise capacity following pediatric burns: Pattern A - reference values of exercise capacity at discharge and at all other assessments ($n = 5$); Pattern B - low exercise capacity at discharge, (consistent) improvement over time, and recovery to reference values within six months ($n = 7$); Pattern C - low exercise capacity at discharge, (consistent) improvement over time, but not reaching reference values within six months, i.e. "at risk" ($n = 6$); Pattern D - low exercise capacity at discharge, no (consistent) improvement over time, and not reaching reference values within six months, i.e. "at risk" ($n = 5$). In case 6-month follow-up scores were not available, it was estimated whether the participant would reach reference values of exercise capacity or not, based on previous scores and the trend observed during follow-up. POpeak/kg = peak power output (in W) attained during the Steep Ramp Test relative to body weight (in kg); dis = discharge; 6w = 6 weeks after discharge; 3m = 3 months after discharge; 6m = 6 months after discharge.

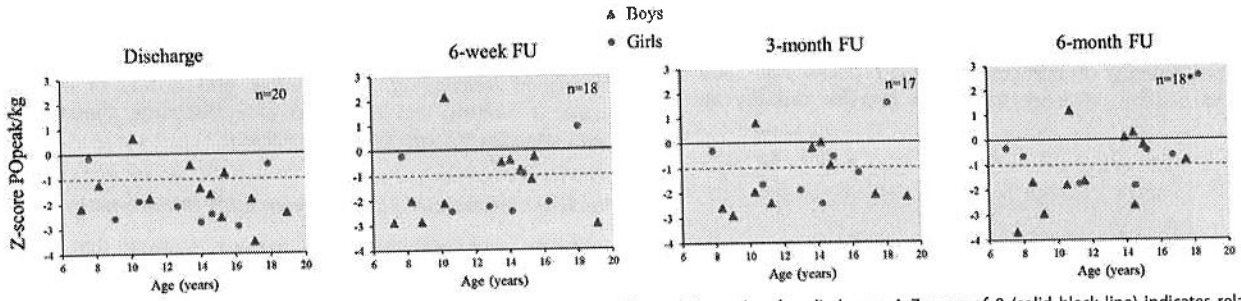

Figure 4. Individual Z-scores of exercise capacity at discharge, and 6 weeks, 3 months, and 6 months after discharge. A Z-score of 0 (solid black line) indicates relative peak power output (POpeak/kg) equal to the mean score of age- and sex-matched healthy controls [32]. A Z-score of −1 (dashed red line) represents relative POpeak/kg one standard deviation below the age- and sex-specific healthy reference value. *19 valid assessments of exercise capacity (POpeak), but body weight (kg) was missing in one of them due to the absence of an electronic scale at the time of assessment. POpeak/kg: peak power output (in W) attained during the Steep Ramp Test relative to body weight (in kg); FU: follow-up.

Table 2. Potential predictors of exercise capacity following pediatric burns, 6 months after discharge—output from univariate multilevel regression modeling.

			POpeak/kg 6 months after discharge		
Potential predictors	*n*	Constant β (SE)	β (SE)	*p*-value	Explained variance
Burn characteristics					
Extent of burn	18	4.607 (0.439)	−0.005 (0.032)	0.876	
Length of hospital stay	18	4.570 (0.505)	−0.001 (0.018)	0.956	
Number of surgeries	18	4.570 (0.505)	−0.001 (0.018)	0.956	
Legs involved	18	3.282 (0.374)	**1.760 (0.441)**	<0.001	**23.4%**
Etiology hot liquids	18	3.950 (0.326)	**1.206 (0.462)**	<0.01	**17.9%**
Sociodemographic characteristics					
Age	18	1.735 (0.697)	**0.236 (0.056)**	<0.001	**22.9%**
Gender	18	4.562 (0.347)	−0.023 (0.556)	0.967	
Overweight	18	5.139 (0.267)	**−1.508 (0.428)**	<0.001	**45.9%**
Sports participation	18	3.723 (0.530)	1.068 (0.601)	0.076	
Behavioral problems	18	4.882 (0.283)	**−1.184 (0.537)**	<0.05	**22.2%**
Low parental education	18	4.718 (0.310)	−0.594 (0.589)	0.313	
Low SES	18	5.092 (0.280)	**−1.386 (0.450)**	<0.01	**25.6%**
Prior assessment					
POpeak/kg at discharge	14	−0.244 (1.118)	**1.182 (0.258)**	<0.00001	**36.9%**
POpeak/kg 6 weeks after discharge	14	0.093 (0.500)	**1.036 (0.111)**	<0.00001	**75.7%**
POpeak/kg 3 months after discharge	14	0.080 (0.312)	**1.036 (0.068)**	<0.00001	**93.1%**

Potential predictors in bold showed significant predictive value for exercise capacity six months after discharge. POpeak/kg: peak power output (in W) attained during the Steep Ramp Test relative to body weight (in kg); SES: socio-economic state; ROM: range of motion.

variance in exercise capacity at 6 months, followed by low SES (25.6%), age (22.9%), and behavioral problems (22.2%).

Prediction of exercise capacity from prior assessment

Univariate multilevel regression analyses performed to find out whether prior assessments can independently predict exercise capacity 6 months after discharge, showed that each prior SRT assessment was a significant predictor. The SRT outcome at discharge explained 36.9%, the SRT at 6 weeks 75.7%, and the SRT at 3 months 93.1% of the variance in exercise capacity 6 months after discharge (Table 2). Visual inspection of the graphs in which individual POpeak/kg scores were presented with respect to age- and sex-specific healthy reference values, showed that only two out of the ten participants who were "at risk" at 6 weeks, did achieve reference values of exercise capacity 6 months after discharge.

Discussion

This study described the course of exercise capacity in pediatric burn patients after discharge from the burn center. Group level exercise capacity improved significantly over time in our study population, but healthy reference values of exercise capacity were not achieved within 6 months after discharge. Individual assessment showed that 48% of the pediatric burn patients scored more than one SD below the age- and sex-specific healthy reference value 6 months after discharge and was therefore considered "at risk" for diminished functioning, participation, and quality of life [5–7]. Prior assessment of exercise capacity with the Steep Ramp Test (SRT) predicted exercise capacity 6 months after discharge, and can therefore be used to identify "at risk" patients at an early stage.

Until now, all longitudinal studies on exercise capacity during the first year after pediatric burns were performed by the research group of the Shriners Hospital for Children in Galveston, U.S.A. [6,14–18,22–27]. It is hard to make a fair comparison between these studies and our findings, as the Galveston patients suffered from more extensive burns compared to our participants (>30% or >40% versus <35% TBSA burned, respectively). Moreover, the Galveston studies focused primarily on the effects of exercise therapy, either or not combined with drug therapy (e.g. oxandrolone, propranolol, metformin, growth hormone), and not on the natural course of exercise capacity. The best option is to compare our findings to the results of the Galveston patients who served as control and did not participate in any structured exercise

[14–16]. In these patients, exercise capacity improved with 3.12 ± 3.5% to 9.35 ± 16.8% from 3 to 6 months after discharge, which is comparable to the 5.5 ± 6.3% improvement found in our study population. Patients who participated in a 12-week structured exercise program during this period showed considerably larger improvements in exercise capacity (up to 24.3 ± 4.7%) [14–16]. In the more recent studies, the exercise program is started immediately after discharge and is offered to all pediatric burn patients (i.e. no control groups). This current exercise regime leads to even larger improvements in exercise capacity (up to 30%) [22–27].

Given the obvious benefits of such a structured exercise program after discharge [6,18,22–27], current practice guidelines state that this should be prescribed to all pediatric burn patients aged ≥7 years who score 'below normal' levels of exercise capacity [43]. However, such an in-hospital program is expensive and the child is away from home, school, family, and friends for an extended period of time. The question is, do all pediatric burn patients who score 'below normal' at discharge from the burn center need this kind of intensive rehabilitation? Thus far, the rehabilitation needs of the general pediatric burn population were unknown. Hence, this preliminary study offers essential new insights. We showed that 75% of the patients scored 'below normal' on exercise capacity at discharge, but half of them achieved healthy levels of exercise capacity within 6 months without specific intervention. The other half did not and these patients do need additional attention.

The current study also showed that the course of exercise capacity varied widely among patients. The large SDs in the rates of change presented in the Galveston studies suggest that this was also the case in their study populations. Unfortunately, none of these studies reported individual scores, so it remains unclear if some of their participants did reach, or approach, healthy reference values, or that exercise capacity was significantly reduced in the entire study population.

To our knowledge, this preliminary study was the first to examine potential predictors of exercise capacity following pediatric burns. Burn severity characteristics, like %TBSA, number of surgeries, and length of hospital stay, did not predict exercise capacity 6 months after discharge. These findings are in line with previous research on functional outcome at 6 months post-burn in patients of the same age and with similar burn characteristics (<1–35% TBSA) [44]. The fact that sports participation was a borderline non-significant predictor ($p = 0.076$), suggests a potential better outcome for those who participated in formal sports activities compared to those who did not. Our finding that SES and behavioral problems were significant predictors of exercise capacity is also in agreement with previous findings, as both sociodemographic factors were also found to be significant predictors of functional outcome [44]. However, as SES and behavioral problems are known to influence physical activity levels as well [45–48], it could be the case that the patients with behavioral problems and/or low SES already had low exercise capacity before the burn injury. Likewise, the five children from our study sample who already achieved healthy reference values of exercise capacity at discharge, might have had excellent exercise capacity before the injury. Nevertheless, no matter how big the decline in exercise capacity after discharge, some improvement was to be expected within 6 months, if only through ending the periods of bed rest and through natural growth and development. Therefore, the inconsistency or even decline in exercise capacity observed in five of our participants is definitely worrying.

Undeniably the most important finding of the current study was the predictive value of prior assessment of exercise capacity. Prior SRT assessment could explain up to 93.1% of the variance in exercise capacity 6 months after discharge. Although further research is required to confirm these preliminary results, this short and feasible bicycle exercise test appears valuable in identifying patients who are likely not to achieve healthy reference values of exercise capacity within 6 months. All pediatric burn patients who are considered "at risk" at 6 weeks after discharge, should receive additional attention.

What this additional attention should include, is still a point of discussion. For now we recommend to encourage sports participation and an active lifestyle in these patients, and provide them with the opportunity to enjoy physical activities in their own environment, together with their family and friends. Regular assessment of their exercise capacity at the burn center is essential though [43]. This might also be a good motivator for them. Proper education of the patients and their parents, (physical education) teachers, and sports trainers/coaches, might also be valuable, as they are not always aware of the benefits of, or even need for, physical activity, and might fear a harmful effect [49]. An additional opportunity might be the use of telerehabilitation; the use of virtual services to deliver health education, rehabilitative exercises, and personalized support [49–51].

Although standard cardiopulmonary exercise testing (CPET) remains the golden standard for the assessment of exercise capacity, the SRT was chosen deliberately for this study, as it has several advantages in daily clinical practice. First, the SRT is easier to perform and does not require expensive equipment for respiratory gas analyses [33]. Participants do not have to wear a face mask or mouthpiece, which makes the SRT more appropriate in anxious young children and patients suffering from facial burns. Second, the actual test duration is much shorter compared to the CPET, 2–3 min versus 8–12 min, respectively [32]. Third, the test is well tolerated by pediatric patients and when they were asked about their preferential maximal exercise test, all patients indicated that they favored performing the SRT over a traditional CPET [34]. Accordingly, lower values for exhaustiveness were reported after the SRT when compared to the CPET [33,34]. Last but not least, POpeak, the primary outcome measure of the SRT, seems to be a better indicator of daily life performance in children and adolescents than maximal oxygen uptake [32,52]. The only disadvantage of the SRT is that maximal effort cannot be identified objectively, as POpeak is generally determined by local muscle fatigue and maximal heart rate is not attained [33].

Strengths and limitations

Although this study should be seen as a pilot study considering the limited number of 24 patients, it is a first and important start to gain insight in the course of exercise capacity in the general pediatric burn population and, morerover, the factors predicting the recovery of exercise capacity. Our study population was considered representative for the Dutch pediatric burn population, with a large variety in demographics and burn characteristics and no differences between participants and non-participants were found. The use of Z-scores enabled a valid comparison of this heterogeneous pediatric patient population with reference values from healthy Dutch peers. Furthermore, our study highlights the importance of focusing on individual scores. As group level exercise capacity was not significantly reduced 6 months after discharge, it might have seemed unnecessary to pay attention to exercise capacity following pediatric burns affecting <35% of

TBSA. However, group level performance is not of interest for individual patients and their parents. Actually, it is important for every individual patient to perform within healthy ranges, and therefore, the eleven "at risk" patients deserve special attention.

Limitations of this study are, first of all, that selection bias might have occurred with especially those who were already interested in sports and physical activity willing to participate. This implies that the proportion of pediatric burn patients who are "at risk" might be even higher than the 48% presented in this study. Secondly, some of the burn and/or sociodemographic characteristics will be mutually related and, accordingly, a combination of characteristics in a multivariate regression model might have been able to explain more of the variance in exercise capacity 6 months after discharge. However, due to the small number of subjects included in this study, it was not possible to perform multivariate multilevel regression analyses. Further research, including larger patient populations, is definitely required to gain insight in the potential mutual dependency of burn and/or sociodemographic characteristics and to enable generating a stronger prediction model that enables identification of "at risk" patients at an early stage. Moreover, if burns are included as a single factor in the multilevel regression analysis, it would even be possible to use data from other pediatric patient populations, e.g. juvenile idiopathic arthritis or childhood cancer, to examine the predictive value of sociodemographic characteristics on the recovery of exercise capacity.

Implications for clinical practice

The current study showed that half of the pediatric patients with burns affecting <35% TBSA did not reach healthy reference values of exercise capacity within 6 months after discharge and were therefore considered "at risk" for diminished functioning, participation, and quality of life [5–7]. It should be clear that exercise capacity following - even minor - pediatric burns deserves more attention. As the SRT outcome at 6 weeks after discharge was able to predict which children had a reduced recovery of exercise capacity, we recommend incorporating the assessment of this short and feasible exercise test during the regular 6-week follow-up visit for all pediatric burn patients older than 6 years of age who have been hospitalized for their burns. Patients who are identified "at risk" should be encouraged to participate in sports and active play on a regular basis, in order to prevent serious deconditioning. Personal support in the form of education and structured exercise using additional (tele)rehabilitation might be valuable as well. Furthermore, it is important to continue to monitor their exercise capacity beyond 6 months.

Implications for future research

The results of the current study are part of a larger multidimensional study which also comprised the assessment of body composition, joint range of motion, muscular strength, physical activity and sedentary behavior, perceived fatigue, and health-related quality of life. These results have to be analyzed and will be discussed in future publications, also in relation to the current findings. Additionally, it would be interesting to assess how our participants will do in several years, and when they reach adulthood. With regard to our speculations about encouraging sports participation and adopting an active lifestyle, it should be evaluated to determine if this has the desired effect.

Further (international) research, including larger patient populations, is definitely required to confirm our preliminary finding that early application of the SRT can identify patients who are likely not to achieve healthy reference values of exercise capacity within 6 months after discharge. We encourage the development of a multivariate multilevel regression model, including burn characteristics, sociodemographic characteristics, and the SRT outcome at discharge, which enables the identification of "at risk" patients already at the point of discharge.

Conclusion

Although group level exercise capacity improved significantly within 6 months after discharge, 48% of the participants did not achieve healthy reference values and was therefore considered "at risk" for diminished functioning, participation, and quality of life. Our results suggest that early application of the SRT can identify those individuals. However, data from larger patient populations are required to strengthen this preliminary conclusion.

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Disclosure statement

The authors report no conflicts interest.

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CHAPTER 7: General discussion

GENERAL DISCUSSION

In order to determine and predict the rehabilitation needs of the general pediatric burn population (aged 6-18 years) beyond the acute care setting, the current thesis aimed to increase knowledge on functioning, specifically physical functioning, following pediatric burns.

First, habitual physical activity and perceived fatigue were assessed in children and adolescents 1-5 years after burn injury (TBSA 10-46%). Results showed that half of the boys and none of the girls met the global recommendations for physical activity. Symptoms of fatigue, particularly in the sleep-rest domain, were shown to be present in part of the population.

Subsequently, the course of exercise capacity during the initial six months after discharge was analyzed in children and adolescents with burns affecting 0.1-41% TBSA. Six months after discharge, half of these children achieved healthy levels of exercise capacity. The other children did not and were therefore considered 'at risk' for diminished functioning and adverse (long-term) health outcomes. Burn severity characteristics (i.e. %TBSA, length of hospital stay, or number of surgeries) could not predict the recovery of exercise capacity. Instead, results showed that assessment of exercise capacity with the Steep Ramp Test (SRT) at an early stage after discharge, can timely identify individuals 'at risk'.

Challenges of measuring functioning beyond pediatric burns

Research on functioning beyond pediatric burns is highly clinically relevant, but challenging for several reasons. First, the pediatric burn population is complex and diverse. Burns range from minor wounds to extensive injuries, with varying etiology, depth and site of burns, and, moreover, there is a wide variety among children with regard to age, sex, and developmental stage. Secondly, functioning is hard to operationalize and standardize, as functioning concerns multiple domains (body functions and structures, activity, and participation) [1] and dimensions (e.g. physical, psychological, and social), which can all be affected by burns [2-4]. Third, each child responds differently to a certain thermal impact and post burn functioning will depend on many factors other than burn characteristics, like physical and social environmental factors, personal factors, and pre-injury levels of functioning. Last but not least, clinical research, especially in this population, is often hampered by methodological issues, like small sample sizes, selection bias, and the lack of standardized outcome measures and valid, reliable, and feasible measurement tools.

As a consequence, it is hard to provide comprehensive and conclusive evidence on functioning beyond pediatric burns. Yet, the current thesis provides some essential new insights which hopefully encourages other research groups to join us regarding this important topic.

Choosing the right measurement tools

The availability of valid and reliable measurement tools is the foundation for scientific research and evidence-based clinical practice. Considering the importance of incorporating systematic (long-term) outcome monitoring in clinical practice, the measurement tools used in the current research were chosen based not only on validity and reliability, but also on feasibility for use in daily clinical practice.

Habitual physical activity can be assessed, amongst others, by self-report (e.g. questionnaires, activity logs, diaries, interviews), direct observation, and the use of electronic devices like heart rate monitors, pedometers, and accelerometers [5-9]. Activity questionnaires are most commonly used because of their cost effectiveness and ease of administration, especially in large populations [8]. However, with self-report it is hard to determine activity intensity and responses may be influenced by recall capacity and social desirability [8,10]. Therefore, objective activity monitoring with an accelerometer, complemented with a short activity dairy, is recommended in pediatric populations [5,6]. However, a large volume of data is generated that must be checked, cleaned, scored, and summarized, which is challenging for researchers and clinicians [9]. My personal experience is that many accelerometer data is left unanalyzed as a result, which is – of course – highly undesirable. Chapter 2 provides a clear description of our accelerometry data processing methods, and a number of important issues considering activity monitoring are discussed. My intention was to inform and support other clinical researchers and clinicians and encourage them to use accelerometry instead of, or complemented with, self-report questionnaires to assess physical activity in pediatric (patient) populations. It is – hopefully – also a first step towards a more standardized use of accelerometry in pediatric burn research and clinical practice in the Netherlands and beyond. This would allow more valid interpretation and comparison within and among study populations. To designate the best technology and methodology, as well as outcomes for habitual physical activity, continued controlled studies among pediatric study populations is advocated for in future research agendas.

Fatigue refers to an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, which is unrelieved by sleep or rest [11,12]. As a subjective symptom, i.e. perceived fatigue, it is preferably measured using self-report [12,13]. To this end, a large number of questionnaires is available, with the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) showing best evidence for use in children [13-17]. This questionnaire is designed to assess both child and parent-proxy perceptions, and recognizes the complexity of fatigue by covering multiple dimensions (i.e. general fatigue, sleep-rest fatigue, and cognitive fatigue) [18]. The Dutch version of

the PedsQL MFS [19] was used in Chapter 3 to assess fatigue in the pediatric burn population. It is important to realize, however, that perceived fatigue does not tell anything about the nature of fatigue (e.g. central, peripheral, muscular, mental) [12] or its underlying causes. To expand our understanding of fatigue after (pediatric) burns, it is deemed essential to examine objective performance fatigability as well, during both motor and cognitive tasks [11,12]. Which tests are most appropriate – i.e. valid, reliable, and feasible – in children with burns must be subject of continued future research on fatigue in children and in those with burn injuries alike.

For **exercise capacity**, the measurement of maximum oxygen uptake (VO_2max) with a standardized cardiopulmonary exercise test (CPET) is widely recognized as the golden standard [20]. However, performing such an exhaustive exercise test poses a serious burden on pediatric patients. Furthermore, children often fail to reach a true plateau in oxygen uptake [21].

In Chapter 4 and 5 the possibilities of the Oxygen Uptake Efficiency Slope (OUES) [22], a measure of exercise capacity that does not require maximal exertion, were explored. Results indicated that the OUES is an objective and reproducible measure with broad applicability, which is relatively independent of exercise intensity/duration, and correlates highly with other exercise parameters, including VO_2max. A major disadvantage of the OUES is, however, that it requires respiratory gas analysis, which is complex, expensive, and not available at all sites. Therefore, the feasibility for use in daily clinical practice is limited. Moreover, clinical interpretation is difficult as the OUES formally has no entity and normative reference values from healthy Dutch children and adolescents are not yet available.

During the course of the cross-sectional study, another alternative for the standardized CPET was introduced: the Steep Ramp Test (SRT) [23,24]. This short bicycle exercise test is based on the peak power output (W) [24], which has been indicated as an appropriate alternative for maximal oxygen uptake assessment in children [25,26] and beyond, and does not require the by times cumbersome and expensive respiratory gas analysis. The SRT has shown to be valid, reliable, and feasible in child populations [24], even if not healthy [27,28]. Moreover, Dutch reference values have been developed for children aged 8-18 years [29]. Considering these advantages, the SRT was chosen to assess exercise capacity in pediatric burn patients (Chapter 6). It is important to realize though, that the SRT is a basic exercise test. If understanding of the comprehensive physiological response to exercise after pediatric burns is aimed for or required for clinical reasons, a standardized CPET with respiratory gas analysis is recommended.

Interpreting results for clinical decision-making

Essentially, there are two distinct approaches to interpret a patient's performance to guide clinical decision-making. The most valid way is to compare a patient's performance to a **criterion-referenced standard**, described as an absolute, predetermined value or cut-off score, reflecting the minimum score that should be achieved for health [30]. For some functional outcome measures, e.g. muscle fitness, assessed as handgrip strength and the standing long jump test [31], and maximal oxygen uptake [32], criterion-referenced standards have been developed to indicate an increased cardiovascular disease risk. Likewise, the World Health Organization provides a criterion-referenced standard for physical activity; not achieving the recommendation of ≥60 minutes of moderate-to-vigorous physical activity per day, is associated with an increased risk of adverse (long-term) health outcomes [33]. Unfortunately, for the majority of functional outcome measures such criterion-referenced standards are not yet available.

As an alternative, individual results can be compared with a **normative-referenced standard**, e.g. the performance of healthy peers [30]. There are, however, some comments to be made regarding the use of healthy peer performance for clinical decision-making.

First, do the scores of 'healthy' children, i.e. those without known health conditions, actually reflect values that are optimal for health? Considering the current trends with regard to overweight and obesity [34-36], and the increasingly sedentary lifestyles of children and adolescents [37,38], this is questionable. In view of this, Dutch growth curves for body mass index have recently been adjusted based on values that are considered optimal for health [39-41] instead of values obtained from the average Dutch child population [36]. The same issue might apply to the normative reference values for exercise capacity that were used in Chapter 6 [29]. Considering the fact that many of the 'healthy' children and adolescents that formed the reference population were overweight and did not achieve the global recommendation for physical activity [29], their exercise capacity might not be optimal for (long-term) health. It can be argued that, for use in clinical decision making, normative reference values on physical fitness measures like the SRT should be based on large groups of children with minimal health risks, i.e. those with healthy weight-for-height [41], who meet the global physical activity recommendation [33], and achieve criterion-referenced standards for muscle fitness [31] and maximal oxygen uptake [32]. If reference values are obtained from the average population, it is important to realize that these scores might not reflect values that are optimal for health. In that case, lower patient scores are all the more worrying.

Second, how can patients best be compared to healthy peers? Basically, there are two options: (1) including a control group with age- and sex-matched healthy children, or (2) comparing patients'

scores to normative reference values obtained from the literature. In the current literature on physical functioning beyond pediatric burns, the first option is most commonly used, i.e. pediatric burn patients are matched to a single age- and sex-matched non-burned child that undergoes the same measurement procedures [42-48], and patients' scores are for instance expressed as a percentage of the healthy counterpart [42-45]. In the current thesis, however, the second method was used, i.e. normative reference values were obtained from the literature and Z-scores [49,50] were calculated for comparison. This is a more reliable and representative option, given the fact that reference values from the literature are based on a large group of non-burned children of a certain age and sex instead of just one. Hopefully the current work will also encourage other researchers to consider the use of existing reference values through the use of Z-scores.

The third, and in fact most important comment to make is that for clinical decision-making it is essential to decide for each specific variable which deviation from healthy peers, or from the optimal in general, indicates an increased risk of adverse (long-term) health outcomes. For SRT outcome, for example, it is recommended to use the third percentile of healthy peers as a cut-off point [29], based on statistical significance. In my opinion though, statistical significance and clinical relevance are two different concepts. That is, a deviation from healthy peer scores does not have to be statistically significant to be clinically relevant for individual health outcomes, especially not if the scores of the reference population are considered non-optimal. In Chapter 3 and 6 it was therefore decided to classify pediatric burn patients as 'at risk' for diminished functioning and adverse (long-term) health outcomes in case they deviated more than one standard deviation from normative reference values. This cut-off point was adopted from other studies on childhood functioning [51,52], but is still based on statistics. It remains subject to further research to identify the most appropriate cut-off point to define 'at risk'. The final answer to this complex issue is to conduct multicenter longitudinal observational studies that provide large population data on physical fitness, health-promoting behavior, and (long-term) outcomes of health and quality of life.

Altogether, the current thesis emphasizes the need for criterion-referenced standards for many functional outcome measures, or otherwise adequate normative reference values, *including* clinically relevant cut-off points to identify patients 'at risk'.

Shift focus from group performance to individual results

An important insight from this thesis is the **wide variation in recovery patterns** among pediatric burn patients. Some patients recovered within a few months, while others still experienced problems even years after the injury, providing a call for additional rehabilitation support beyond the acute care period.

The majority of pediatric burn research focuses primarily on group performance and not (also) on individual results. As a consequence, essential information might be overlooked. In Chapter 6 it was shown, for example, that exercise capacity expressed as a group mean approached healthy values six months after discharge. From this one could conclude that with the present care, the general pediatric burn population achieves healthy levels of exercise capacity in several months. Assessment of individual results revealed, however, that one-half of the children did not achieve healthy values of exercise capacity within this period (Z-score -1 or lower), and was therefore considered 'at risk' for diminished functioning and adverse (long-term) health outcomes. These children do deserve additional rehabilitation care. This example demonstrates that focusing on individual results or on subfractions of the population – those 'at risk' – can lead to fundamentally different conclusions, especially in clinical research with small, heterogeneous groups, like pediatric burn patients. Simply knowing that a group is doing well, does not mean that none of the individuals needs additional rehabilitation support.

For this reason, it is recommended to shift the primary focus of future (pediatric) burn research from group performance to individual results as well as subfractions of the population based on Latent Class Analyses [53].

Functioning beyond pediatric burns

This thesis provides an important contribution to the current knowledge on physical functioning beyond pediatric burns. However, it is important to realize that there is still a long way to go.

Thus far, pediatric burn research focused either on impairments in body functions and structures [42-48,54-68], or on activity and participation outcomes [69-74]. However, in order to direct and optimize burn rehabilitation, it is essential to **examine how the various domains of functioning interact**. As a next step we therefore intend to merge all the findings of our multidimensional research line and investigate if, and how, impairments in body functions and structures affect activity and participation, and therewith quality of life, beyond pediatric burns.

Likewise, it is important to gain **more insight in the role of contextual factors** (personal factors and (physical and social) environmental factors) on functioning beyond pediatric burns [71,75]. To this end, we should focus not only on the children who experience problems, but also on those who do well. Moreover, much can be learned from barriers and facilitators experienced in children with other physical disabilities [76-78], as these might also play a role in children with burns.

Hopefully new insights from these efforts will **open up additional opportunities for intervention** in order to facilitate a timely, tailored and, optimal recovery for all pediatric burn patients. A great step ahead would be international collaboration in longitudinal research projects as well as in the context of comparative studies, where the role of culture on burn care and its outcomes is studied.

Clinical implications

The current thesis indicates that many pediatric burn patients are 'at risk' for diminished functioning and adverse (long-term) health outcomes, based on habitual physical activity and exercise capacity. Therefore, **physical activity and exercise capacity deserve more rehabilitation support beyond the acute care setting**, even in patients with minor burns.

For early identification of individual rehabilitation needs, it is essential to gain insight in factors that can predict the recovery of functioning after discharge. This thesis is an important step forward by showing the **predictive value of early assessment** of exercise capacity with the Steep Ramp Test (SRT). SRT outcomes at six weeks explained 76% of the variance in exercise capacity six months after discharge, and SRT outcomes at three months explained 93%. Other significant but weaker predictors were fire/flame burns, younger age, being overweight, being diagnosed with behavioral problems, and low socio-economic state, all negatively associated with exercise capacity six months after discharge. In our study population, burn severity characteristics (i.e. extent of the burns, length of hospital stay, and number of surgeries) were not predictive, which is in accordance with previous findings on functional outcome in a comparable group of pediatric burn patients [71].
Based on the current findings, and in accordance with the global recommendations for exercise prescription after burns [79], it is recommended to **systematically evaluate exercise capacity,** in all pediatric burn patients aged ≥6 years. In our opinion, this should be done preferably about six weeks after discharge. The SRT can be used for this purpose. Early assessment of exercise capacity will help identifying individual rehabilitation needs, which is essential to be able to provide tailored care.

Bearing in mind the long-term health risks associated with pediatric burns, it can be argued that exercise capacity and other relevant health outcomes should be monitored over an extensive period of time [80]. In which case these outcomes may be incorporated in existing global outcome registries, like the Burn Model Systems in the U.S.A. [81], the Burns Registry of Australia and New Zealand [82], and the Burn Outcome Registry Netherlands. Beyond that, awareness of the long-term physical consequences of burns during childhood should be created among general practitioners and the general pediatric health care system.

Last but not least, the current thesis suggests that **fatigue,** a major issue in adult burn survivors [83,84], **is also prevalent in pediatric burn patients,** even years after the injury. Unfortunately, the underlying causes of fatigue after burn injury are yet unknown. Numerous explanations have been proposed in the literature, including a prolonged increase in metabolic rate, loss of skeletal muscle mass, reduced exercise capacity, muscle weakness, psychological distress, depression, and poor sleep quality [83,84]. Next to determining the prevalence, severity, and predictors of fatigue after burn injury based on current long-term outcome registries [83,84], additional research is required in order to determine the nature of fatigue after burn injury and its underlying causes. Both perceived fatigue and performance fatigability [11,12] must be part of such research. Hopefully this will open up opportunities to prevent fatigue after burn injury, or at least reduce the severity of symptoms and therewith the impact on daily life.

Future perspectives

Part of the future perspectives have already been discussed, that is:

- Understanding the (reciprocal?) link between impairments in body functions and structures, activity limitations, and participation restrictions beyond pediatric burns;
- Increasing our knowledge on the role of contextual factors on functioning beyond pediatric burns;
- Finding additional opportunities for intervention to optimize functioning and quality of life beyond pediatric burns;
- Continuing efforts to understand underlying mechanisms of the long-term health risks after pediatric burns;
- Understanding and monitoring fatigue after (pediatric) burns and find ways to prevent it or at least reduce the severity of symptoms;
- Improving international collaboration and coordination of burn research so that larger datasets can be subject of joint research.

Apart from these more general perspectives, it would be interesting to assess how the participants described in Chapter 6 will do in several years, and when they reach adulthood. As a first step, our research group recently initiated a follow-up assessment on the longitudinal study, in which physical fitness, habitual physical activity, fatigue, and health-related quality of life are assessed five years after discharge.

In the youngest, which is also the largest, group of pediatric burn patients, i.e. those aged 0-4 years at the time of injury, the vast majority has merely superficial partial-thickness burns which heal spontaneously without scarring within two or three weeks. Accordingly, the physical consequences described in this thesis will, in all probability, not apply to this group. To verify this assumption, it would be interesting to investigate long-term outcomes of health and functioning in this population. Moreover, it is essential to pay attention to these long-term outcomes in the exceptional group of young pediatric burn patients who did suffer from deep partial-thickness and/or full-thickness burns.

In adults, even more comprehensive issues related to functioning and (long-term) health outcomes are to be expected [83-95]. Therefore, our research group is currently establishing a similar multidimensional line of research in adults burn survivors, in order to determine the recovery of functioning beyond burns in adults during the initial six months after discharge, including also its predictors, and facilitators and barriers.

Finally, to fully understand functioning beyond burns, real life experience from patients is crucial. Therefore, it is deemed essential to actively involve patients in research [96-99]. Moving forward, burn survivors and/or their representatives should be actively involved in all stages of the research process, and will be in ours.

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