Assessing the physiological demands of daily life in persons with lower limb amputation

van Schaik, Loeke

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Loeke van Schaik

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Promotores

Prof. dr. R. Dekker
Prof. dr. J.H.B. Geertzen

Copromotor

Dr. K. van Kammen

Beoordelingscommissie

Prof. dr. J.P.P.M. de Vries
Prof. dr. J.S. Rietman
Prof. dr. C.A.M. van Bennekom

Paranimfen

Redmar Berduszek

Patrick Domerchie

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Chapter 1

General introduction

GENERAL INTRODUCTION

Worldwide, lower limb amputation (LLA) is a significant cause of disability, resulting from various underlying conditions such as vascular disease, diabetes mellitus (DM), trauma, and malignancy. The incidence of LLA varies widely across populations and time periods, with most available data originating from high-income countries that maintain national vascular registries [1,2]. Trauma-related LLAs have notably increased in recent years, particularly in regions such as the Middle East and North Africa, where armed conflict and war are major contributing factors [3]. In contrast, LLAs in high income countries are predominantly associated with chronic conditions like vascular disease and DM. Several high-income countries have reported a declining trend in major LLA rates [1]. For instance, Germany reported a 7.3% decrease in LLA incidence between 2015 and 2019 [4]. The United Kingdom has also observed a general decline, although with notable regional disparities linked to socioeconomic deprivation [5]. In the Netherlands, the majority of LLAs are due to vascular disease and diabetes mellitus [6]. The annual incidence is estimated at 18–20 per 100,000 persons, a rate comparable to other Western European countries [1]. Nonetheless, variations between studies may reflect regional differences in healthcare access, prevention strategies, and population characteristics.

Given that vascular disease and DM are the predominant causes of LLA in the Netherlands, the affected population typically consists of older adults with multiple comorbidities [6]. These demographic characteristics differ substantially from those of persons undergoing LLA due to trauma or malignancy. Despite these distinctions, current literature on prosthetic ambulation often includes heterogeneous study populations or focuses solely on trauma-related LLAs. From a physiological perspective, persons with vascular-related LLA differ markedly from those with traumatic LLA in terms of cardiorespiratory fitness. Age is a major contributing factor, as maximal oxygen uptake ($\dot{V}O_2peak$), a widely used indicator of cardiorespiratory fitness, naturally declines with age [7,8]. Furthermore, comorbidities such as heart failure and chronic obstructive pulmonary disease (COPD) are frequently observed in the vascular LLA population. These conditions are known to substantially reduce cardiorespiratory fitness when compared to healthy controls [9,10].

Taken together, these demographic, clinical, and physiological differences highlight the challenges of generalizing findings from existing literature to the actual population encountered in daily rehabilitation practice in the Netherlands.

Mr. X is a 66-year old man with a medical history of type 2 diabetes mellitus and peripheral arterial disease. He underwent a transtibial amputation due to chronic, non-healing ulceration on the foot. Prior to the amputation, Mr. X had experienced a prolonged period of physical inactivity, resulting in significant deconditioning.

REHABILITATION AFTER LOWER LIMB AMPUTATION

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The World Health Organization (WHO) defines rehabilitation as "*a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment*" [11]. Despite this global definition, rehabilitation practices vary significantly across regions and countries due to differences in healthcare systems, available resources, and the prevalence of specific health conditions. Such variation can also occur within countries and even between rehabilitation centres, despite the existence of standardized, evidence-based guidelines such as the VA/DoD Clinical Practice Guideline for Rehabilitation of Individuals with Lower Limb Amputation [12], or national guidelines such as those issued by the Dutch Society of Rehabilitation Physicians [13]. Access to rehabilitation facilities remains limited in low and middle income countries, whereas industrial regions such as Western Europe offer more comprehensive and accessible rehabilitation services, including specialized centres that apply a multidisciplinary approach.

In the Netherlands, post-hospital destinations for persons with LLA include returning home or going to specialized rehabilitation centres, skilled nursing facilities, or geriatric rehabilitation centres [14]. The choice of destination depends on factors such as the person's health status, biological age, and available social support, with the aim of ensuring appropriate care and support for recovery. Rehabilitation in the Netherlands, regardless of the post-hospital setting, generally involves a multidisciplinary team that includes rehabilitation physicians, physiotherapists, occupational therapists, psychologists, and, when needed, prosthetists [13]. Whenever possible, rehabilitation begins prior to the amputation and continues during hospital admission. After surgery, the multidisciplinary team assesses the most suitable post-hospital destination for the person with LLA. The initial postoperative phase focuses on stump healing and shaping, and promoting independence in daily functioning.

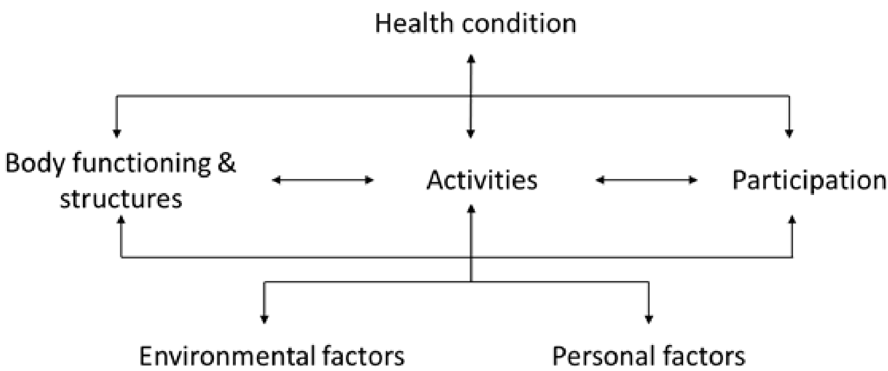
Throughout the rehabilitation process, it is assessed whether the person with LLA is able to train with and function using a prosthesis. Not all persons with LLA will be able to ambulate with a prosthesis; some will function without one. Factors that can hinder prothesis use include reduced load-bearing capacity of the contralateral leg, balance issues and severely limited physical condition or fitness.

Mr. X. was discharged home from the hospital after a transtibial amputation. He was medically stable, had sufficient functional abilities for home mobility using a wheelchair and walking frame, and received support from his family. His home environment was accessible, and he was motivated to participate in outpatient rehabilitation. These factors together supported the decision for home discharge with continued therapy in an outpatient setting.

IMPACT OF LOWER LIMB AMPUTATION ON DAILY LIFE

The consequences of LLA on daily functioning can be comprehensively understood using the International Classification of Functioning, Disability and Health (ICF) model (Figure 1). Developed by the World Health Organization, the ICF model provides a structured framework to describe how health conditions affect a person's functioning, encompassing physical, psychological, and environmental components [15]. In the context of LLA, rehabilitation efforts address all domains of the ICF model. These include physical and psychosocial adjustment, supported by essential therapies such as physiotherapy and occupational therapy, alongside psychological support to facilitate emotional and mental adaptation.

Figure 1. International Classification of Functioning, Disability and Health model. (Bron: WHO, 2001 [15]).



Persons with LLA may experience reduced mobility, impaired balance, and pain, including phantom limb pain [16–18]. Performing activities of daily living (ADLs) such as walking, climbing stairs or household chores often become challenging. The energy required to perform these activities is influenced by factors such as intensity, duration, physical fitness, and movement efficiency [19–23]. Standard classifications such as metabolic equivalent of task (MET) values [24] may underestimate the true physiological burden of ADLs in persons with LLA.

Consequently, persons with LLA may face increased fatigue and diminished endurance, which can negatively affect participation in work, social engagements, and recreational activities, ultimately impacting overall quality of life. Functioning after LLA is shaped by a range of factors, including age, comorbidities, psychological resilience, and motivation. Environmental aspects, such as the accessibility of buildings, the availability of assistive devices, and the presence of a supportive social network, further contribute to a person's ability to function independently. By integrating these diverse components, the ICF model provides a comprehensive approach to assess the impact of amputation and to guide the development of personalized rehabilitation goals and interventions.

A key determinant of functioning is physical capacity, which falls under the ICF domain of *Body Functioning and structures*. This domain includes physical/physiological functions of body systems, such as muscular strength, joint flexibility, balance, and both aerobic and anaerobic endurance [15,25]. Among these, balance has been identified as a significant predictor of successful prosthetic ambulation. Nevertheless, all physical components are theoretically linked to walking ability and the achievement of functional goals, highlighting the importance of identifying which variables may serve as effective targets for rehabilitation.

Despite the acknowledged relevance of physical components, current knowledge remains limited regarding the role of anaerobic capacity in persons with LLA. Similarly, the relationship between aerobic capacity and the ability to perform ADLs is not yet well established in this population. Individual, physiological, and contextual differences, such as age, comorbidities, level of amputation, and social circumstances, highlight the complexity of functioning after LLA and underscore the challenges of generalizing findings from previous research, often conducted in younger, healthier populations, to the more diverse and typically older demographic encountered in daily clinical practice in the Netherlands.

CARDIORESPIRATORY FITNESS

Maximum aerobic capacity, commonly referred to as **$\dot{V}O_2$max**, represents the highest rate at which a person can consume oxygen during intense physical activity. It is typically expressed in millilitres of oxygen per kilogram of body weight per minute (ml/kg/min) and is widely regarded as the gold standard for assessing aerobic fitness and cardiovascular endurance [43]. $\dot{V}O_2$max is measured during a graded cardiopulmonary exercise test (CPET), where the intensity increases progressively until a plateau in oxygen uptake is reached or the person reaches exhaustion. In able-bodied individuals, $\dot{V}O_2$max is influenced by factors such as age, gender and training status [44]. Endurance-trained individuals, such as runners or triathletes, generally exhibit higher $\dot{V}O_2$max values, indicating that aerobic training can significantly improve this parameter. Normative reference values for $\dot{V}O_2$max are available and stratified by age and gender, for example Wasserman [45], the American College of Sports Medicine [30] and specifically for the Dutch populations the LowLands Fitness Registry [46].

$\dot{V}O_2$peak refers to the highest oxygen uptake recorded during a CPET, but unlike $\dot{V}O_2$max, it does not necessarily reflect the person's true maximal capacity [47]. $\dot{V}O_2$peak is often used when a plateau in oxygen uptake is not observed, which may occur due to early test termination caused by fatigue, discomfort, or physical limitations, as is often the case in clinical populations such as persons with LLA [45]. Therefore, in this thesis, the term $\dot{V}O_2$peak will be used to describe the highest measured oxygen uptake during testing.

First ventilatory threshold (VT1) represents the point at which the body transitions from primarily aerobic metabolism to a combination of aerobic and anaerobic metabolism, leading to rising lactate levels in the blood and a higher breathing rate to ventilate the excess carbon dioxide produced during anaerobic metabolism. VT1 typically occurs at 40-60% of $\dot{V}O_2$peak in the general population [31]. Activities below VT1 are sustainable for longer periods and are associated with lower intensity. Exercise above VT1 becomes more challenging. Therefore, VT1 is considered a relevant parameter for both functional assessment and the prescription of individualized training programs.

Metabolic costs (or energy costs) refer to the amount of energy required by the body to perform a specific activity, typically measured in oxygen consumption (ml O_2/kg/min). It is influenced by several factors, including the intensity and duration of the activity, the person's fitness level, body mass, movement efficiency, and biomechanical technique [48]. In clinical populations, such as persons with LLA, understanding metabolic costs is essential for evaluating the physiological burden of ADLs and for designing safe and effective rehabilitation programs.

Mr. X expressed rehabilitation goals focused on regaining independence in self-care, household tasks, and short-distance walking with a prosthesis. He also aimed to resume grocery shopping and driving to maintain social participation. Using the ICF model, these goals span multiple domains, including body functions, activities, and participation.

CARDIORESPIRATORY FITNESS AND METABOLIC COSTS IN PERSONS WITH LLA

Cardiorespiratory fitness, commonly assessed through peak oxygen update ($\dot{V}O_2$peak) is consistently reported to be lower in persons with LLA compared to able-bodied persons [26–28]. These lower values are possibly due to inactivity and deconditioning in relation to comorbidities prior the LLA, as well as to reduced physical activity levels post-LLA. In addition, pre-operative physical fitness may influence post-operative recovery and rehabilitation outcomes, as suggested by findings in other clinical populations. However, for persons with LLA data is lacking [29].

When comparing $\dot{V}O_2$peak values to age- and gender-matched reference values for able-bodied males, persons with traumatic LLA generally fall within the 'average' category, whereas those with vascular LLA are typically classified as 'poor' [27,30]. For example, Wezenberg et al. reported $\dot{V}O_2$peak values of 28.1 ± 6.8 ml/kg/min in the traumatic LLA group (n = 26) and 17.1 ± 1.0 ml/kg/min in the vascular LLA group (n = 10), both consisting predominantly of males aged 60–70 years, but with varying amputation levels [27].

Although $\dot{V}O_2$peak has been reported in some studies, little is known about the VT1 in persons with LLA. Given that VT1 typically occurs at 40–60% of $\dot{V}O_2$peak in the general population it can be assumed that VT1 is also markedly reduced in this population, further limiting the sustainability of ADLs [31]. Such limitations in aerobic capacity are likely to contribute to the increased metabolic cost of walking, which has consistently been found to be higher in persons with LLA compared to able-bodied controls [23,32,33]. This increased metabolic cost is attributed to several factors, including altered gait mechanics, the effort required to move the prosthesis, amputation level, walking surface, and the use of assistive devices [28,34–36]. Nevertheless, several studies suggest that persons with LLA compensate for this elevated metabolic cost demand by reducing their self-selected walking speed, thereby lowering absolute oxygen consumption while maintaining functional mobility [21,32,37–40].

Despite these insights, important knowledge gaps remain. Specifically, there is limited understanding of VT1 in persons with LLA and its relationship to functional capacity during ADLs. Furthermore, the interaction between $\dot{V}O_2$peak, VT1, and performance of ADLs remains underexplored, particularly in relation to rehabilitation outcomes and long-term participation.

RELATIVE AEROBIC LOAD IN ACTIVITIES OF DAILY LIVING

Understanding relative aerobic load during ADLs is crucial, as it reflects the physiological effort required in relation to an individual's cardiorespiratory fitness, typically expressed as a percentage of their VT1 or $\dot{V}O_2$peak [41]. This means that ADLs requiring the same absolute oxygen consumption as in able-bodied persons may impose a substantially higher physiological strain on persons with reduced cardiorespiratory fitness. In persons with LLA, data on relative aerobic load during ADLs remain limited, with just a few studies focusing primarily on prosthetic walking. For example, Wezenberg et al. [32] reported that persons with vascular LLA walked at a relative aerobic load approximately 45% higher than those with traumatic LLA.

The American College of Sports Medicine (ACSM) classifies physical activities based on their metabolic equivalent of task (MET) values [24], with light-intensity activities defined as those requiring less than 3 METs (equivalent to approximately 10.5 ml O_2/kg/min). However, these classifications are based on able-bodied populations and are not directly applicable to specific populations, including persons with LLA [33,42]. For example, an ADL categorized as light intensity according to ACSM standards [30] may represent a substantially higher relative effort for a person with LLA. If that person with LLA has a $\dot{V}O_2$peak limited to 14 ml/kg/min, the same ADL could approach or even exceed 75% of their peak oxygen uptake, thereby constituting a high-intensity activity for them.

This discrepancy highlights the importance of individualized assessment of relative aerobic load in rehabilitation programs. Standardized intensity classifications may underestimate the true physiological burden of ADLs in persons with LLA, potentially resulting in unrealistic goal-setting or inappropriate training prescriptions.

In the first weeks of rehabilitation, Mr. X experienced severe fatigue during and after therapy, which prevented him from practicing daily tasks and participating in social activities as he had planned. This mismatch between expectations and actual capacity led to frustration and emotional strain.

Although his goals remain relevant and meaningful, they need to be adjusted in scope and timing to match his current physical condition. Assessing Mr. X's cardiorespiratory fitness is very relevant, as it offers objective insight into his physical limitations and forms the basis for setting realistic and personalized rehabilitation goals.

AIMS AND OUTLINE OF THIS THESIS

Cardiorespiratory fitness plays a critical role in mobility, independence, and participation in persons with LLA and is closely linked to quality of life and rehabilitation outcomes. Given the potentially low fitness levels and the high physiological demands associated with ADL in this population, gaining insight into cardiorespiratory fitness and relative aerobic load is essential to effective rehabilitation.

The overarching aim of this thesis is to investigate current knowledge regarding cardiorespiratory fitness, metabolic costs, and relative aerobic load during activities of daily living (ADLs) in persons with LLA. The thesis is organized into two main parts. The first part reviews the existing literature and identifies ADLs that are considered important by persons with LLA. The second part focuses on the assessment of cardiorespiratory fitness, specifically peak oxygen uptake ($\dot{V}O_2$peak), and evaluates the relative aerobic load associated with selected ADLs.

Chapter 2 presents a systematic review of the literature on metabolic costs during ADLs in persons with LLA. It examines the methodologies used, the variables reported, and the specific ADL tasks studied. **Chapter 3** explores the perspectives of persons with LLA and rehabilitation healthcare professionals regarding the most relevant ADL tasks, highlighting potential differences in goal-setting and rehabilitation priorities.

Chapter 4 provides a retrospective analysis of cardiopulmonary exercise testing (CPET) data from persons with LLA. It aims to assess their cardiorespiratory fitness and compare $\dot{V}O_2$peak values to reference data from able-bodied populations. Additionally, it investigates potential predictors of aerobic capacity, including age, amputation level, and aetiology. **Chapter 5** describes a pilot study that tests a protocol for measuring oxygen consumption during five standardized ADL tasks in persons with LLA. These tasks include both cyclic and non-cyclic activities, and oxygen consumption is measured using the excess post-exercise oxygen consumption (EPOC) method.

Based on these measurements, the relative aerobic load of each task is calculated as a percentage of the individual's VT1 or $\dot{V}O_2$peak. This approach enables the evaluation of whether specific ADLs exceed sustainable intensity thresholds and provides insight into the physiological demands of everyday activities.

Collectively, the findings presented in this thesis aim to contribute to the development of individualized assessments and physiologically informed, personalized rehabilitation programs for persons with LLA. They may also contribute in establishing reference values that reflect the diversity of the LLA population, thereby supporting the development of tailored clinical decision-making tools.

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2

Chapter 2

Metabolic costs of activities of daily living in persons with a lower limb amputation: a systematic review and meta-analysis

Loeke van Schaik, Jan H.B. Geertzen, Pieter U. Dijkstra, Rienk Dekker

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ABSTRACT

Objective: to systematically review the literature on the metabolic costs of activities of daily living (ADL) in persons with a lower limb amputation (LLA).

Data sources: a literature search was undertaken in the Pubmed, Embase, CINAHL, CENTRAL, and PsycINFO databases using keywords and synonyms for LLA, metabolic costs, and ADL. The last search was performed on November 29th, 2017.

Study selection: studies were included if they met the following 2 criteria: participants were adults with a (unilateral or bilateral) LLA and metabolic costs were measured while participants performed a physical activity or ADL.

Data extraction and synthesis: data of 1,912 participants from 61 studies were included in the systematic review and meta-analysis. The studies used different terms to describe metabolic costs. Participants were recruited in different settings, relatively healthy, with few comorbidities. Limited data were available on metabolic costs of other activities than walking with a prosthesis. A linear mixed model analysis was performed based on the means reported, with study as unit of analysis and test results of different groups and measurement conditions as repeated measures within the unit of analysis. Predictors entered in the analysis were e.g. level and reason of amputation, age, weight, and height. During walking, oxygen consumption (ml O_2/kg/min) and heart rate (beats/min) increased with a higher walking speed and a more proximal amputation. Additionally, oxygen consumption was determined by the interaction terms walking speed x amputation level and walking speed squared. Heart rate was determined by the interaction term walking speed squared.

Conclusion: During walking, oxygen consumption (ml O_2/kg/min) and heart rate (beats/min) increased with a higher walking speed and a more proximal amputation. Data on metabolic costs of other activities were limited. The poor quality of the studies and the relatively healthy participants limited generalizability of the results of the meta-analysis.

The protocol for this systematic review and meta-analysis was registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#index.php, CRD42016050990).

Keywords: lower extremity, amputation, metabolic costs, activities of daily living, meta-analysis.

INTRODUCTION

In rehabilitation medicine, the main goals for persons with a lower limb amputation (LLA) are walking with a prosthesis and regaining functional capacity with regard to activities of daily living (ADL) [1–3]. To be able to achieve these goals, certain levels of physical and aerobic capacity are required [4,5].

In the Netherlands, more than 90% of LLAs are due to vascular disease and/or diabetes mellitus (DM) [6,7]. In the UK and USA, 75% and 87% of LLAs are due to vascular disease, respectively [8]. Persons with a LLA who have (peripheral) vascular disease (PVD) are mostly elderly and have comorbidities resulting from atherosclerosis, which limits their physical and aerobic capacity [9–11]. In general, aerobic capacity decreases with age, and studies have shown that elderly participants with a LLA have a lower aerobic capacity than controls [12,13]. The $\dot{V}O_2max$ test is the criterion measure of aerobic capacity, and it is a valid predictor of cardiorespiratory capacity [14]. To date, however, few studies have measured $\dot{V}O_2max$ in persons with a LLA. Furthermore, these studies used different test protocols [10,15,16]. They reported lower levels of $\dot{V}O_2max$ in participants with a LLA compared with controls. These differences are probably due to deconditioning or comorbidities.

A previous systematic review looked at the influence of physical capacity on regaining the ability to walk (with a prosthesis) [17]. No sufficient evidence was found for aerobic and anaerobic capacity as potential predictor for walking ability. Another systematic review investigated factors that predict walking ability after a LLA [18]. One of these factors was fitness of the participants. The main finding of this review was the substantial heterogeneity in testing methods and outcome measures of the included studies, which hampered a meta-analysis. Both systematic reviews did not primarily aim to analyse metabolic costs in participants with a LLA, and both only reviewed walking as activity.

One study reported the relative aerobic load of walking, measured as a percentage of the $\dot{V}O_2peak$ [19]. The relative aerobic load of walking was higher in participants with a LLA than in controls. Another study reported that participants with a LLA who had higher levels of physical fitness (defined as the maximum oxygen uptake during exercise as a proportion of predicted maximum oxygen uptake) were more likely to walk with a prosthesis than participants with a LLA with lower levels of physical fitness [10].

For the general population, the metabolic costs of ADL are well reported in the compendium of physical activities, the so called Metabolic Equivalent of Task (MET)-values [20]. However, these reference values seem not to apply for persons with a disability. For example, in persons after stroke, the required metabolic costs for certain activities are higher compared to the MET-values [21]. For persons with LLA knowledge about the required metabolic costs for ADL, in combination with maximum aerobic capacity, is lacking. However, this knowledge is relevant for optimizing training programs and setting functional goals for rehabilitation.

The specific aims of this systematic review and meta-analysis are 1) to analyse what is known about the metabolic costs of different ADL in participants with a LLA; 2) to explore which methods and outcome measures are used to evaluate these metabolic costs; and 3) to determine whether metabolic costs are influenced by level of amputation, reason for amputation, and walking speed.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used for conducting this systematic review and meta-analysis [22].

Protocol

The protocol for this systematic review and meta-analysis was registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO/#index.php, CRD42016050990).

Study identification and selection

A literature search was performed in the Pubmed, Embase, CINAHL, CENTRAL, and PsycINFO databases. No language or date restrictions were applied. The last search was performed on November 29th, 2017. Different search terms for LLA were used, combined with various search terms for metabolic costs and physical activities and/or ADL (S1 File). Two reviewers (LvS, RD) independently assessed titles and abstracts. In case of disagreement between reviewers, the record was included for full text analysis. Full text assessment was performed by the aforementioned reviewers, who used the same criteria for inclusion and exclusion. Any further disagreements were resolved by consensus through discussion. Cohen's kappa was calculated for the title and abstract assessment and the full text assessment of the selection process. The reference lists of studies included in the systematic review were checked for other relevant studies, which were subsequently assessed following protocol. When after full text assessment more than 50 studies resulted, studies with a total study population < 10 were excluded because the outcomes lacked precision.

Inclusion and exclusion criteria

Inclusion criteria were as follows: participants were adults with a (unilateral or bilateral) LLA and metabolic costs were measured while participants performed a physical activity or ADL. Editorials, (expert) opinions, comments, reviews, and off- topic studies were excluded. Studies on toe or midfoot amputations, amputations other than a lower extremity, or endoprostheses were also excluded, as were studies with children or animals and model studies.

Quality assessment

Quality assessment was independently performed by two reviewers (LvS, RD) using the Agency for Healthcare Research and Quality (ARHQ) methodology checklist [23]. Additionally, it was assessed whether equipment for measuring oxygen consumption was validated and whether walking speed during testing was reported.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 23.[a] Descriptive statistics (mean and standard deviation) were calculated for study variables. Initially, effect sizes were calculated based on study data. For oxygen consumption one study, however, reported uncommonly small standard deviations relative to other studies, resulting in extremely large effect sizes [24]. The authors were contacted to verify whether the standard deviations were truly standard deviations or perhaps standard errors of the mean. The authors did not respond. Additionally, 7 studies did not reported standard deviations [25–31]. For heart rate, 5 studies did not report standard deviations [25,29–32]. Therefore, a linear mixed model analysis was performed (maximum likelihood method and AR1 covariance structure) on the means reported. The study was used as a unit of analysis and the study results of different groups and measurement conditions were used as repeated measures within the unit of analysis (multilevel structure). Forest plots were not made because effect sizes were not used in the analysis.

The outcome oxygen consumption (expressed as ml O_2/kg/min) was analysed using the following potential predictors: level of amputation, reason for amputation, age, weight, height, and walking speed. Only studies that reported oxygen consumption (ml O_2/kg/min) were selected (Table 2). When possible, outcomes were converted to ml/kg/min. If this was not possible based on the reported data within the study, the study was excluded for the analysis. Potential predictors were entered into the linear mixed model analysis. If the model fit (-2LL statistic) increased significantly, the predictors remained in the model. Cause of amputation was categorized in trauma and vascular, level of amputation as below knee and above knee. Studies with mixed groups (when it was not possible to analyse subgroups based on level and reason of amputation) were excluded from the analysis.

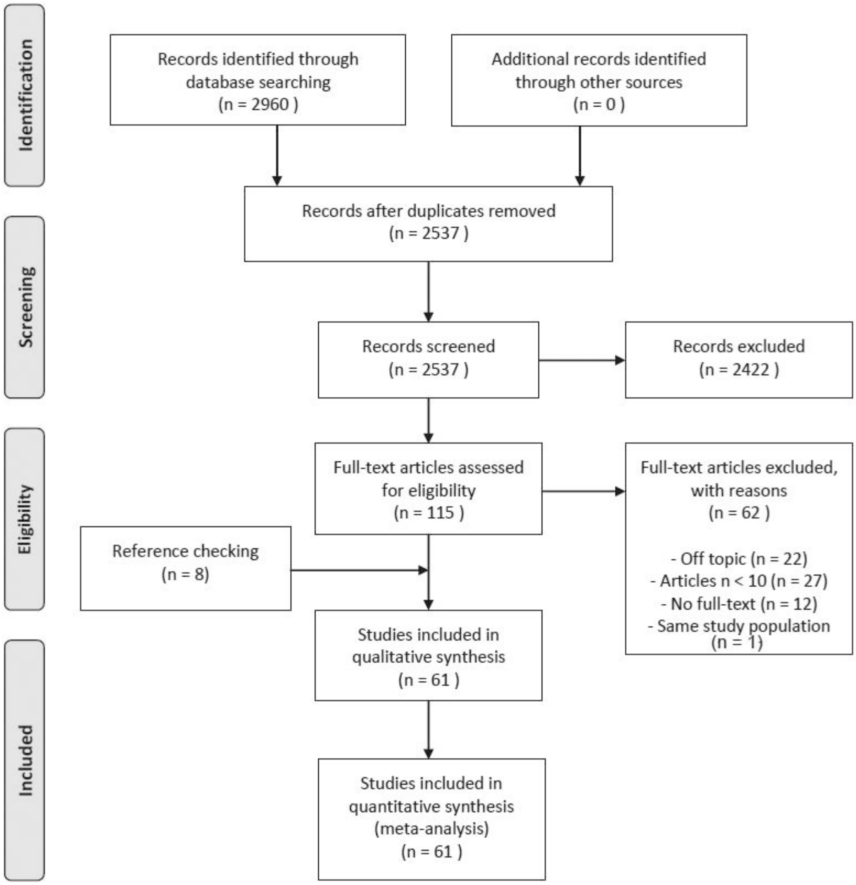
In a few studies [16,33–35] (n= 4) a treadmill with an incline was used. Data regarding treadmills with an incline were not included in the meta-analysis because of the small number of studies. Some studies did not specify whether the walking surface was level. The inclusion or exclusion of those studies in the meta-analysis did not affect the results. Therefore, studies that did not specify the treadmill incline were included, and it was assumed the walking surface was level. Interaction terms of the predictors significantly associated with oxygen consumption were explored. A similar analysis was performed for heart rate as an outcome measure.

RESULTS

Study inclusion

A total of 2,960 potentially suitable records were found in the database search. After removing duplicates, 2,537 records remained (Fig 1). After title and abstract assessment, 2,422 records were excluded (agreement 98%, Cohen's kappa: 0.71), leaving 115 records for full text assessment. Of 12 records, no full text was available (yet). After full-text analysis, 22 studies were excluded because they were off topic (agreement was 96%, Cohen's kappa: 0.88). A further 8 studies were identified from the reference lists and were assessed for inclusion, resulting in a total of 89 studies. Given the fact that more than 50 studies were identified, studies with a sample size less of than 10 participants were excluded (n = 27). Two studies were found that partially included the same study population (in one study persons with a Syme amputation were included and in the other study they were excluded) [36,37]. The former study was included in this study [36]. In total 61 studies were included. None of the included studies were written in another language than English or Dutch.

Figure 1. Flowchart showing the inclusion process.



Participant characteristics

The 61 included studies (n =1,912) were heterogeneous. The mean (SD) number of participants was 13.5 (13.2). The groups ranged from 10 to 101, and subgroups ranged from 3 to 44. There were different reasons for amputation and/or levels of amputation. Time since amputation ranged from 68 days to 27 years (Table 1). The majority of participants were male (68%, n=1,299), and for 17% (n=324) of the participants gender was not specified. The majority of studies (n= 57) included (subgroups of) participants with a transtibial amputation or a transfemoral amputation. A few studies [38–40] included participants with other levels of amputation. In 12 studies data of participants with different levels of amputation were pooled into a single group. The reason for amputation was not described in 8 studies. Eighteen studies included mixed groups with regard to reason for amputation, and in 8 studies the reason for amputation was described as 'other than vascular.' In 19 studies the use of walking aids was described (or it was stated explicitly that no aids were used). Comorbidities were reported in 8 studies [10,11,40–45].

Table 1. Participant characteristics of the included studies.

Authors, year	n (% men) vs. Control (% men)	Age ±SD (range)	Level amputation (% n)	Reason amputation (%) vasc	trauma	onco	other	Years since amputation ±SD (range) *months
Ganguli, 1973[29]	10 (-)	29.9±11	TT (100)	-	-	-	-	-
	C 16 (100)	28.4±7.1	n.a.					
James, 1973[33]	37 (100)	42.8±12.8	TF (100)	-	-	-	-	18 (2-48)
	C 26 (100)	39.6±14.0	n.a.					
Ganguli, 1974[46]	6 (-)	26.2±10.2	TT (100)	-	-	-	-	6-12*†
	C 6 (100)	34.5±6.2	n.a.					
Ganguli, 1975[30]	10 (100)	27.3±7.1	LLA‡	-	-	-	-	-
	10 (100)	29.9±1	TT (100)	-	-	-	-	-
	C 16 (100)	28.4±7.1	n.a.					
Waters, 1976[4]	13 (-)	60	TF (100)	100				1.2
	13 (-)	63	TT (100)	100				1.4
	15 (-)	57	Syme (100)	100				1.1
	15 (-)	31	TF (100)		100			10.0
	14 (-)	29	TT (100)		100			14 (-)
	C 50 (-)	-	n.a.					

Huang, 1979[47]	6 (83)	30.4± 8.7	TF (100)	-	-	-	-	-
	6 (50)	38.2±12.9	TT (100)	-	-	-	-	-
	4 (50)	33.5±12.1	TF bil (100)	-	-	-	-	-
	C 25 (20)	(19-43)	n.a.					
Pagliarulo, 1979[48]	15 (80)	28.9±11.2	TT (100)				100§	> 1†
DuBow, 1983[32]	6 (83)	61±11.3	TT bil (100)	100				1.9±1.1†
	C 8 (75)	55±7	n.a.					
Nowroozi, 1983[38]	8 (63)	36.75±17.75	HD (100)			100		-
	10 (70)	40±13.2	HP (100)					-
	C 11 (45)	30.4±10.9	n.a.					
Isakov, 1985[11]	14 (93)	60.5 (50-75)	TF (100)	100				1*
	3 (100)	35.3 (26-48)	TF (100)		100			> 5
Pinzur, 1992[42]	25 (-)	57.8	TF (20), KD (20), TT (20), Syme (20), midfoot (20)	100				> 6*†
	C 5 (-)	54.5	n.a.					
Gailey, 1993[49]	10 (100)	37.2±11.0	TF (100)				100§	13.6
	10 (100)	34.6±9.8	TF (100)					15.4
	C 10 (-)	33.2±9.6	n.a.					
Jaegers, 1993[50]	11 (100)	-	TF (100)				100‖	-
	C 6 (100)	-	n.a.					
Boonstra, 1994[51]	29 (83)	41±13	TF (100)	3.5	59	34	3.5	19±13
Gailey, 1994[25]	39 (100)	47±16	TT (100)				100§	> 6*
	C 21 (100)	31±6	n.a.					
Torburn, 1995[43]	10 (100)	50.6±15.6	TT (100)		100			-
	7 (100)	62.0±8.3		100				-
Hoffman, 1997[52]	5 (80)	22±3	TF bil (100)		60		40	12.4 (2-24)
	C 5 (80)	22±6	n.a.					
Chin, 2002[10]	8 (-)	72.2±2.1	TF (100)	100				-
	9 (-)	63.2±2.1	TF (100)	100				-

Schmalz, 2002[53]	7 (100)	49±17	TT (100)		100			23±19
	8 (100)	22±17						18±17
	6 (100)	33±6	TF (100)					13±6
	6 (100)	37±9						13±9
Bussmann, 2004[54]	10 (90)	64.6±9.6	TF (20), KD (20), TT (60)	-	-	-	-	68 days (39-131 days)
	C 10 (-)	61.3±11.4	n.a.					
Datta, 2005[55][¶]	10 (70)	38 (23-46)	TF (100)		80	20		≥5
Chin, 2006[56]	4 (100)	24.0±7.6	TF (100)		75	25[#]		-
	C 14 (71)	25.2±4.0	n.a.					
Chin, 2006[39]	34 (71)	67.0±5.6	HD (15), TF (85)	29			71[§]	-
	15 (67)	67.1±5.7	HD (7), TF (93)	60			40[§]	-
Paysant, 2006[24]	10 (100)	39.2 (21-65)	TT (100)		100			17.4 (2-38)
	C 20 (100)	39.7	n.a.					
Hagberg, 2007[57]	41 (73)	49±11.5	TF (100)		71	24	5	27±14.5
	C 22 (73)	49±8.3	n.a.					
Seymour, 2007[58]	13 (85)	46±13	TF (92), KD (8)				100[§]	16±15[*†]
Bussmann, 2008[59]	9 (100)	55.4 (21-73)	TT (100)		100			15.6 (3-61)
	C 9 (100)	55.9 (21-76)	n.a.					
Genin, 2008[60]	10 (100)	34.7±5.1	TF (53)		100			11.2±4.2
	9 (100)	35.3±7.3	TT (47)					
	C 13 (77)	27.8±5.2	n.a.					
Kaufman, 2008[61]	15 (80)	42.9±9	TF (100)	7	47	40	7	20±10
Traballesi, 2008[44]	16 (69)	61±11	TF (67)	100				-
	8 (75)	56±17	TT (33)					-
Wright, 2008[62]	10 (100)	40.5±11.9	TT bil (20), TF bil (30), KD bil (10), TT/TF (40)		80		20	> 22 (2-48)
Hamamura, 2009[40]	44 (64)	66.7±5.1	HD (23), TF (77)	27			73[§]	-
	20 (60)	68.7±5.6	HD (5), TF (95)	55			45[§]	
Houdijk, 2009[63]	11 (-)	46±9	TT (100)	27	73			>1[†]
	C 11 (-)	47±11	n.a.					

Tekin, 2009[34]	10 (100)	27.7±5.3	TT (100)		100			50.3±54.2*
	C 9 (100)	28.4±4.2	n.a.					66.1±49.6*
Goktepe, 2010[35]	64 (100)	29.1±4.5	TF (15), TT (50), partial foot (35)		100			62.6±50.9*
Andrysek, 2011[64]	19 (86)	33.4	TF (93), KD (7)	7	57	21	14	13.2
Hagberg, 2011[65]	28 (71)	49±14.3	HD (7), TF (46), KD (18), TT (29)		61	29	11	18±17†
	C 31 (65)	47±10.2	n.a.					
Kark, 2011[66]	6 (67)	65±18	TF (100)	17	83			median 22.5 (IQR 40.8)
	10 (80)	62±20.8	TT (100)	20	80			median 8.0 (IQR 26.8)
	C 28 (43)	59.0±13.0	n.a.					
Mohanty, 2012[67]	30 (87)	34.1±4.4	TT (100)		100			>1*†
Schnall, 2012[26]	12 (100)	26.9±5.5	TT (100)		100			≥ 6*
	C 12 (100)	20.9±2.8	n.a.					
Sokhangoei, 2013[31]	24 (100)	33 (20-40)	TT (100)		100			13.7±6.8
	C 24 (100)	29.3	n.a.					
Wezenberg, 2013[19]	10 (80)	66.3±5.9	TF (30), TT (70)	100				3.8±3.6
	26 (69)	60.7±5.6	TF (38), TT (62)		100			36.2±20.7
	C 21 (67)	60.8±5.9	n.a.					
Bell, 2014[68]	26 (-)	32±6.1	TF (100)		100			≥2
Erjavec, 2014[41]	101 (63)	69.4 (53-84)	TF (100)	100				-
Esposito, 2014[69]	13 (100)	28.9±5.3	TT (100)		100			6.6±6.2*
	C 13 (100)	26.5±6.0	n.a.					
Gjovaag, 2014[16]	12 (50)	42.8±13.5	TF (100)				100§	≥2
	C 12 (50)	43.0±11.7	n.a.					
Rowe, 2014[70]	17 (88)	52.2±12.9	TT (100)	59	12		29	8.3±7.6
Vllasolli, 2014[37]	22 (91)	40.6±12.5	TF (100)		91		9	17.1±10.5
	61 (85)	39.7±13.1	TT (100)		95		5	14.5±7.5
	6 (83)	36.2±6.2	Syme (100)		100			11.3±2.4
Delussu, 2016[71]	20 (85)	66.6±6.7	TT (100)	65	30	5		0.5†

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Esposito, 2016[72]	6 (83)	29±6	TT (100)		100			2*†
	C 6 (83)	23±5	n.a.					
Guirao, 2016[45]	10 (60)	50.3±16.1	TF (100)	40	40	20		8.1
Starholm, 2016[73]	8 (50)	37.0±10.9	TF (100)				100§	≥2
	C 8 (50)	39.0±12.3	n.a.		100			27±22*
Andrysek, 2017[74]	10 (60)	20.9±3.1	TF (100)		40		60	6.8±4.5
Esposito, 2017[75]	14 (-)	27±5	TF (100)		100			23±11*
	C 14 (-)	26±6	n.a.					
Gardinier, 2017[76]	10 (100)	46.5 (20-60)	TT (100)	-	-	-	-	>6*
	C 10 (100)	48.4 (20-63)	n.a.					
Gjovaag, 2017[28]	8 (50)	37.0±10.9	TF (100)				100§	15.9±13.9†
	C 8 (50)	39.0±12.3	n.a.					
Jarvis, 2017[27]	10 (100)	28±4	TT (100)		100			39±27*
	10 (100)	29±3	TF (100)		100			35±7*
	10 (100)	29±4	TF bil (100)					
	C 10 (100)	30±6	n.a.					
Lacraz, 2017[77]	15 (75)	46.3±12.7	TT (100)		100			17.6±15.2
Ladlow, 2017[78]	10 (100)	32±5	TT (60), KD (20), TF (20)		100			24±15*
	10 (100)	29±4	TT bil (10), KD bil (20), TF bil (30), TT/TF (20), KD /TF (20)		100			39±14*
	C 10 (100)	32±6	n.a.					
Mutlu, 2017[79]	13 (-)	44.0±15.9	TF (-), TT(-), Syme (-)	-	-	-	-	15.6±14.2†
Weinert, 2017[80]	8 (-)	38±3	TT (100)		100			≥0.5†
	9 (-)	28±4	TF (100)		100			≥0.5†
	10 (-)	29±4	TF bil (100)		100			≥0.5†
	C 10 (-)	29±4	n.a.					

N number participants; C controls; - not reported; vasc vascular; onco oncology; TT transtibial amputation; n.a. not applicable; KD knee disarticulation; TF transfemoral amputation; bil bilateral; HP hemipelvectomie; HD hipdisarticulation; IQR interquartile range
* months since amputation reported with 1 decimal, no decimal if not reported in the studies
† prosthetic years
‡ not reported in text or table what level of amputation

§ reported as nonvascular
|| trauma or osteosarcoma, no percentages/numbers reported
¶ data reported in other study[81]
# data in text and table differ from each other within the study, data from the table were used

Study quality

Agreement for the quality assessment was 93% (Cohen's kappa: 0.89). The mean quality score was 6.6, ranging from 3 to 10 points out of 14 possible points (S1 Table). In 43 of the 61 studies inclusion criteria were reported. Only 22 studies reported exclusion criteria. In 8 studies the timeframe of recruitment was reported. The majority of studies (n=56) reported walking speed(s). Most studies (n=56) used validated measurement equipment. In a few studies (n=5) the type of validation was not explicitly specified.

Study characteristics

All studies had an observational design. Three studies [32,42,67] tested the same measurement conditions repeatedly. Almost all studies tested walking as an activity, but there was a great variety in the applied test protocols, test surroundings, and tested walking speeds between studies (Table 2). Furthermore, different terms for metabolic costs were used, as well as different outcome measures. Oxygen consumption (ml O_2/kg/min) and heart rate (beats/min) were the most frequently reported outcome measures of metabolic costs in 39 and 36 studies, respectively (Table 2, S2 Table). Therefore, these 2 outcome measures were used in the meta-analysis.

Table 2. Study characteristics of the included studies.

Author, year	Activity	Surrounding	Metabolic cost outcome measures	Walking speed (km/h)*	Oxygen consumption mean(SD) for walking	Heart rate mean(SD) for walking
Ganguli, 1973	Sitting, standing up, stand erect, walking, stair ascending, stepping	Indoor	Oxygen consumption (l/min), energy expenditure † (cal/min/kg), peak HR†	3	-	-
James, 1973	Walking level and 5° inclination	Treadmill	HR, oxygen uptake (l/min/kg), blood lactate	1.5, 2.7 and 3.9	-	TF 95(2), 104(2), 118(2) 5° inclination 103(2), 119(2), 148(2) Controls: 87(2), 93(2), 95(2) 5° inclination 92(2), 103(2), 116(2)
Ganguli, 1974	Walking	Indoor	Energy expenditure (kcal/kg/km and kcal/km), peak HR‡	3, 4 and 5	-	TT 102(18), 116(21), 113(23) Controls 100(10), 105(9), 112(9)
Ganguli, 1975	Sitting, standing up, stand erect, walking, stair ascending, stepping	Indoor	Energy expenditure (kcal/min) and peak HR	3	-	TT 114(-) Controls 94(-)
Waters, 1976	Walking with prosthesis and with crutches (without prosthesis)	-	oxygen uptake (ml/kg/min), net oxygen cost (ml/kg/m), relative energy cost (%), HR, RQ	SSWS	TF vasc 12.6(2.9), TT vasc 11.7(1.6), Syme vasc 11.5(1.5), TF trauma 12.9(3.4), TT trauma 15.5(2.9)	TF vasc 126(17), TT vasc 105(17), Syme vasc 108(13), TF trauma 111(12), TT trauma 106(11)
Huang, 1979	Walking	Indoor and outdoor	Energy cost (cal/ft/kg), oxygen consumption (ml/ft/kg)	SSWS	-	-
Pagliarulo, 1979	Walking with prosthesis and with crutches (without prosthesis)	Outdoor	HR, oxygen consumption, energy cost (ml/kg/min and ml/kg/m), RR, BP	SSWS, slow and fast	With prosthesis: 15.5(2.8), without prosthesis 22.3(4)	With prosthesis 106(10), without prosthesis 135(22)

DuBow, 1983	Walking and wheel-chair	Indoor	Oxygen consumption (ml/min/kg), HR, %PMHR	SSWS and wheel ergometer	Bil.TT 7.8(2.2),controls 6.9(1.7)	Bil.TT 116(-), controls 92(-)
Nowroozi, 1983	Walking	-	Oxygen consumption (ml/min/kg), HR	SSWS, slow and fast	HD SSWS 11.1(1.7), SSWS slow 9.3(2.1), SSWS fast 14.5(0.9) HP SSWS 11.5(3.5), SSWS slow 8.8(3.7), SSWS fast 13.7(4.9) Controls SSWS 9.8(1.8)	HD SSWS 99 (-), SSWS slow 105(-), SSWS fast 123(-) HP SSWS 97(-), SSWS slow 92(-), SSWS fast 115(-)
Isakov, 1985	Walking	-	Increase in HR and oxygen consumption (ml/min)	SSWS	-	-
Pinzur, 1992	Walking	Treadmill	Oxygen consumption (ml/min/kg)	Rest, normal and maximal	-#	-
Gailey, 1993	Walking	Indoor	Oxygen up-take (-), HR	2 and 4	TF CAT CAM 10.4(1.3) and 15.1(1.9) TF QUAD 11.7(2.7) and 19.0(5.5) Controls 8.5(1.1) and 11.1(1.9)	TF CAT CAM 101(13) and 116(15) TF QUAD 101(11) and 120(16) Controls 84(9) and 90(9)
Jaegers, 1993	Walking	Treadmill	Oxygen uptake (l/min), HR	SSWS + 6 differ-ent speeds	-	
Boonstra, 1994	Walking	Treadmill	Energy expenditure (J/s/kg)	2 and 3	-	
Gailey, 1994	Walking	Indoor	Oxygen uptake (l/min and l/min/kg), HR	SSWS	12.9(-), Controls 10.9(-)	103(-). Controls 87(-)

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Torburn, 1995	Walking	-	HR, energy consumption (ml/kg/min), RQ	SSWS	[$]TT trauma SACH 18.4(3.0), Carbon Copi II 18.0(3.6), Seatle light 17.2(3.6), quantum 17.1(2.7), flex-foot 17.8(3.5) TT vasc SACH 13.4(2.8), Carbon Copi II 13.6(1.7), Seatle light 13.7(2.7), quantum 13.1(2.2), flex-foot 12.4(2.3)	-[#]
Hoffman, 1997	Walking	Indoor	Oxygen uptake (l/min), HR	SSWS, 1.2, 2.2 and 3.3	-[#]	-[#]
Chin, 2002	Cycling	Indoor one leg cycling	$\%\dot{V}O_2max$	n.a.	-	-
Schmalz, 2002	Walking	Treadmill	Oxygen rate (ml/min/kg), HR	Different speeds	[$]TT trauma 1S71 13.5(0.9) and 16.1(1.4), 1D10 13.3(0.8) and 15.5(1.5), 1D25 13.6(0.7) and 15.7(1.2), 1C40 13.5(0.9) and 15.7(1.2), flex foot 13.6(1.2) and 15.6(1.2). TF trauma SSWS 3C1 15.1(1.1), C-leg 14.2(1.2). SSWS slow 3C1 12.9(0.9), C-leg 12.1(1.1), SSWS fast 3C1 16.8(1.4), C-leg 16.2(2.1)	-
Bussmann, 2004	Walking	Indoor	HR rest, HR during walking, % HRR	SSWS and fixed-speed test (speed increased every min)	-	-
Datta,2005	Walking	Treadmill	Oxygen cost (ml/kg/m)	Start 2.5, 0.5 increments at 3min interval, up to 5	-[#]	-

Chin, 2006	Walking	-	Oxygen uptake (ml/kg/min) Oxygen cost (ml/kg/m)	1.8, 3.0, 4.2 and 5.4	TF C-leg 11.6(2.6), 15.6(4.3), 20.1(3.6), 26.9(5.2) TF IP 12.4(5.7), 16.3(4). 21(4.3), 28.1(5.4) Controls 8.7(1.9), 10.4(2.5), 13.3(3.1), 17.3(3.2)	-
Chin, 2006	Cycling	-	%$\dot{V}O_2$max	n.a.	-	-
Paysant, 2006	Walking (asphalt, mown lawn and high grass)	Outdoor	Oxygen uptake (ml/kg/min), oxygen cost (ml/kg/m), HR	-	TT gras flat 15.1(0.2), grass uneven 18.3(0.2), asphalt 14.6(0.2). Controls grass flat 14.1(0.2), grass uneven 15.7(0.1), asphalt 13.4(0.2)	TT gras flat 101(9), grass uneven 115(17), asphalt 101(16). Controls grass flat 103(12), grass uneven 107(14), asphalt 99(10)
Hagberg, 2007	Walking	Indoor	HR, PCI	SSWS	-	111(16) Controls 94(14)
Seymour, 2007	Walking	Treadmill	HR, oxygen consumption (ml/kg/min), oxygen cost (ml/kg/m)	SSWS and fast SSWS	TF/KD SSWS C-leg 12.6(1), NMC 13.5(2) TF/KD SSWS fast C-leg 16.0(2), NMC 17.2(2)	TF/KD SSWS C-leg 102(14), NMC 103(16) TF/KD SSWS fast C-leg 102(16), NMC 104(15)
Bussmann, 2008	Walking	-	HR rest, HR during walking, % HRR	-	-	91(16) Controls 90(16)
Genin, 2008	Walking	Outdoor	Gross cost (J/kg/m), net cost (J/kg/m)	1.1 to 8.3	-	-
Kaufman, 2008	Walking	Treadmill	Objective measurements of energy efficiency (ml/kg/m)	1.6, 3.2 and 3.8	-	-
Traballesi, 2008	Walking	Treadmill and indoor	HR, energy cost (ml/kg/m)	SSWS	TT treadmill 12.3(2.5), floor 13.5(2.4) TF treadmill 13.0(3.5), floor 13.2(3.1)	TT treadmill 106(28), floor 110(27) TF treadmill 108(14), floor 110(13)
Wright, 2008	Walking	Indoor	HR, PCI	SSWS	-	104(16) Controls 85(-)
Hamamura, 2009	One leg cycling test	Indoor	%$\dot{V}O_2$max	n.a.	-	-

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Houdijk, 2009	Walking	Treadmill	Metabolic energy consumption (J/kg/s) and metabolic energy cost (J/kg/m)	SSWS and 4.7	-	-
Tekin, 2009	Walking	Treadmill	EEI (ml/kg/min)	1.5 and 3 , 0° en 5° inclination	TT trauma 7.5(1.3), 9.5(2.1), 5° inclination 8.3(1.8) and 10.3(2.4). Controls (salvage) 7.6(1.20), 9.5(2.1), 5° inclination 8.3(1.8), 11.0(1.4)	-
Goktepe, 2010	Walking	Treadmill	oxygen consumption (ml/kg/min), oxygen cost (ml/kg/m)	1.5 and 3 , 0° en 5° inclination	TT 7.1(1.7), 9.3(2.4), 5° inclination 7.6(1.8) and 10.9(2.4). TF 7.7(2.1), 10.8(2.2), 5° inclination 8.4(2.0), 11.2(1.9)	-
Andrysek, 2011	Walking	Indoor	HR, PCI	SSWS and fast SSWS	-	-
Hagberg, 2011	Walking	Indoor, test-retest	HR, PCI	SSWS	-	106(15), 108(17) Controls 96(12), 97(12)
Kark, 2011	Walking	-	HR, oxygen consumption (ml/kg/min), oxygen cost (ml/kg/m)	SSWS	-#	-
Mohanty, 2012	Walking with prosthesis and walking with axillary crutches without prosthesis	Indoor	Oxygen uptake (ml/min), HR, energy expenditure (kcal/min)	SSWS	-	Walking with prosthesis 82(6), walking with crutches 91(7)
Schnall, 2012	Walking and with 32.7kg load	Treadmill	Oxygen consumption (ml/kg/min)	4.8 and 5.5	TT trauma 22.2(-), 26.4(-) Controls 20.4(-), 23.8(-)	-
Sokhangoei, 2013	Walking	Treadmill	HR, PCI	2, 3 and 4	-	TT 108(-), 113(-), 123(-). Controls 98(-), 101(-), 108(-)

Wezen-berg, 2013	Walking Cycling	Treadmill	Peak oxygen consumption (ml/kg/min), oxygen cost (ml/kg/m), energy expenditure walking (ml/kg/min)	SSWS ± 15% en 30% One leg cycling test	Trauma 13.5(2.2) Vasc 12.2(2.5) Controls 13.8(2.1)	-
Bell, 2014	Walking	-	HR, oxygen cost (ml/kg/min)	SSWS 4 and 4.6	17.3(5), 17.3(2.7)	127(18), 124(23)
Erjavec, 2014	Walking and hand wheel ergometer	-	Oxygen up-take (ml/kg/min), HR	6MWT	-	114(-)
Esposito, 2014	Walking	Treadmill	Oxygen consumption (ml/kg/min), HR	SSWS and 5 standardized velocities	TT 9.5(1.1), 10.9(0.9), 12.7(1.1), 15.5(1.6), 19.1(2.3). Controls 9.6(1.0), 10.9(1), 12.8(1.1), 15.5(1.6), 12.8(1.1), 18.9(1.8)	TT 92(11), 97(12), 105(13), 116(15), 130(18). Controls 79(14), 83(14), 88(14), 95(14), 103(15)
Gjovaag, 2014	Walking and run-ning	Treadmill	$\dot{V}O_2$max (ml/kg/min), HR, RER, Walking economy (ml/kg/m)	SSWS, inclina-tion 3,5% in the 3rd min, until exhaustion, jogging 7-8, inclination 1% every 60 sec till 5,2%, increased speed with 1 ev-ery 60 sec until exhaustion	TF 12.2(1.6) Controls 13.4(1.0)	-
Rowe, 2014	Walking	Indoor and treadmill	Energy expenditure (MET), HR	Normal and music guided	-	SSWS treadmill 110(11), music guided 118(14), SSWS indoor 114(11)
Vllasolli, 2014	Walking	-	HR, PCI	SSWS	-	-
Delussu, 2016	Walking	Indoor	VE (L/min),oxygen consump-tion (ml/kg/min), CO_2 production (ml/kg/min), RER, HR	SSWS	TT SACH 14(4), TT 1M10 13(4)	TT SACH 117(28), TT 1M10 117(27)

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Esposito, 2016	Walking	Indoor and treadmill	Oxygen consumption ($\dot{V}O_2$)	Enforced 4.5	TT ESR 13.4(0.9), BiOM 11.3(0.9), controls 12.2(1.2) 5° inclination ESR 23.1(2.5), BiOM 21.6(0.9), controls 20.9(2.2)	-
Guirao, 2016	Walking	Indoor	PCI	SSWS	-	-
Starholm, 2016	Walking	Treadmill and indoor	$\dot{V}O_2$max, oxygen uptake (ml O_2/kg/min), walking economy (ml O_2/kg/m), VE, RER, HR	SSWS	TF indoor 12.4(1.5), 15.8(3.4), treadmill 12.4(2.1), 15.6(2.8) Controls indoor 13.2(4), 14.6(1.9) Treadmill 13.4(4.4), 15.5(2.6)	-
Andrysek, 2017	Walking	Indoor	HR, PCI	SSWS and fast SSWS	-	-
Esposito, 2017	Walking	Treadmill and indoor	Oxygen rate (ml O_2/kg/min), metabolic cost (ml O_2/kg/m), HR	SSWS and 5 standardized velocities	TT 13.7(2.4), 15.8(2), 18.7(2.1), 22.7(2) SSWS indoor 19.2(3.2) Controls 9.6(1), 10.9(0.9), 12.7(1.2), 15.5(1.3), SSWS indoor 14.4(2)	TT 97(12), 105(14), 114(13), 125(15) SSWS indoor 116(17). Controls 79(14), 83(14), 88(11), 95(14), SSWS indoor 91(12)
Gardinier, 2017	Walking	Indoor	Oxygen consumption (ml/kg/min), cost of transport (J/N*m)	SSWS	TT 14.5(1.9), 14.3(1.7) Controls 13.3(0.8)	-
Gjovaag, 2017	Walking	Treadmill and indoor	Oxygen uptake (ml/kg/min), %$\dot{V}O_2$max, energy cost of walking (ml/kg/m)	SWSS, speeds 12.5% and 25% slower and faster than SWSS	TF 15.9(-) Controls 14.1(-)	-
Jarvis, 2017	Walking	Indoor	Oxygen cost (ml/kg/m), oxygen consumption (ml/kg/min)	SSWS	TT 12.3(-), TF 13.3(-), bil TF 16.2(-) Controls 11.3(-)	-
Lacraz, 2017	Walking	Treadmill	Oxygen cost (ml/kg/m), oxygen consumption (ml/kg/min), HR	SSWS	-[#]	-

Ladlow, 2017	Walking	Treadmill	MET, RPE	Enforced and with 3° and 5° inclination	-	-
Mutlu, 2017	Walking, stair ascending/ descending	Indoor	6MWT, BP, HR	SSWS, 10 stairs up & down tests with/without 250g extra load	-	81(9), with extra load 85(9)
Weinert, 2017	Walking	Indoor	Oxygen consumption (-)	SSWS	-	-

n.a. not applicable; - not reported; SSWS self-selected walking speed; TT transtibial amputation, TF transfemoral amputation, KD knee disarticulation, bil bilateral; HR heart rate; BP blood pressure; PSPC pneumatic swing-phase control; NMC non-microprocessor control knee, ESR energy storing and return, BiOM bionic powered ankle–foot prosthesis 6MWT 6-min walking test; RQ respiratory quotient; RR respiratory rate (breaths/min); PCI physiological cost index ((mean HR(work)-mean HR(rest))/gait speed); %PMHR % predicted max heart rate; %HRR % heart rate reserve; EEI energy expenditure index; RER respiratory exchange ratio; MET Metabolic Equivalent of Task
* all walking speeds are converted to km/h
† result only in figures
‡ no outcome measure/numbers published
[$] 5 different prosthetic feet
[#]results displayed only in figures, no numbers

2

Meta-analysis

The heterogeneity of the study populations, test protocols and the inconsistent reporting influenced the possibilities for statistical analysis.

When study was used as the unit of analysis, for oxygen consumption 23 studies were included in the mixed model analysis. The following significant predictors for oxygen consumption (ml O_2/kg/min) were found: level of amputation, walking speed, and the interaction terms walking speed squared and walking speed x amputation level (Fig 2, Table 3). When adding reason of amputation to the model, 4 studies were excluded because of missing data, the model fit did not improve and the coefficients were not significant. Similar findings occurred when walking over ground vs. treadmill walking was added to the model.

Figure 2. Oxygen consumption, regression lines, and the reported means for oxygen consumption (mL O_2/kg/min) of the included studies.

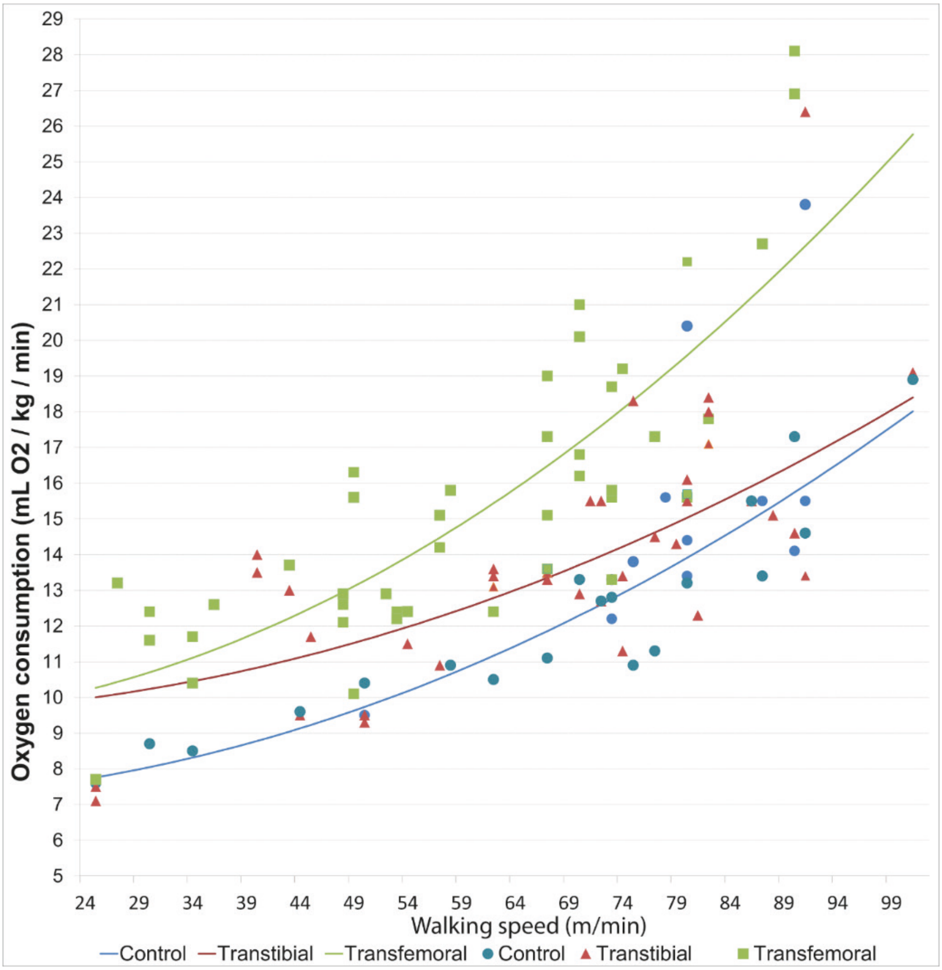

Table 3. Estimated mean oxygen consumption (ml O_2/kg/min) based on the meta-analysis.

Predictor	Beta	Std. Error	P value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	7.2	1.4	<0.001	4.3	10.0
Transfemoral	2.2	1.0	0.025	0.3	4.1
Transtibial	2.4	1.1	0.036	0.2	4.6
Walking speed (m/min)	$-3.6*10^{-3}$	$3.8*10^{-2}$	0.925	$-7.9*10^{-2}$	$7.2*10^{-2}$
Walking speed^2 (m/min)	$1.1*10^{-3}$	$3.1*10^{-4}$	0.001	$4.8*10^{-4}$	$1.7*10^{-3}$
Transfemoral * walking speed^2	$5.5*10^{-4}$	$1.8*10^{-4}$	0.002	$2.0*10^{-4}$	$0.9*10^{-3}$
Transtibial * walking speed^2	$-1.9*10^{-4}$	$1.9*10^{-4}$	0.306	$-5.7*10^{-4}$	$1.8*10^{-4}$

Included studies [4,16,17,22,23,25,26,32,33,41,42,46,47,51,54,56,66,67,69-71,73,74].

For heart rate, 20 studies were included in the mixed model analysis. Significant predictors for heart rate were amputation level, walking speed, and walking speed squared. No other interaction terms or other factors (e.g. reason of amputation and treadmill vs. over ground) were found to be significant (Fig 3, Table 4).

Figure 3. Heart rate, regression lines, and the reported means for heart rate (beats/min) of the included studies

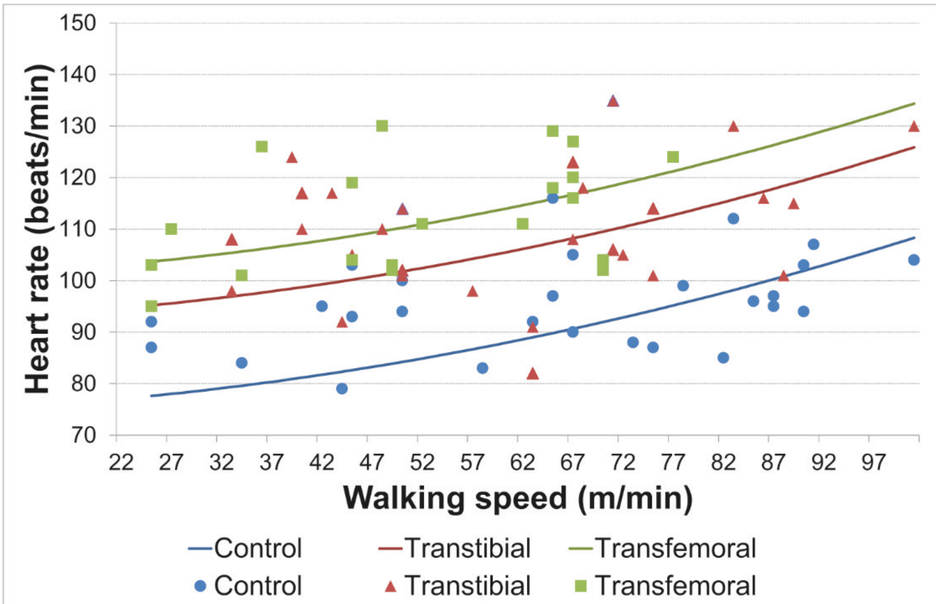

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Table 4. Estimates mean heart rate (beats/min) based on meta-analysis.

Predictor	Beta	Std. Error	P Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	74.5	4.8	<0.001	64.9	84.0
Transfemoral	26.1	2.2	<0.001	21.6	30.5
Transtibial	17.6	2.1	<0.001	13.4	21.8
Walking speed (m/min)	$5.7*10^{-2}$	$1.5*10^{-1}$	0.703	-0.2	0.3
Walking speed^2 (m/min)	$2.8*10^{-3}$	$1.2*10^{-3}$	0.028	$3.0*10^{-4}$	$5.2*10^{-3}$

Included studies: [4,23,28-31,39,42,44,46,47,55,56,63,65,67-69,73,77].

DISCUSSION

Sixty-one studies (reporting on 1,912 participants) were included in this systematic review and meta-analysis. A linear mixed model was used to analyse the data. It was found that reported mean oxygen consumption (ml O_2/kg/min) was influenced by amputation level, walking speed, and the interaction terms walking speed squared and walking speed x amputation level. Multiple previous studies reported that higher metabolic costs are associated with a more proximal level of amputation [4,5,13,82]. Previous studies also found that participants with a LLA adapt their self-selected walking speed (SSWS) in order to compensate for the higher metabolic costs [4,19,43,57]. The extent to which the SSWS is reduced depends on level of amputation [4,19,57]. The effect of walking speed on metabolic costs is also found in our analysis (Fig 2). In the multilevel analysis an increase in oxygen consumption was found at higher walking speeds, with a significant difference between reported means for controls and participants with a transfemoral amputation. However, there was no significant difference between reported means for controls and participants with a transtibial amputation. This lack of difference can be due to the included studies. For example, one study [69] measured the oxygen consumption in participants with a traumatic transtibial amputation and controls at walking speeds up to >100 m/min (Fig 2). Compared with the controls, the oxygen consumption of the participants at the highest walking speed was not significantly different (19.1±2.3 ml O_2/kg/min vs. 18.9±1.8 ml O_2/kg/min). In the multilevel analysis an interaction effect between walking speed squared and group was found, indicating that the effect of walking speed squared was not the same for groups. This interaction effect can be related to amputation level, but also to differences between studies including differences in methodology i.e. measurement procedures, general health, body weight, height, physical condition, and or age of the participants. However source studies report too inconsistently to be able to include these confounders in the regression analyses. The curve is based on the regression coefficients of the linear mixed model analysis of the reported means in the studies. Different study designs and heterogeneity in study populations may influence the reported means and therefore the regression curve.

One of the most noteworthy findings was that reason of amputation was not a predictor in the multilevel analysis , which may be related to the limited number of studies analysing participants with a vascular amputation. Additionally, many studies did not report on reason of amputation, had a mixed group of reasons of amputation, without specifying outcomes for separate groups. When adding reason of amputation to the mixed model analysis, 4 studies were excluded and coefficients were not significant. However, some previous studies report higher metabolic costs for walking in participants with a vascular LLA [4,19]. One study reported that the metabolic costs (measured by oxygen consumption (mL O_2/kg/min)) of walking in participants with a traumatic LLA at SSWS were equal to those of controls, whereas the SSWS of the LLA group was slower than that of the control group [19]. In the group of participants with a vascular LLA, SSWS was slower. Even when participants with a vascular LLA adapted their SSWS, the metabolic costs were higher [63]. However, this study included mixed groups for level of amputation. When walking faster than their SSWS, 2 studies found higher oxygen consumption for participants with a traumatic LLA compared to controls [19,57].

The other frequently used outcome measure of metabolic costs was heart rate (beats/min). Studies reported heart rate were not all the same studies included in the analysis for oxygen consumption. Therefore, a different study population is analysed (Table 2), with a total of 20 included studies. The majority of studies using this specific outcome measure did not include participants with a LLA due to PVD. Generally, measuring heart rate is more accessible compared to oxygen consumption or $\dot{V}O_2$max, because in most of the settings equipment for measuring oxygen consumption and/or $\dot{V}O_2$max is not available. Furthermore, it is questionable whether heart rate is a good predictor of metabolic costs in persons with an amputation due to vascular disease and/or DM, because they often have comorbidities such as cardiovascular disease and are likely to use medication that influences their heart rate. Significant predictors of heart rate as an outcome measure were walking speed, amputation level, and walking speed squared. Reason for amputation was not a significant predictor of heart rate.

As stated previously, the $\dot{V}O_2$max-test is seen as the criterion measure of physical and aerobic capacity. Only a few studies [10,16,62,69] measured (%)$\dot{V}O_2$max in participants with a LLA. Only one study reported the relative aerobic load of walking, measured as a percentage of the $\dot{V}O_2$peak [19]. For walking, the relative aerobic load was found to be higher in participants with a LLA than in controls. Another study reported that participants with a LLA who had higher levels of physical fitness (defined as the maximum oxygen uptake during exercise as a proportion of predicted maximum oxygen uptake) were more likely to walk with a prosthesis than participants with a LLA with lower levels of physical fitness [10]. Therefore, $\dot{V}O_2max$ may be used as an indicator for walking ability and for (physical) training in persons with a LLA. Additionally, it is relevant to know an individual's aerobic capacity in combination with the metabolic costs of daily activities, to be able to evaluate the individual strain of ADL. Possible explanations for the lack of $\dot{V}O_2max$-testing in persons with a LLA are comorbidities, lack of knowledge of this type of testing, lack of knowledge of the interpretation of the test results, costs, and lack of facilities.

Previous systematic reviews did not primarily aim to analyse metabolic costs of ADL in participants with a LLA [17,18]. They found no sufficient evidence for a relation between other measures of physical capacity, such as aerobic and anaerobic capacity, and walking ability. The main finding was the heterogeneity in measurement methods and outcome measures. This finding is in keeping with the results from our study. Studies included in our systematic review and meta-analysis were also heterogeneous with respect to number of participants, participant characteristics, study characteristics, statistical analyses, test protocols, and outcome measures. The heterogeneity and the poor reporting influenced our statistical analysis. It was not possible to make forest plots or use effect sizes in the meta-analysis, therefore a conventional meta-analysis was not possible. A linear mixed model analysis was performed on the means reported, with study as unit of analysis and study results of different groups and measurement conditions as repeated measures within the unit of analysis. Despite the shortcomings of the source studies we were able to identify 2 factors (amputation level and walking speed) influencing oxygen consumption and heart rate. By combining several studies a more precise estimate was found than in single studies. All studies were of observational design, were blinding participants or investigators was not possible. In 43 of the 61 studies inclusion criteria were reported, and in only 22 studies reported exclusion criteria (S1 Table), therefore it is not clear if there was a selection bias. The majority of the included studies did report the tested walking speeds and used validated equipment. Because of the limited reporting, it was not possible to analyse predictors such as age, height, and type of prosthesis (prosthetic knee/foot), because too few studies reported sufficient details. When the aforementioned predictors were added to the statistical model, the number of studies available for analysis decreased considerably, thereby preventing further analysis. Consequently, no conclusions could be drawn from these predictors.

Of the included 61 studies, 3 studies reported on metabolic costs for walking stairs [29,30,79]. One of these studies compared heart rate for walking stairs with and without extra weight in participants with LLA and found that in both situations heart rate increased [79]. The other 2 studies measured metabolic costs (kcal/min) and heart rate [29,30]. They found a significant difference for metabolic costs (kcal/min), but no significant difference in heart rate for ascending stairs compared to controls. One other study measured different walking conditions outdoors (asphalt, mown lawn and high grass) in high functioning participants with traumatic transtibial amputations [24]. They reported significant increase in oxygen consumption (ml O_2/kg/min) and heart rate for walking in high grass, no significant differences for the other 2 conditions were found. As previously mentioned, the rehabilitation of persons with a LLA is not only aimed at walking with prosthesis, but also at regaining functional capacity and independency with regard to ADL. However, limited data is available on metabolic costs of other activities than walking with a prosthesis.

Study limitations

The results of this systematic review and meta-analysis were dependent on the quality of research of the available studies. The included studies reported poorly on details of the study populations and potential predictors of metabolic costs in participants with a LLA. Because of the heterogeneity and the limited reporting, the mixed model analysis was performed with reported means, with study as unit of analysis. Furthermore, the studies included relatively healthy participants and, as mentioned before, data on metabolic costs for other ADL than walking is very limited.

Future research

Further research on the metabolic costs of walking, and daily activities in persons with a LLA is relevant in order to gather data that will help with setting functional goals, optimizing individual training, and evaluating LLA-rehabilitation. Study populations and subgroups should be described with sufficient detail regarding reason for amputation, age, gender, and level of amputation to improve generalizability. The inclusion of participants with different levels of amputation in a mixed group should be avoided.

From a clinical perspective, it is important to assess the metabolic costs of ADL and the physical capacity of persons with a LLA in order to optimize their rehabilitation program, train them at an optimal walking speed, improve their potential to walk with a prosthesis, and help them regain functional capacity with regard to ADL.

Conclusion

In general oxygen consumption and heart rate for persons with transtibial and transfemoral amputation while walking are higher than for controls. A higher walking speed is associated with a higher oxygen consumption and this increase was stronger for persons with a transfemoral amputation compared to controls. Source studies report inconsistently, therefore it is not possible to include other possible confounders in the analyses such as age and cause of amputation.

Limited information is available on metabolic costs of other activities than walking. The quality of the included studies was low; therefore, the results of this systematic review should be regarded with some caution.

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SUPPLIER

a. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.

SUPPORTING INFORMATION

S1. File. Details of the full search strategy

Pubmed:

(("Lower Extremity"[Mesh]) AND "Amputation"[Mesh] OR Syme amputation[tw] OR above ankle amputation[tw] OR transtibial amputation[tw] OR knee-exarticulation[tw] OR knee exarticulation[tw] OR knee disarticulation [tw] OR knee-disarticulation [tw] OR above knee amputation[tw] OR transfemoral amputation[tw] OR hip exarticulation[tw] OR hip-exarticulation[tw] OR hip disarticulation[tw] OR hip-disarticulation[tw] OR Syme amputee*[tw] OR above ankle amputee*[tw] OR transtibial amputee*[tw] OR above knee amputee*[tw] OR transfemoral amputee*[tw] OR lower extremity amputation[tw] OR lower extremity amputee[tw] OR lower limb amputation[tw] OR lower limb amputee[tw] OR leg amputation[tw] OR below-knee amputation [tw] OR below knee amputation[tw] OR Lower extremity amputee*[tw] OR lower limb amputee*[tw] OR leg amputee*[tw] OR below-knee-amputee*[tw] OR below knee amputee*[tw] OR lower limb prosthe*[tw] OR leg prosthe*[tw] OR artificial leg[tw])
AND (("Metabolism"[Mesh] OR energy[tw] OR metabol*[tw] OR aerobic[tw] OR net value[tw] OR joule*[tw] OR calor*[tw] OR pci[tw] OR physiological cost index[tw] OR anaerobic[tw] OR energetic [tw])))
AND (("Activities of Daily Living"[Mesh] OR Activities of Daily Living[tw] OR adl[tw] OR (("Walking"[Mesh]) OR "Monitoring, Ambulatory"[Mesh]) OR "Gait"[Mesh] OR walk*[tw] OR gait[tw] OR "Bicycling"[Mesh] OR bicycl*[tw] OR stair[tw] OR dress*[tw] OR cook*[tw] OR ambulant[tw] OR ambulation[tw] OR self-care[tw] OR self care[tw] OR home activit*[tw] OR drive[tw] OR driving[tw] OR transfer[tw] OR garden*[tw] OR human activit*[tw] OR run*[tw])))

Embase:

‘leg amputation’/exp OR ‘leg prosthesis’/exp OR 'leg amputation':ti,ab OR 'transtibial amputation':ti,ab OR 'syme amputation':ti,ab OR 'above ankle amputation':ti,ab OR 'knee amputation':ti,ab OR 'transfemoral amputation':ti,ab OR 'hip exarticulation':ti,ab OR 'hip disarticulation prosthesis':ti,ab OR 'leg amputation' OR 'transtibial amputation' OR 'syme amputation' OR 'above ankle amputation' OR 'knee amputation' OR 'transfemoral amputation' OR 'hip exarticulation' OR 'hip disarticulation prosthesis' OR ‘amputees’ OR amputee:ti,ab
AND 'metabolic rate'/exp OR 'metabolism'/exp OR 'energy cost'/exp OR metabolism:ab,ti OR energy:ab,ti OR metabolic:ab,ti OR 'metabolic rate':ab,ti OR 'metabolism':ab,ti OR 'calorie'/exp OR 'calorie':ab,ti OR calorie OR 'metabolic equivalent'/exp OR 'metabolic equivalent':ab,ti OR 'met value':ab,ti OR 'physiological cost index':ab,ti OR 'pci':ab,ti OR metabolism OR energy, OR metabolic OR 'met value' OR 'physiological cost index' OR 'pci'
AND ‘human activities’/exp OR ‘daily life activity’/exp OR ‘human activities’:ab,ti OR ‘daily life activity’:ab,ti OR ‘walking’/exp OR ‘walking’:ab,ti OR ‘gait’:ab,ti OR ‘physical acitity’/exp OR ‘physical activity’:ab,ti OR ‘self care’/exp OR ‘self care’:ab,ti OR ‘running’:ab,ti

Cinahl:

(MH "Lower Extremity+") OR "lower extremity" AND (MH "Amputation+") OR "amputation" OR (MH "Below-Knee Amputation") OR (MH "Above-Knee Amputation") OR (MH "Amputation, Traumatic") OR "lower limb amputation" OR MH "Leg") OR "leg" OR (MH "Limb Prosthesis") MH "Below-Knee Amputation") OR (MH "Above-Knee Amputation") OR (MH "Amputation, Traumatic") OR "knee amputation" OR (MH "Disarticulation") OR "transtibial amputation" OR "above knee amputation" OR "hip disarticulation" OR (MH "Limb Prosthesis") OR "artificial leg"
AND (MH "Metabolism+") OR "metabolism" OR (MH "Basal Metabolism+") OR (MH "Energy Metabolism+") OR (MH "Energy Conservation, Metabolic") OR "energy" OR "energy cost" OR "met value" OR "metabolic equivalent" OR "pci" OR "physiological cost index" OR (MH "Basal Metabolic Rate") OR "calorie" OR "metabolic rate"
AND (MH "Activities of Daily Living+") OR "adl" OR (MH "Grooming+") OR "grooming" OR (MH "Oral Hygiene+") OR (MH "Home Rehabilitation+") OR (MH "Occupational Therapy+") OR (MH "Physical Therapy+") OR (MH "Rehabilitation, Psychosocial+") OR (MH "Rehabilitation, Pulmonary+") OR (MH "Running+") OR "running" OR (MH "Walking+") OR "walking" OR (MH "Human Activities+") OR "human activities" OR (MH "Gait+") OR "gait" OR (MH "Self Care+") OR "self care" OR (MH "Cycling") OR "cycling" OR "biclycling" OR (MH "Stair Climbing") OR "stairs" OR "climbing stairs"

PsychINFO:

DE "Amputation" OR DE "Phantom Limbs" OR DE "Prostheses"
AND (DE "Metabolic Rates" OR DE "Metabolism" OR DE "Basal Metabolism" OR DE "Biosynthesis" OR DE "Carbohydrate Metabolism" OR DE "Catabolism" OR DE "Lipid Metabolism" OR DE "Metabolites" OR DE "Protein Metabolism") OR (DE "Energy Expenditure")) OR (DE "Calories")) OR metabolic equivalent OR physiological cost index OR calorie OR energy
AND (DE "Activities of Daily Living") OR (DE "Running")) OR (DE "Walking")) OR (DE "Gait")) OR (DE "Physical Activity" OR DE "Exercise")) AND (DE "Self Care Skills" OR DE "Ability" OR DE "Activities of Daily Living" OR DE "Daily Activities" OR DE "Hygiene" OR DE "Independent Living Programs" OR DE "Rehabilitation" OR DE "Skill Learning")

CENTRAL:

[Amputation] or [amputees] OR [artificial limb] or amput* or prosthes* or artificial limb or transtibial amputat* or through knee amputat* or transfemoral amput* or Syme amputation or above ankle amputation or knee-exarticulation or knee exarticulation or knee disarticulation or knee-disarticulation or above knee amputation or hip exarticulation or hip-exarticulation or hip disarticulation or hip-disarticulation or Syme amputee* or above ankle amputee* or transtibial amputee* or above knee amputee* or lower extremity amputation or lower extremity amputee or lower limb amputation or lower limb amputee or leg amputation or below knee amputation or Lower extremity amputee* or lower limb amputee* or leg amputee* or below knee amputee* or lower limb prosthe* or leg prosthe* or artificial leg
AND [energy metabolism] or [metabolism] energy OR metabol* OR aerobic OR net value OR joule* OR calor* OR pci OR physiological cost index OR anaerobic OR energetic
latory OR walk* OR gait OR Bicycling OR bicycl* OR stair OR dress* OR cook* OR ambulant OR ambulation OR self-care OR self care OR home activit* OR drive OR driving OR transfer OR garden* OR human activit* OR run*

S2. AHRQ Cross-Sectional/Prevalence Study Quality Assessment checklist

Quality Item*- Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Ganguli, 1973	Y	N	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
James, 1973	Y	?	?	?	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Ganguli, 1974	Y	N	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Ganguli, 1975	Y	N	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Waters, 1976	Y	Y	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Huang, 1979	Y	N	N	N	N	N	N	Y	Y	N	N.A.	Y	N.A.	?	4
Pagliarulo, 1979	Y	N	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
DuBow, 1983	Y	Y	?	N	Y	N	Y	Y	Y	N	N.A.	Y	N.A.	Y	8
Nowroozi, 1983	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Isakov, 1985	Y	N	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Pinzur, 1992	Y	N	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Gailey, 1993	Y	Y	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Jaegers, 1993	Y	N	N	N	N	N	N	Y	Y	N	?	Y	N.A.	Y	5
Boonstra, 1994	Y	Y	N	N	Y	Y	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Gailey, 1994	Y	Y	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Torburn, 1995	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Hoffman, 1997	Y	N	N	N	N	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Chin, 2002	Y	Y	N	N	Y	N	N	N.A.	Y	N	N.A.	Y	N.A.	Y	6
Schmalz, 2002	Y	N	Y	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Bussmann, 2004	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	Y	Y	10
Datta,2005	Y	?	?	?	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Chin, 2006	Y	Y	N	N	N	N	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Chin, 2006	Y	Y	N	N	Y	N	N	N.A.	Y	N	N.A.	Y	N.A.	Y	6
Paysant, 2006	Y	Y	N	Y	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Hagberg, 2007	Y	Y	N	N	Y	N	N	?	Y	N	N.A.	Y	N.A.	N	5
Seymour, 2007	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Bussmann, 2008	Y	Y	Y	N	Y	N	N	N.A.	N	N	N	Y	N.A.	Y	6
Genin, 2008	Y	N	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Kaufman, 2008	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Traballesi, 2008	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Wright, 2008	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Hamamura, 2009	Y	Y	Y	N	Y	N	N	N.A.	Y	N	N.A.	Y	N.A.	Y	7
Houdijk, 2009	Y	N	N	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Tekin, 2009	Y	Y	Y	Y	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	9
Goktepe, 2010	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Andrysek, 2011	Y	Y	N	N	Y	N.A.	N	Y	Y	N	N.A.	Y	N	Y	7
Hagberg, 2011	Y	Y	N	N	Y	N	Y	?	Y	N	N.A.	Y	N.A.	?	6
Kark, 2011	Y	N	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7

Mohanty, 2012	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Schnall, 2012	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	7
Sokhangoei, 2013	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	?	6
Wezenberg, 2013	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Bell, 2014	Y	Y	Y	Y	Y	N.A.	N	Y	Y	N	N.A.	Y	N.A.	Y	9
Erjavec, 2014	Y	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N.A.	Y	8
Esposito, 2014	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Gjovaag, 2014	Y	N	N	N	N	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Rowe, 2014	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Vllasolli, 2014	Y	Y	N	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	?	6
Delussu, 2016	Y	Y	N	N	?	N.A.	N	N	Y	N	N.A.	N	N.A.	Y	4
Esposito, 2016	Y	N	N	N	?	N.A.	N	N	N	N	N	Y	N.A.	Y	3
Guirao,2016	Y	Y	Y	Y	Y	N.A.	N	Y	Y	N	N.A.	Y	Y	Y	10
Starholm, 2016	Y	Y	N	N	?	N.A.	N	Y	Y	N	N.A.	Y	N.A.	Y	6
Andrysek, 2017	Y	Y	N	N	Y	N.A.	N	N	Y	N	N	Y	N.A.	Y	6
Esposito, 2017	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Gardinier, 2017	Y	Y	Y	Y	Y	N	N	Y	N	N	N.A.	Y	N.A.	Y	8
Gjovaag, 2017	N	N	Y	N	?	N	N	Y	Y	N	N.A.	Y	N.A.	Y	5
Jarvis, 2017	Y	Y	N	Y	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Lacraz, 2017	Y	Y	Y	Y	Y	N.A.	N	N	Y	N	N.A.	Y	N	Y	8
Ladlow, 2017	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Mutlu, 2017	Y	Y	Y	N	Y	N	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Weinert, 2017	Y	Y	Y	N	Y	N.A.	N	Y	Y	N	N.A.	Y	N.A.	Y	8
Total	60	43	22	8	40	1	3	50	57	0	1	60	2	56	

Y yes, N no, N.A. not applicable, ? not specified/unknown.
*1. Was the source of information for the reported outcome measurements mentioned? 2. Were inclusion criteria reported? 3. Were exclusion criteria reported? 4. Was the timeframe of recruitment reported? 5. Were subjects consecutively recruited or population-based? 6. Were evaluators of subjective components masked to other aspects of the subjects? 7. Have any assessments been undertaken for quality assurance purposes (test/retest of primary outcome measurements)? 8. Was the used equipment validated or were there references to validation in previous publications? 9. Were all participants included in the analysis? 10.Was confounding assessed and/or controlled for? 11. Were missing data reported? 12. Were patient response rate and completeness of data collection reported? 13. Were follow-up, incomplete data, or loss to follow-up reported? 14. Was tested walking speed reported?

S3 Table. Frequencies of the reported outcome variables.

Main outcome variables	Studies (n)
HR (beats/min)	39
$\dot{V}O_2$/oxygen uptake / oxygen consumption (ml/kg/min, L/min)	35
Oxygen cost (ml/kg/m)	16
PCI	8
(%)$\dot{V}O_2$max	6
$\dot{V}O_2$ peak	1
Peak HR	3
% HRR	2
Energy expenditure (kcal/min)	2
Energy expenditure (J/s/kg)	1
Energy expenditure (kcal/kg/km and kcal/km)	1
Energy expenditure (cal/min/kg)	1
Gross cost / net cost (J/kg/m)	1
RER	3
Metabolic energy consumption (J/kg/s)	1
Metabolic energy cost (J/kg/m)	1
Basal energy expenditure energy cost (cal/ft/kg)	1
Blood lactate	1
RR	1
BP	2
METs	1
Relative energy cost (%)	1
RQ	2
EEI (ml/kg/min)	1

HR heart rate; PCI physiological cost index; %HRR % heart rate reserve; RER respiratory exchange ratio; RR respiratory rate; BP blood pressure; METs metabolic equivalent of task; RQ respiratory quotient; EEI energy expenditure index

2

3

Chapter 3

The most important activities of daily functioning; the opinion of persons with lower limb amputation and healthcare professionals differ considerably

Important daily activities according to persons with lower limb amputation

Loeke van Schaik, Jan H.B. Geertzen, Pieter U. Dijkstra, Rienk Dekker

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ABSTRACT

The aim of this study is to determine the 15 most important daily activities according to persons with lower limb amputation (LLA) and healthcare professionals. Persons with LLA (n=125) and healthcare professionals (n=44) filled in a questionnaire. Participants had to select 10 items out of a list of 40 items on the domains activity and/ or participation. Selection criterion was what they considered to be most important to perform independently and order the selected 10 items from most to least important. Mean rank scores of the 15 highest scored items according to participants with LLA were compared with the mean rank scores given by professionals, using the Mann-Whitney U test with a Hochberg adjustment for multiple testing. Participants with LLA rated 5 activities as significantly more important compared to professionals; 'driving a car', 'bicycling', 'ascending/descending stairs', 'heavy exercise' and 'preparing meals'. Healthcare professionals rated 4 activities as significantly more important compared to persons with LLA; 'going to the toilet', 'getting in and out bed', 'walking around outdoors' and 'walking around indoors'. A significant difference in rating importance was present in 9 out of 15 activities between persons with LLA and healthcare professionals. This result makes it all the more clear how complex shared decision making can be and how important it is for healthcare professionals to communicate with the person with LLA.

Keywords: activities of daily living, lower limb amputation, daily functioning, healthcare professionals.

INTRODUCTION

Persons with lower limb amputation (LLA) often experience limitations in performing activities of daily living (ADL), participation [1,2] and can experience a lower quality of life (QoL) [2–4]. Factors associated with QoL in persons with LLA are reduced mobility, limitations in ADL, participation, social support, and age [4,5]. Rehabilitation medicine aims to enable persons with LLA to function independently again and to participate in social life. To achieve these goals, it is important to know the individual goals of the person with LLA and what they find important in life.

In the Netherlands, the majority of persons with LLA are elderly and main reason for LLA is vascular disease and/or diabetes mellitus (DM) [6,7]. These characteristics may influence individual goals and level of functioning. Ideally, the goals for rehabilitation are set by both the person with LLA and the healthcare professional(s). However, expectations in early stage rehabilitation can be vague, which can lead to uncertainty and passivity by persons with LLA [8]. Tools as the Canadian Occupational Performance Measure can be used for prioritizing activities at the start of the rehabilitation and can provide relevant information about individual priorities [9]. However, in general, little is known about what is perceived as the most important ADL according to persons with a disability or disease, including those with a LLA [10]. Additionally, the perspective of the person with a disability or disease is usually not included in the used outcome measures [10]. Assessment tools are developed by healthcare professionals, but may lack to correlate with the goals of persons with (in this case) LLA. In order to optimize the rehabilitation programme for persons with LLA, it is important to get insight in the most important activities according to persons with LLA.

Therefore, the aim of this study is to objectify the most important ADL according to persons with LLA, and compare these outcomes with those activities deemed most important by healthcare professionals working with persons with LLA. Additionally subgroups of persons with LLA will be compared. The findings may provide further insight into the importance of certain ADL amongst persons with LLA and may guide clinicians on where to direct their focus in the rehabilitation process.

METHODS

Medical ethical commission

The Medical Ethics Assessment Committee for Research of the University Medical Center of Groningen declared that this study did not fall within the Dutch law on Medical scientific Research involving humans. Consequently, formal approval from the committee was not required for this research (2016.393) and exemption was granted.

Study Design

In this observational study, data is collected using questionnaires filled in by persons with LLA, and by healthcare professionals working with persons with LLA. Part of the methodology of this study was based on that of a previous study [11].

Participants in this study were included if they had LLA at Syme level or higher, ≥18 years of age, and understood Dutch language. All participants received written information about the study prior to taking the questionnaire and written informed consent was obtained. The questionnaires were distributed on paper at different prosthetic workshops in the Northern regions of the Netherlands and persons with LLA could sign up by email through the amputee association.

Healthcare professionals were included in the study if they were working with persons with LLA at the time of the study. The questionnaires were distributed on paper to professionals working in the Northern regions and were distributed in the ‘Werkgroep Amputatie en Prothesiologie’, which is a nationwide collaboration of rehabilitation specialists working within the field of LLA in the Netherlands.

From September 2016 to November 2016 the questionnaires were distributed amongst persons with LLA and healthcare professionals. The aim was to include at least 50 persons with LLA. Because the number of participants with LLA was too low, a second distribution round was performed from September 2018 to November 2018.

Composite of the questionnaire

The International Classification of Functioning (ICF)-model was used to create an overview for activities and participation [1,12]. In order to create this overview, a scoping database search (PubMed, Embase and Google Scholar) was performed to select studies using measurement instruments for activities and participation items, conform the ICF domains self-care, mobility, domestic life, major life areas and community/social life. Studies were excluded when they contained measurement instruments conform the ICF domains learning and applying knowledge, general tasks and demands, communication, interpersonal interactions, and relationships. If in 50 studies (ordered chronologically, starting with most recent) no new measurement instruments were found data saturation regarding items was assumed.

An overview was created containing all items for activities and/or participation identified in the instruments. Some instruments contained both items from the included ICF domains (e.g. self-care) and excluded ICF domains (e.g. communication). Only items that could be categorized under the previously mentioned domains, based on the ICF model, were included in the overview. Additionally, treatment- related items (e.g. use services provided by a medical clinic, hospital or rehabilitation center) were excluded. Duplicates or similar items were merged into one item. Lastly, the list was checked by the research group for possible missing items. In total, 40 items were included (Appendix 1).

Questionnaire

Two questionnaires were developed, one for persons with LLA and one for healthcare professionals.

In the questionnaire for participants with LLA, participant characteristics (gender, age and comorbidities) and amputation characteristics (e.g. aetiology, side, level of amputation, time since LLA, and time since wearing prosthesis) were asked. Thereafter, participants were asked to select 10 out of the 40 items that they considered to be most important to perform independently (Appendix 1). Participants had to order these 10 items, from most to least important, scored 10 to 1 respectively. Additionally, participants were asked if they missed any important daily activity in the 40 item list. Finally, the questionnaire ended with four statements regarding the clearness and complexity of the questionnaire. The following statements were included: “the instructions prior the questionnaire made clear what was expected of me”, “it was easy to distinguish the items in the overview”, “it was easy to choose the 10 items that I found most important” and “the asked questions were easy to understand”. The answering options of the statements were; strongly agree, agree, neutral, disagree and strongly disagree [11].

The questionnaire for healthcare professionals working in the field of LLA asked for personal and professional characteristics and thereafter the questionnaire was the same as for participants with LLA.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 23.[a] Descriptive statistics are presented using means and standard deviations (SD) and nominal data as percentages and frequencies. The 15 items with the highest mean scores for participants with LLA were selected. The choice for 15 items was arbitrary. The mean rank scores of these 15 items were compared with the mean rank scores given by healthcare professionals for these items, using the Mann-Whitney U test with a Hochberg adjustment for α [13].

Participants with LLA were divided into six subgroups based on age (≤65 years vs. >65), gender (male/female), time since LLA (≤12 months vs. >12 months), level of amputation (above knee amputation (AKA) vs. below knee amputation (BKA)), reason of LLA (vascular vs. non-vascular aetiology) and unilateral vs. bilateral. For these subgroups the same statistical analysis was performed.

RESULTS

The overall response rate was 63% for participants with LLA (325 questionnaires distributed, 205 returned) and 67% for healthcare professionals (70 questionnaires distributed, 47 returned). In the group participants with LLA, 80 questionnaires were excluded due to various reasons. The majority of excluded questionnaires used the same ranking number multiple times, making ranking impossible. In the group healthcare professionals 3 questionnaires were excluded because of missing data. In total, data of 125 participants with LLA and 44 healthcare professionals were included (Table 1). The majority of participants with LLA were male (69%, n=86) and the mean age was 61.4 years. The majority of healthcare professionals worked as a rehabilitation specialist (n=21) with an average of 13.4 years of experience in the field of LLA. The characteristics of the participants with LLA who filled in the questionnaire incorrectly are presented in Appendix 2. Characteristics of participants with LLA who filled in the questionnaire correctly and incorrectly did not differ significantly.

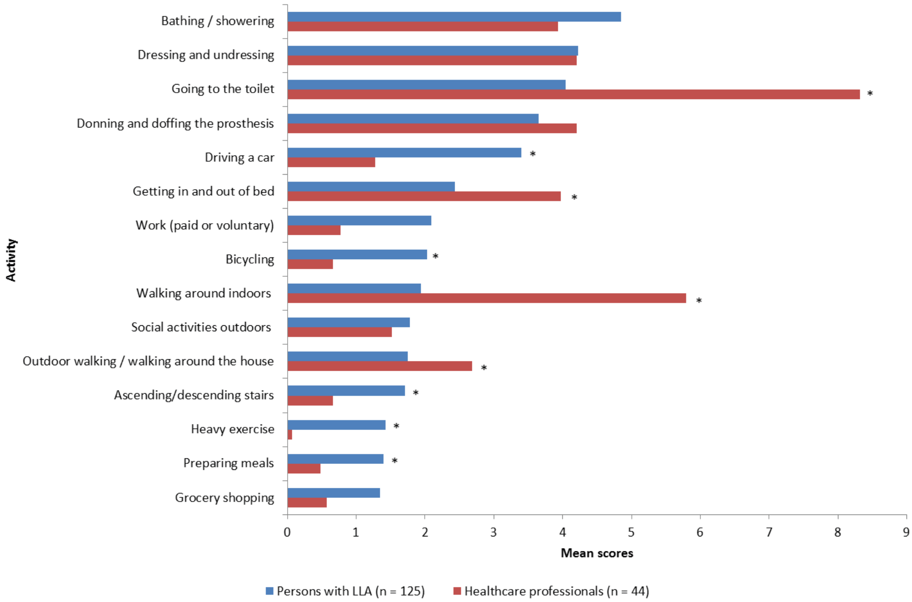
Table 1. Demographic characteristics of the included participants, mean ± SD

Characteristics participants with LLA (number of valid observations)		
	Men	86 (68.8)
Age (years) (n=125)		61.4 ± 13.7
Height (cm) (n = 123)		176 ± 10.7
Weight (kg) (n = 123)		78.5 ± 17.4
Smoking n (%) (n = 125)		17 (21)
Age at the time of LLA (months) (n=124)		204.0 ± 229.1
Wearing prosthesis (hours per day) (n=123)		12.6 ± 4.9
LLA level n (%) (n=124)		
Unilateral (n=114)	Transtibial	50 (40.3)
	Transfemoral	48 (38.7)
	Knee disarticulation	11 (8.8)
	Hip disarticulation	3 (2.4)
	Hemipelvectomy	1 (0.8)
	Syme	1 (0.8)
Bilateral (n=11)	Transtibial	6 (4.8)
	Transfemoral	2 (1.6)
	Knee disarticulation and transtibial	1 (0.8)
	Transtibial and transfemoral	1 (0.8)
	Transfemoral and forefoot	1 (0.8)
LLA aetiology n (%) (n=122)	Trauma	50 (41.0)
	Vascular diseases (with or without DM)	30 (24.6)
	Oncological	15 (12.1)
	Congenital malformation	4 (3.3)
	Infection	13 (10.7)
	Others	10 (8.2)
Characteristics healthcare professionals (number of valid observations)		
Gender (%) (n=44)	Men	23 (52.3)
Age (years) (n=43)		45.2 ± 9.8
Occupation n (%) (n=44)		
	Rehabilitation specialist	21 (47.7)
	Physiotherapist	8 (18.2)
	Occupational therapist	5 (11.4)
	Certified prosthetist/orthotist	8 (18.2)
	Other	2 (4.6)
Experience in the LLA field (years) (n=43)		13.4 ± 8.8

SD standard deviation

Participants with LLA rated 'driving a car', 'bicycling', 'ascending/descending stairs', 'heavy exercise' and 'preparing meals' significantly higher than professionals. Professionals rated the items 'going to the toilet', 'getting in and out of bed', 'walking around indoors' and 'outdoor walking/walking around the house' significantly higher than participants with LLA (Figure 1, Appendix 3). Additionally, 26 participants with LLA mentioned they missed a specific item. These items varied from 'ride through the forest with a wheelchair' to 'babysitting the grandchildren' to 'canoeing'. There were no similar items mentioned by multiple participants.

Figure 1. The 15 most important activities to perform independently from perspective of participants with LLA and healthcare professionals, ordered by highest rating by participants with LLA.



* indicates a significant difference between subgroups: p-value smaller than the Hochberg adjusted alpha.

The results of the 6 subgroups based on age, gender, time since LLA, level of amputation, reason of LLA and unilateral vs. bilateral LLA are presented in Appendix 4. In the subgroup analysis for age (Appendix 4a), the items 'work' and 'heavy exercise' are rated significantly higher by participants ≤65 years compared to participants >65 years. In the subgroup analysis for aetiology (Appendix 4e) participants with vascular aetiology rated 'going to the toilet', 'getting in and out of bed', 'walking around indoors', 'walk outside on even ground' and 'get in and out of a car' significantly higher than participants with other reasons for LLA. No significant differences were found in the other subgroups.

The results of the feasibility statements are presented in Appendix 5. The majority of the participants with LLA and healthcare professional agreed with the statements “the instructions prior the questionnaire made clear what was expected of me” and “the asked questions were easy to understand”. However, for the item “It was easy to choose the items that I found most important” both groups (strongly) disagree with this statement, respectively 65% and 57%.

DISCUSSION

The aim of this study was to objectify the most important ADL according to persons with LLA and compare them with the scores from healthcare professionals. The 5 most import items determined by participants with LLA were ‘bathing/showering’, ‘dressing/undressing’, ‘going to the toilet’, ‘donning and doffing your prosthesis’ and ‘driving a car’ (Fig 1). For 9 of the 15 most important items a significant difference was found between the 2 groups. Participants with LLA scored 5 activities higher compared to healthcare professionals; ‘driving a car’, ‘bicycling’, ‘ascending/descending stairs’, ‘heavy exercise’ and ‘preparing meals’. Healthcare professionals scored the activities ‘going to the toilet’, ‘getting in and out bed’, ‘walking around indoors’ and ‘walking around outdoors’ higher compared to participants with LLA. These substantial differences are remarkable, since the group of participants with LLA was heterogeneous regarding age, aetiology and level of amputation. From a clinical perspective, our findings indicate that healthcare professionals should question persons with a LLA prior to and during the rehabilitation process about the activities they find important to perform independently. If persons with a LLA have difficulties answering these questions a list of activities as shown in Appendix 1 may be helpful.

The statistical analysis performed was based on the top 15 according to participants with LLA, because the aim of the study was to compare the perspective of the participants with LLA with the healthcare professionals and not the other way around. The top 15 activities as scored by the healthcare professionals contained 9 similar items and 6 different items compared to participants with LLA.

In this study, the participants with LLA were representative for the Dutch amputee population regarding age, gender and level of amputation. However, considering aetiology for amputation, the participants with LLA due to trauma is relatively overrepresented compared to participants with LLA due to vascular disease and/or DM [6,7]. This distribution might influence the results because persons with a traumatic LLA are usually younger at time of amputation and have no/fewer co-morbidities. It is possible that ‘heavy exercise’ ended up in the overall top 15 due to the relatively large group of traumatic LLA, but it did not end up in the top 15 of the subgroup participants with a vascular LLA (Appendix 4e).

When looking at the different subgroups of participants with LLA (Appendix 4), the ranking of items and mean scores differs. For example 'bicycling' is higher prioritized by participants with BKA, ≤65 years or LLA>12 months compared to participants with an AKA, >65 years or LLA≤12 months. Additionally, bicycling is a typical Dutch activity. In the Dutch population, riding a bicycle and/or driving a car are the main means of transportation. Though in other countries, there can be other specific activities. Previous studies found, based on ICF model, that important concepts of walking and mobility are similar in different countries, with some specific activities based on culture or religion (e.g. praying positions and the use of motorised public transportation) [1,14].

In the subgroup analysis for age (Appendix 4a), the items 'work' and 'heavy exercise' are rated significantly higher by participants ≤65 years compared to participants >65 years. This difference can be explained by the fact that in the Netherlands persons retire from work around the age of 65. In the subgroup analysis for reason of amputation (Appendix 4e) participants with vascular aetiology rated 'going to the toilet', 'getting in and out of bed', 'walking around indoors', 'walk outside on even ground' and 'get in and out of a car' significantly higher than participants with other reasons for LLA. An explanation might be that persons with a vascular aetiology for LLA are usually elderly, have co-morbidities and have a lower physical capacity. Therefore, it is possible that basic ADL are intense (or difficult) enough.

No significant differences were found for the other subgroups, although in some figures the difference in mean scores seems substantial (e.g. the items 'ascending/descending stairs' and 'bicycling' in the subgroup unilateral vs. bilateral LLA (Appendix 4f)). This lack of significance can be explained by the small number of participants in a subgroup (n=11 participants with bilateral LLA) and the large SD's. This problem may also be the case in the figure time since LLA (Appendix 4c), with only 12 participants with LLA≤12 months. In this subgroup basic ADL is scored higher compared to participants with LLA>12 months, but not significant. This difference was expected, because the first goals after recent LLA are becoming independent for the basic ADL.

When analysing the results of the feasibility statements, both participants with LLA and healthcare professionals found it difficult to choose the 10 most important items and rank them. For participants with LLA with a high level of functioning, one of the explanations can be the fact that basic ADL such as dressing/undressing are taken for granted and they focus on more complex activities, where for less mobile participants the goals of basic ADL are already difficult enough. For healthcare professionals, a possible explanation for the experienced difficulty in selecting the 10 most important items can be that every person with LLA is unique in age, aetiology and level of amputation, living environment and personal preferences. Since no specific instructions were given, they possibly filled in the questionnaire with a specific subgroup of persons with LLA in mind.

One of the limitations of the study is the sample size and the aetiology distribution, which is not representative of the population persons with LLA in the Netherlands. Also, there can be a selection bias. Probably the more healthy, higher participating persons with LLA (younger age, traumatic aetiology) participated in the study. Additionally, it was difficult for both groups to choose only 10 items where more items could be of importance. Although the response rate was relatively high, multiple questionnaires where not completed correctly. One of the main reasons for exclusion was when the participant scored multiple items with the same number, possibly indicating that these items are perceived equally important. Consequently, these data could not be used in the statistical analysis. It might also be possible items were missing in the overview. However, because participants mentioned no items multiple times, this chance is low. Lastly, it could be that other participant characteristics are of importance, which were not included in this study.

Conclusion

A significant difference in rating importance was found for 9 out of 15 activities between persons with LLA and healthcare professionals.

This result highlights the importance of shared decision making and communication with the person with LLA in order to optimize their rehabilitation program. Healthcare professionals should carefully assess the personal importance of each activity when providing care, including prescribing a prosthesis, for persons with LLA.

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Supplier

a. SPSS Inc. 233 S Wacker Dr. 11th Fl. Chicago. IL 60606.

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APPENDICES

Appendix 1. The 40 items in the questionnaire.

ICF domains	Items
Self-care	Bathing/showering
	Dress and undress
	Donning and doffing your prosthesis
	Going to the toilet
	Treat your stump
	Treat your foot and nails
Mobility	Get in and out of bed
	Sit and get up (e.g. chair)
	Walk around indoors on an even ground
	Walk outside around the house
	Walk outside on an even ground
	Walk outside on an uneven ground (e.g. snow, ice, gravel, grass)
	Walk up and down a steep hill
	Walk up and down a few steps
	Walk up and down stairs
	Hop over an obstacle on the floor (e.g. doorsill)
	Keep walking/standing when people bump in to you
	Get up from the floor if you fall
	Get in and out of a car
	Walk on the streets and sidewalks
	Keep up with others when walking
	Walk while carrying an object, food or drinks
	Lift heavy objects (e.g. groceries)
	Pick up an object from the floor
	Travel with public transport
	Drive yourself
	Bike yourself
	Sexual functioning
Domestic life	Prepare meals (plan, prepare and serve a main course)
	Perform 'light' household tasks (e.g. washing dishes, making beds)
	Perform 'heavy' household tasks (e.g. mopping, cleaning windows and vacuuming)
	Grocery shopping
	Maintain your own house/garden/car
Major life areas	Hold a job (paid or voluntary)
Community and social life	Undertake social activities (e.g. visit clubs, church and friends)
	Go on trips (e.g. visit the zoo or museum)
	Use public services (e.g. town hall, the bank and hospital)
	Participate in relaxing activities (e.g. painting)
	Participate in moderate physical activities (e.g. riding a bike)
	Participate in heavy physical activities (e.g. running, lifting heavy objects)

Appendix 2. Demographic characteristics of the participants of the excluded questionnaires, mean ± SD.

	Men	45 (57.0)
Age (years) (n=79)		64.1 ± 14.1
Height (cm) (n = 79)		176 ± 10.4
Weight (kg) (n = 78)		80.5 ± 17.5
Unilateral (n=77)	Transtibial	46 (60)
	Transfemoral	27 (35)
	Knee disarticulation	2 (3)
	Hip disarticulation	2 (3)
Bilateral (n=3)	Transtibial	2 (67)
	Knee disarticulation and transtibial	1 (33)
LLA aetiology (%) (n=80)	Trauma	28 (35)
	Vascular diseases (with or without DM)	29 (36)
	Oncological	6 (8)
	Congenital malformation	1 (1)
	Infection	8 (10)
	Others	8 (10)

SD standard deviation

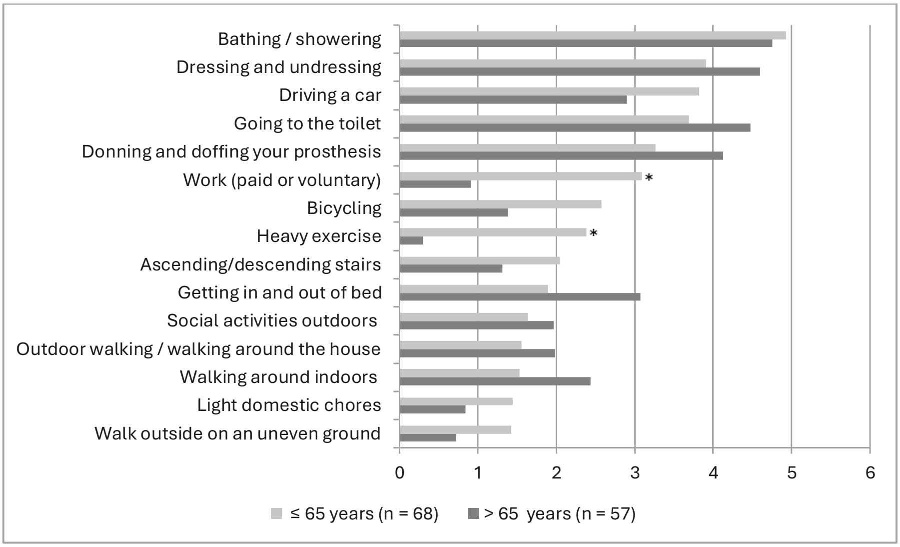
Appendix 3. The mean scores of the 15 most important activities to perform independently from perspective of persons with LLA compared to professionals.

	participants with LLA (n = 125)	**professionals (n = 44)**	**p**	**Hochberg adjusted alpha**
Bathing / showering	4.8	3.9	0.15	0.04
Dressing and undressing	4.2	4.2	0.87	0.05
Going to the toilet	4.0	8.3	<0.001*	0.003
Put the prosthesis on and off	3.7	2.4	0.31	0.043
Driving a car	3.4	1.3	<0.001*	0.007
Getting in and out of bed	2.4	4.0	0.03*	0.03
Work (paid or voluntary)	2.1	0.8	0.10	0.037
Bicycling	2.0	0.7	0.01*	0.013
Walking around indoors	1.9	5.8	<0.001*	0.01
Outdoor walking / walking around the house	1.8	2.7	0.02*	0.020
Social activities outdoors	1.8	1.5	0.70	0.047
Ascending/descending stairs	1.7	0.7	0.01*	0.017
Grocery shopping	1.4	0.6	0.07	0.033
Preparing meals	1.4	0.5	0.02*	0.023
Heavy exercise	1.4	0.1	0.03*	0.027

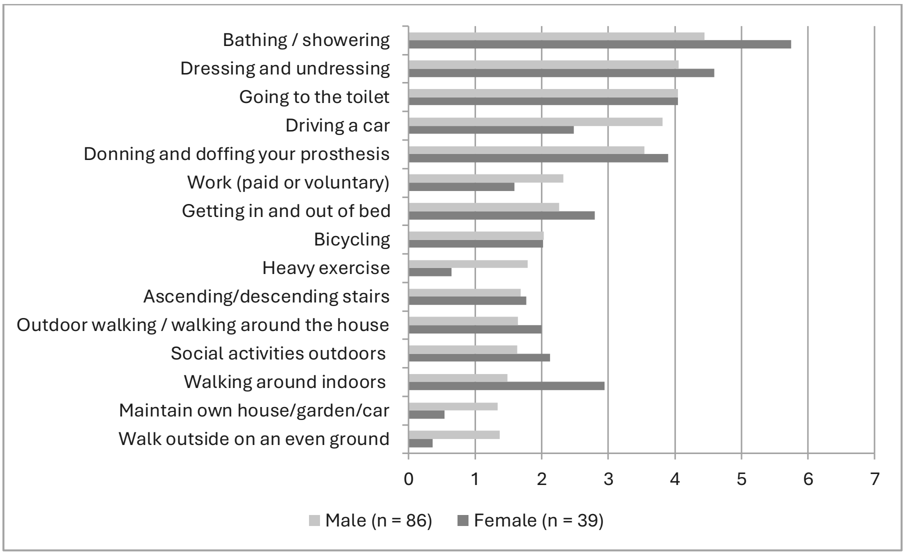
* indicates a significant difference between subgroups: p value smaller than the Hochberg adjusted alpha.

Appendix 4. Figures illustrating differences between of the subgroups of persons with a lower limb amputation.

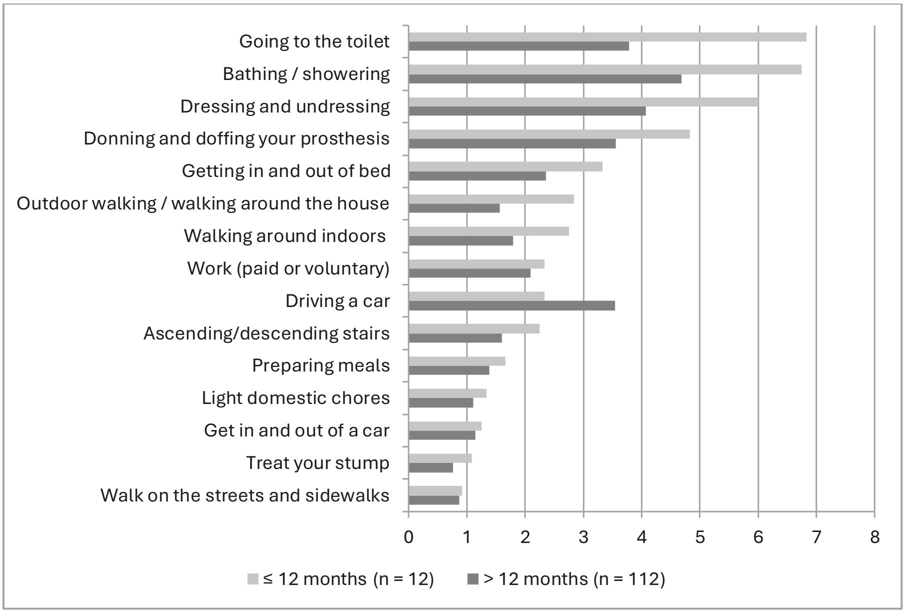
a. Participants ≤65 years vs. 65 years.



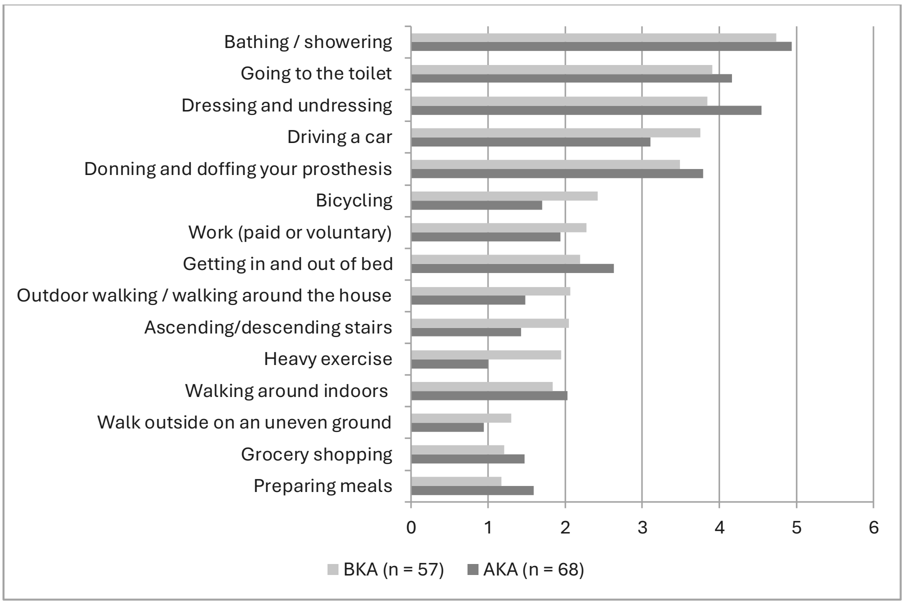
b. Male vs. female



c. Time since amputation: ≤ 12 months vs. > 12 months



d. Below knee amputation (BKA) vs. above knee amputation (AKA)



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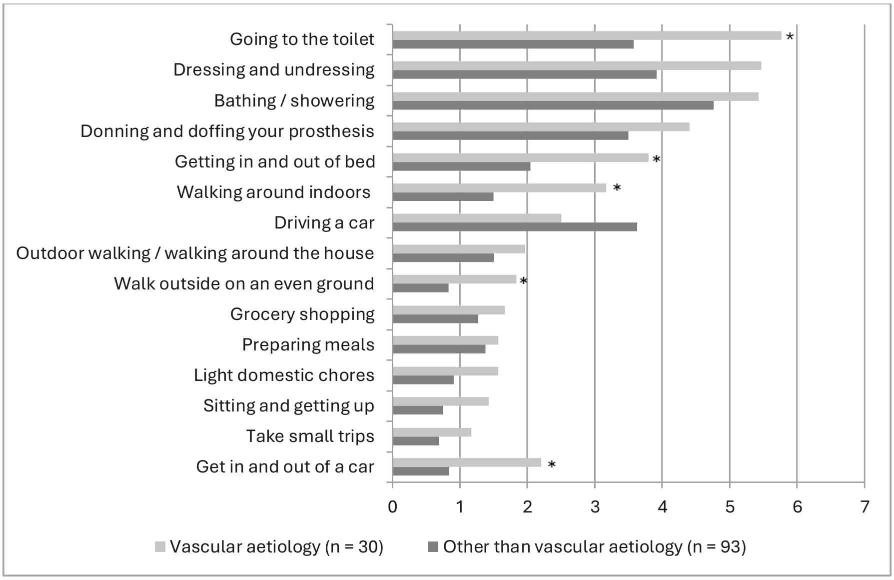
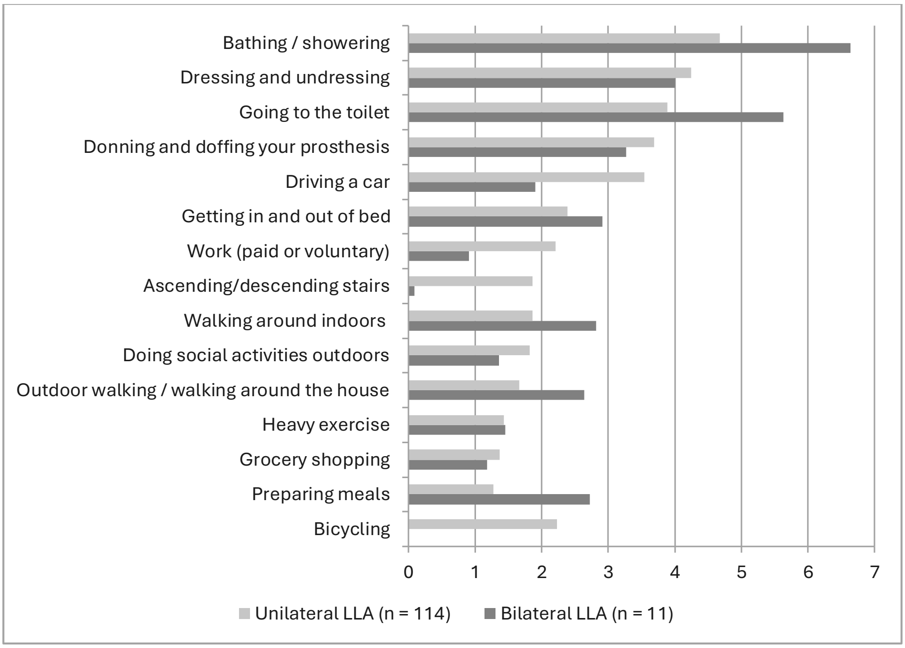
e. Reason of amputation; vascular vs. non- vascular aetiology



f. Unilateral LLA vs. bilateral LLA.



* Indicates a significant difference between subgroups: p value smaller than the Hochberg adjusted alpha.

Appendix 5. Feasibility scores of the questionnaires participants with LLA and professionals.

Statement		**Participants with LLA (n = 124)**	**Professionals (n = 44)**
"The instructions prior the questionnaire made clear what was expected of me" (%)	Strongly agree	39 (31.5)	25 (56.8)
	Agree	72 (58.1)	2 (4.5)
	Neutral	10 (8.1)	3 (6.8)
	Disagree	3 (2.4)	2 (4.5)
	Strongly disagree	0	
"It was easy to distinguish the items in the overview" (%)	Strongly agree	57 (46.7)	21 (47.7)
	Agree	32 (26.2)	8 (18.2)
	Neutral	11 (9.0)	9 (20.5)
	Disagree	5 (4.1)	2 (4.5)
	Strongly disagree		
"It was easy to choose the items that I found most important" (%)	Strongly agree	3 (2.4)	1 (2.3)
	Agree	13 (10.6)	10 (22.7)
	Neutral	27 (22.0)	8 (18.2)
	Disagree	52 (42.3)	20 (45.5)
	Strongly disagree	28 (22.8)	5 (11.4)
"The asked questions were easy to understand" (%)	Strongly agree	42 (33.9)	17 (39.5)
	Agree	64 (51.6)	23 (53.5)
	Neutral	14 (11.3)	2 (4.7)
	Disagree	4 (3.2)	1 (2.3)
	Strongly disagree	0	0

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Chapter 4

Cardiorespiratory fitness in persons with lower limb amputation

Loeke van Schaik, Ilse J. Blokland, Klaske van Kammen, Han Houdijk, Jan H.B. Geertzen, Rienk Dekker

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ABSTRACT

The aim of this study is to gain insight in the cardiorespiratory fitness of persons with lower limb amputation (LLA) during rehabilitation, and in potential factors influencing their cardiorespiratory fitness. We performed a retrospective cohort study using data from cardiopulmonary exercise tests. Included participants were adults with LLA. Main outcome was cardiorespiratory fitness expressed as $\dot{V}O_2$peak (ml/min/kg) and was directly determined using breath-by-breath gas analysis. $\dot{V}O_2$peak was compared to reference values for able-bodied controls. Multivariate regression analysis was performed to investigate potential factors related to $\dot{V}O_2$peak in persons with LLA. Potential factors were age, BMI adjusted, gender, level of amputation, aetiology of amputation, unilateral/bilateral, type of ergometry and use of beta blockers. Data of 74 participants with LLA are presented; 84% male (n=62), mean age 58.9 (SD 11.6), mean BMI 26.7 (SD 5.6), 44 participants have a LLA above the knee, 30 below the knee. Overall $\dot{V}O_2$peak was lower in persons with LLA compared to reference values for able-bodied controls, with mean $\dot{V}O_2$peak for the total LLA group of 14.6±4.1 ml/kg/min. In the multivariate regression analysis, only age was a significant predictor for lower $\dot{V}O_2$peak (Regression Coefficient: -0.15, 95%CI [0.23, 0.069], r^2=0.166). These results indicate that the cardiorespiratory fitness in persons with LLA is low, while they actually need more energy to walk and perform other daily activities. Cardiorespiratory fitness is not closely associated with the analysed demographic or clinical factors and will have to be determined on an individual basis for use in daily practice.

Keywords: lower limb amputation, cardiorespiratory fitness, rehabilitation, physical fitness, cardiopulmonary exercise test

INTRODUCTION

To better engage persons with lower limb amputation (LLA) in their rehabilitation process, it is important to have insight into their individual physical capabilities. In the Netherlands there are different discharge destinations for persons after LLA, namely home, nursing home or rehabilitation center[1]. This choice is made, among other things, on the basis of the pre-existent level of physical functioning. In general, older people with LLA, who have often been inactive for a long time, go to a nursing home for rehabilitation. The persons who were more mobile before LLA usually undergo clinical or outpatient rehabilitation in a rehabilitation center. It is of particular interest to evaluate the individual physical capabilities of persons with LLA who are referred to a rehabilitation center as there is evidence that persons with LLA who have higher levels of physical fitness are more likely to gain ability to walk with a prosthesis[2–4]. Insight into maximum cardiorespiratory fitness (CRF) can therefore be helpful to identify persons with below average physical fitness and compose better rehabilitation programs to train and improve CRF. Improved CRF can enable persons with LLA to reach their individual rehabilitation goals, improve walking abilities, improve independence and quality of life[2,5–7]. Knowledge about individual CRF can also be used to discuss, guide and manage expectations from the perspective of both the person with LLA and the professional[8–10].

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Cardiopulmonary exercise tests (CPETs) are used to reliably determine a person's maximum CRF, expressed as maximum oxygen uptake ($\dot{V}O_2$peak). In the general population, reference values for $\dot{V}O_2$peak are available, classified by gender and age[11–13]. It is known that the CRF decreases with increasing age and that men have higher levels of CRF compared to women[14]. In persons with LLA, limited studies are available on CRF. The reported CRF in persons with LLA is lower compared to those of able-bodied controls[14–18]. It should be noted that in some of these studies the CRF is not directly measured using breath-by-breath gas analysis, but an estimation is made based on submaximal tests or heart rate and therefore have limited reliability[18,19].

Different types of ergometers are used in LLA studies; arm-crank ergometer, one leg ergometer or combined arm-leg ergometer[17,20–22]. In able-bodied individuals lower cardiorespiratory values are reported using arm-crack ergometry vs. leg ergometry, due to the limited muscle mass engaged in arm ergometry which causes reduced stress on the cardiovascular system[23]. However, in persons with LLA, a recent study compared $\dot{V}O_2$peak measured with arm-crank ergometer vs. one leg ergometry and found no difference in $\dot{V}O_2$peak values[21]. This outcome can probably be explained by the fact that the muscle mass of one leg is equal to that of two arms. Furthermore, lower values are reported for one leg ergometry vs. two leg ergometry in persons with

LLA[22]. These findings suggests that both ergometers can be used to assess $\dot{V}O_2$peak in persons with LLA, but research is needed to confirm that the type of ergometer does not influence the measured $\dot{V}O_2$peak values.

As mentioned above, only a few studies reported on CRF in persons with LLA. The main limitations of these studies are the small sample size and the inclusion of participants with LLA due to nonvascular reasons[17,21]. Because the majority of persons have a LLA due to peripheral vascular disease, these results are not representative of the entire population of persons with LLA[24]. In general, persons with cardiovascular comorbidities are more likely to have lower CRF[15,25]. Therefore, it is hypothesized that the CRF values in the vascular LLA group are even lower compared to the reported values in persons with LLA due to nonvascular reasons. Given the comorbidity and deconditioning in persons with vascular LLA, it is even more important to gain knowledge about their CRF.

Therefore, the aim of this study is to provide insight in the CRF in persons with LLA during rehabilitation, regardless of the level or cause for LLA. Additionally, the aim is to analyse which factors (age, BMI adjusted, gender, level of amputation, aetiology of amputation, unilateral/bilateral, type of ergometry and use of beta blockers may predict the level of CRF.

METHODS

Participants

This study included adults (≥18 years) with LLA who were referred for CPET as part of their rehabilitation process at the Rehabilitation Center of Heliomare between January 2018 and November 2022. For this retrospective study, data was used from the CPET-database of Heliomare. Inclusion of the participants was according to the American College of Sports Medicine criteria[26]. The CPET-database was reviewed by the medical ethical committee of Vrije Universiteit Medical Centre Amsterdam and approved by the local ethical committee of Heliomare. Informed consent was gained from the participants with LLA. Participants were selected based on ICD codes. When the same participant performed more than one CPET, for example for test-retest purpose, data of the first CPET was selected.

Data collection

The following descriptive data was collected from the database: age, gender, BMI, amputation level, aetiology of amputation, date of amputation, use of beta-blockers and type of ergometry. BMI was determined using the adjusted body weight, calculated as described previously [27,28].

Cardiopulmonary exercise test measurements

The CPET was performed with an arm ergometer or a cycle ergometer[22], under supervision of a certified clinical exercise physiologist and/or physician. The protocol depended on the type of ergometer. For the arm ergometer it was a ramp protocol, for the one-legged ergometer a block protocol. After a 3-minute rest and 3-minute warm up (0 Watt), the physician determined the protocol based on the estimated maximum CRF, as previously described[18,29]. The test ended if the participant could not maintain a cycle pace >50 revolutions per minute, or if the physician had another reason to stop. Afterwards, 3-minute cooling down followed. Breath-by-breath gas exchange, ECG and oxygen saturation were continuously monitored.

Specific outcomes of the CPET recorded in the database include: peak oxygen uptake ($\dot{V}O_2$peak) (ml/kg/min) (the maximum of the 30 second averaged $\dot{V}O_2$ was considered $\dot{V}O_2$peak), peak respiratory exchange ratio (RER) during exercise phase of the test, peak heart rate (HR) (beats/min), and peak power (Watts).

$\dot{V}O_2$peak is the highest level of oxygen uptake attained during the CPET for that person, regardless of reason for test termination. Note that although other literature may refer to this variable as $\dot{V}O_2$max[16,30–32], in persons with LLA (but also in other patient groups) it is possible the maximum effort is limited due to others reasons than the capacity for oxygen uptake, for example balance problems or musculoskeletal pain. Hence for this study the term '$\dot{V}O_2$peak' is used.

The $\dot{V}O_2$peak-value was considered valid when the participant reached a RER>1.1 or HR>85% predicted maximal HR. This is conform daily practice following American College of Sports Medicine criteria[23].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 28. P-values <0.05 were considered significant.

Participant characteristics were presented with mean and standard deviation (SD), median and range or frequencies and percentages in case of nominal data.

The CPET outcomes $\dot{V}O_2$peak (ml/kg/min), RER peak, peak HR (beats/min), and peak power (Watts) were presented with mean and SD.

Individual $\dot{V}O_2$peak values were presented based on age and gender. Because in the general population CRF depends on age and gender, we continue to use this subdivision in the figures.

Multivariate regression analysis

Multivariate regression analysis was performed to predict $\dot{V}O_2$peak in participants with LLA. Factors that were analysed as potential predictors were age, BMI adjusted, gender, level of amputation, aetiology of amputation, unilateral/bilateral, type of ergometry and use of beta blockers. The variable 'aetiology of amputation' was categorized in two groups: vascular/diabetes mellitus (DM) vs. other (e.g. trauma/oncological/infection). Level of amputation was categorized in two groups: below the knee (BK) (Syme or transtibial) vs. levels above the knee (AK) (knee disarticulation, transfemoral or hip disarticulation).

First, an exploratory analysis was performed to determine which independent variables were associated with $\dot{V}O_2$peak. Because on group level the $\dot{V}O_2$peak was not normally distributed, non-parametric testing (Mann Whitney U-test or Spearman Rho) was used. All factors showing an association, as defined by $P<0.20$, were selected for further analysis.

Subsequently, if the association between two factors was biologically plausible, we performed a Pearson Chi-Square test of association and, if significant, avoid the collinearity between the two factors by only entering the variable with the strongest association in the regression analysis.

Finally, to determine predictive value, the selected factors were entered in a multivariate linear regression analysis following a backward stepwise procedure. Factors with the highest p-values were removed until all remaining factors were significant ($p\leq0.05$). Given the non-normal distribution of $\dot{V}O_2$peak, the regression analysis was checked with a bootstrapping procedure. In case of no difference, the original confidence intervals were presented. Otherwise, robust estimates were presented.

RESULTS

Data of 79 participants was available. One participant performed the CPET from a wheelchair and was excluded. CPET results of four individuals were excluded for not reaching maximal effort (RER<1.1 and predicted HR<85%), which was due to musculoskeletal pain. None of the participants had to stop the CPET due to cardiovascular events. No obvious ECG abnormalities or drops in blood pressure were observed. Descriptive statistics are presented in Table 1. Comorbidity is based on reporting in the referral letter or CPET form.

Table 1. Descriptive characteristics participants

		Mean (SD) or number (% (range))
Gender (male)[a]		62 (84%)
Age (years)[a]		58.9 (11.6) (range 25-79)
BMI*[a]		26.7 (5.6) (range 17.1-43.3)
Level of amputation [a]	Below knee amputation	44 (59.5%)
	Above knee amputation	30 (40.5%)
Aetiology of amputation [b]	Vascular/DM	47 (63.5%)
	Other total	24 (32.4%)
	- Trauma	6
	- Oncology	5
	- Infection	7
	Other	6
Unilateral vs. bilateral [a]	Unilateral	69 (93.2%)
	Bilateral	5 (6.8%)
Type of ergometer [a]	Arm ergometer	45 (61%)
	One leg cycle ergometer	29 (39%)
Comorbidity[b]	Vascular disease	44
	Diabetes mellitus	23
	Hypertension	10
	COPD	4
	Polyneuropathy	3
	Cerebrovascular accident	3
Use of beta blockers [c]	Yes	17 (23.0%)
	No	51 (68.9%)
Time since amputation in months**[a]		1.4 (0.4-452.0)***

SD standard deviation; * [a] n = 74; [b] n=71; [c] n = 68; BMI was calculated with the adjusted weight value[27]; **At the time of the cardiopulmonary exercise test (CPET); *** Median (range) instead of Mean (SD)

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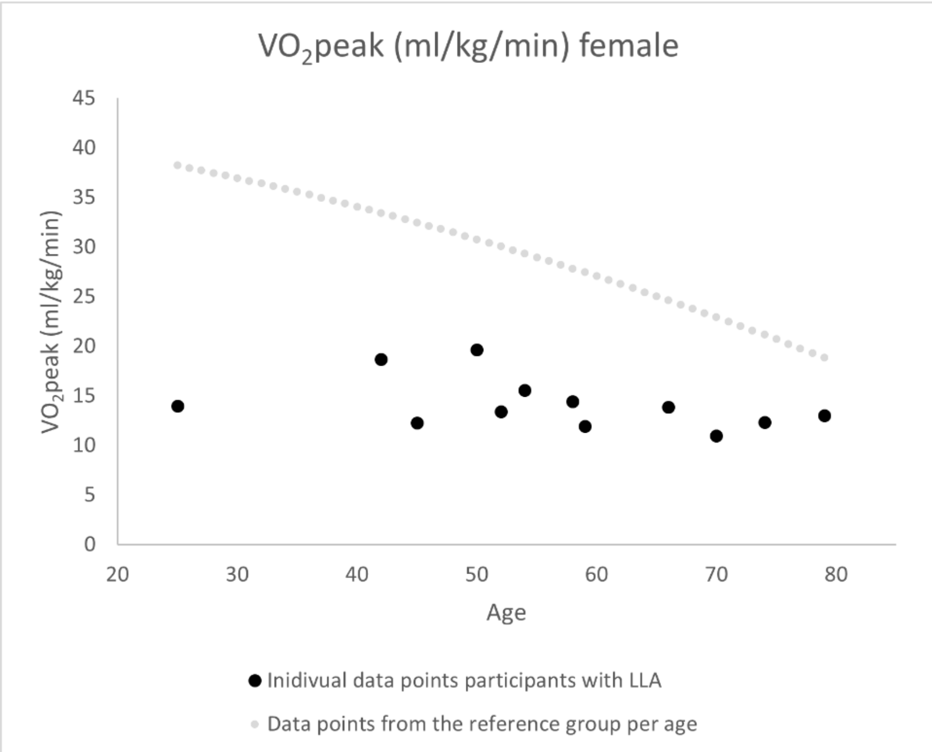
Cardiopulmonary exercise test

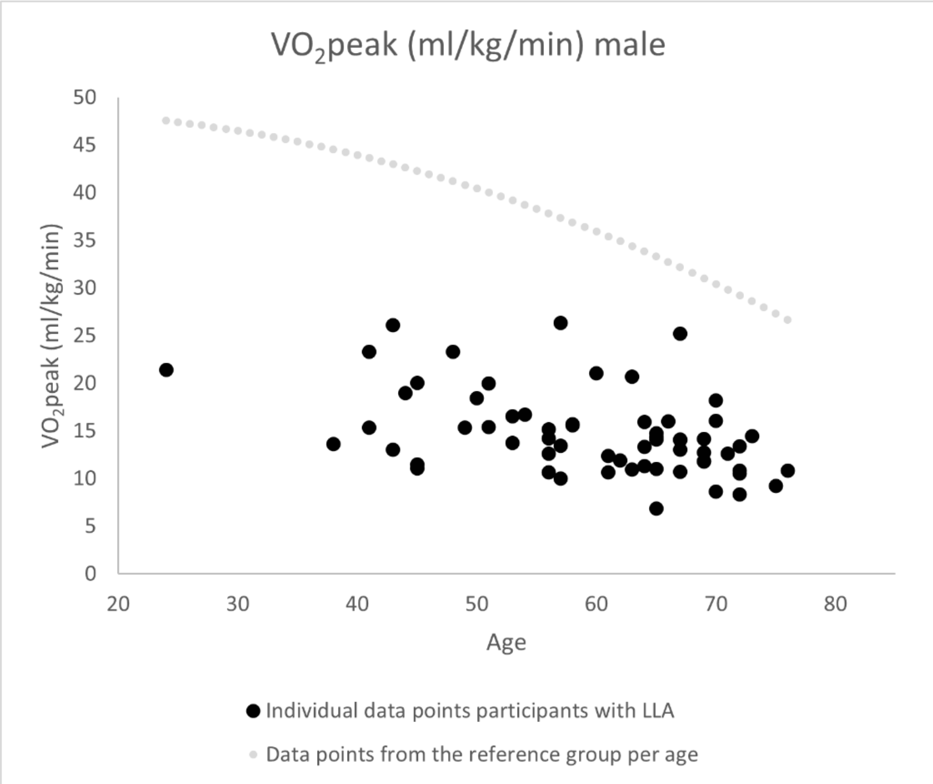
Descriptive CPET data for the 74 participants with LLA are presented in Table 2. Mean $\dot{V}O_2$peak was 14.6±4.1 ml/kg/min. In Figure 1a and Figure 1b the individual $\dot{V}O_2$peak data points for female and male participants respectively are presented as a function of age along with the reference based on data for able-bodied controls in the Dutch/Flemish population[13]. In male participants mean $\dot{V}O_2$peak was 14.6 (±4.4) ml/kg/min, with a mean age of 59.5 (±11.6) years. In the age-matched reference group, males had a reported $\dot{V}O_2$peak of 38.5 (±9.0)[13]. Female participants had a mean $\dot{V}O_2$peak of 14.1 (±2.6) ml/kg/min, with a mean age of 56.2 (±10.9). In age-matched reference group, reported mean $\dot{V}O_2$max was 29.5 (±7.8) [13].

Figure 1 a. VO_2peak in females; individual data points participants and reference line able bodied



VO_2peak in females; individual data points participants and reference line able-bodied[13].

Figure 1 b. $\dot{V}O_2$peak in males; individual data points participants and reference line able bodied



VO_2peak in males, the individual data points participants and reference line able-bodied[13].

Table 2. Descriptive results of the cardiorespiratory exercise test

	Mean ± SD	**Range**
$\dot{V}O_2$peak (ml/kg/min) [a]	14.6 ± 4.1	6.8-26.3
RER peak [a]	1.2 ± 0.1	1.03-1.59
Peak heart rate (beats/min) [b]	137.5 ± 27.2	80.0-194.0
Peak heart rate (%pred) [b]	0.87 ± 0.2	0.54-1.27
Peak power (Watts)[a]	71.1 ± 31.7	18.0-170.0

SD standard deviation; [a] n = 74; [b] n = 73

Multivariate linear regression

Test-values and p-values per factor are presented in Table 3. Factors used in the multivariate linear regression analysis were age, BMI adjusted, aetiology of amputation and use of beta blockers ($p<0.20$). Because of the potential association between aetiology of amputation and the use of beta blockers, a Pearson Chi-square analysis was performed but it was not significant (χ^2=2.920, p=0.087). Hence both factors were included in the regression analysis.

Table 3. The test-values and p-values for the possible predictors for $\dot{V}O_2$peak

	Test-values	p-value
Age	-0.465 ^{A}	<0.001*
BMI adjusted	-0.192 ^{A}	0.101**
Gender	389.0 ^{B}	0.943
Unilateral vs. bilateral	154 ^{B}	0.622
Aetiology of amputation	780 ^{B}	0.024*
Level of amputation	806 ^{B}	0.218
Use of betablockers	590 ^{B}	0.056**
Kind of ergometry	691 ^{B}	0.992

^{A} Spearman rho; ^{B} Mann Whitney-U test * p<0.05, **p<0.20

The final model (Table 4) indicates that the only significant predictor was age, showing that increased age is associated with lower predicted $\dot{V}O_2$peak. The regression coefficient for age was -0.15, meaning that with every 10 years increment in age, $\dot{V}O_2$peak decreased by 1.5ml/kg/min. The explained variance of the final model was 17% (average r^2=0.166).

Table 4. Multivariate linear regression analysis results

Predictor	Regression coefficient	Std. Error	P Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Intercept	23.32	2.34	<.001	18.64	28.00
Age	-.15	.04	<.001	-.23	-.069

DISCUSSION

This study aimed to determine the peak CRF ($\dot{V}O_2$peak) of persons with LLA during clinical our outpatient rehabilitation in a representative center in the Netherlands. Our results showed that in general, the $\dot{V}O_2$peak in the included participants with LLA is lower compared to reference values for the able-bodied population, and that age was the only significant predictor for $\dot{V}O_2$peak in the included participants with LLA.

Our results in both male and female participants (Table 2) were more than 50% lower than the respective age-matched normative values[12,13]. Overall, they were also lower on average than the previously reported $\dot{V}O_2$peak values in persons with non-vascular LLA of 28.1 (6.7) ml/kg/min [18,19,33] and close to the values reported for vascular LLA of 17.1 (4.1) ml/kg/min[19]. Despite the heterogeneity in participant characteristics, there was no single participant in this study exceeded the reference line of able-bodied controls (Fig. 1a/ 1b), possibly due to deconditioning, comorbidities and changed body composition with the loss of (a part of) the leg.

Additionally, previous studies report that walking with a prosthesis requires more energy than walking for able-bodied[34]. The combination of higher energy costs in walking and the reduced CRF makes that persons with LLA use a much larger part of their physical capacity which influences self-selected walking speed but also affect participation and quality of life[34,35].

The multiple regression analysis only revealed age as a significant predictor for CRF. In our sample, older age was correlated with lower CRF, which is also seen in the able-bodied population[14]. In the able-bodied population, males show higher $\dot{V}O_2$max values compared to females[13]. In our sample, however, gender was not found as a significant predictor for $\dot{V}O_2$peak. This finding can be explained by the limited number of female participants(n=12). Moreover, the hypothesis was that the $\dot{V}O_2$peak values for the vascular LLA group would be lower compared to the LLA group with other causes. We did not find this, probably due to the heterogeneity in participant characteristics (for example level of LLA) and the small sample size, with a relatively small number of non-vascular LLA. The explained variance of the final model was 17%, which supports the suggestion that due to the small sizes of the subgroups, the data are too heterogeneous to obtain a well-fitted model.

In the general LLA population in the Netherlands, mean age is 74.2 years and more than 90% of the LLA is due to vascular/DM reasons[24,36]. Therefore, although there were no specific inclusion criteria, this study sample is not quite representative of the general LLA population in the Netherlands. This is probably due to the fact the CPETs took place in a rehabilitation centre meaning there is a selection bias because in the Netherlands not everyone with LLA is referred to a rehabilitation centre. The majority of elderly with LLA, often with more comorbidities, are admitted to a nursing home for their rehabilitation[37] as mentioned before in the introduction. Possibly the current data is still an overestimate of $\dot{V}O_2$peak in the entire population of individuals with LLA.

In this study, participants were tested on an arm ergometer or on a one-leg cycle ergometer, group sizes respectively 44 and 30. Our results showed no significant association between type of ergometry and $\dot{V}O_2$peak(Table 3). Given these findings, both types of ergometer could be considered appropriate for determining the $\dot{V}O_2$peak in individuals with LLA. In able-bodied, there is a difference in $\dot{V}O_2$peak values depending on type of ergometer[23]. However, our findings are consistent with previous findings using arm ergometry vs. one leg ergometry in persons with LLA[21] and values reported in persons after knee surgery[38]. The CPET ergometer can be selected according to the capabilities or preference of individuals with LLA.

All participants were able to perform the CPET without complications. Despite the variety of comorbidities, none of the participants had to stop the test due to any serious (cardiorespiratory) events. Only four participants did not reach the required RER or >85% predictive HR for a valid test, all due to musculoskeletal pain. Therefore, when following the American College of Sports Medicine inclusion guidelines, a CPET can be safely performed in persons with LLA regardless of cardiovascular comorbidities.

Strength and limitations

To our knowledge, this is the largest study that examined CRF in persons with LLA using breath-by-breath gas analysis during CPET. Although some CPET data used here were previously reported [18], this was done to increase the sample size for examining several plausible predictors. Although 74 participants is a decent sample size in amputation research, the main difficulty remains the heterogeneity. To analyse specific predictors such as gender or aetiology of LLA, which are theoretically likely predictors for CRF, a larger sample size for these subgroups is required. Another strength is that in this study, $\dot{V}O_2$peak was directly determined using breath-by-breath gas analysis during a CPET. This is in contrast to some other studies in which CRF was predicted based on HR or submaximal testing [20]. Furthermore, as mentioned before, the measurements took place in a rehabilitation centre, therefore the reported $\dot{V}O_2$peak is not necessarily generalizable for the total LLA population.

Conclusion

Cardiorespiratory fitness ($\dot{V}O_2$peak) in participants with LLA in a rehabilitation setting (clinical or outpatient) is low compared to the reference values reported for age and gender matched able-bodied controls. Higher age is associated with lower $\dot{V}O_2$peak in persons with LLA. To gain more insight into other potential predictors and establish reference values for persons with LLA, more data is needed to be able to compare larger subgroups. CPET for determining CRF in persons with LLA is feasible and it would be recommended to include CPET as a standard test during rehabilitation in order to evaluate individual CRF to better organize the rehabilitation program with regard to fitness training.

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5

Chapter 5

Relative aerobic load of daily activities in individuals with lower limb amputation; a pilot study

Loeke van Schaik, Klaske van Kammen, Saskia W.M. Huiberts, Jan H.B. Geertzen, Han Houdijk, Rienk Dekker

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ABSTRACT

BACKGROUND: Individuals with lower limb amputation (LLA) often experience reduced physical capacity and increased aerobic demands during activities of daily living (ADL), which may impact participation and quality of life. Measuring the relative aerobic load of ADL is essential to set realistic rehabilitation goals, however data on short and non-steady-state ADL tasks in this population are limited.

OBJECTIVE(S): This pilot study aimed to evaluate the feasibility of a newly developed protocol for assessing the relative aerobic load of five selected ADL tasks in individuals with LLA, and to determine the applicability of the excess post-exercise oxygen consumption (EPOC) method for these measurements.

METHODOLOGY: Six participants with unilateral LLA (mean age 58.8 ± 9.0 years; five males, one female), including three with transtibial, one with knee disarticulation, and two with transfemoral amputation, all classified as K2–K3 ambulators, completed a cardiopulmonary exercise test (CPET) during the first assessment session. During the second assessment session, within a two-week interval, they performed five standardized tests reflecting ADL tasks: the 6-Minute Walk Test (6MWT), Timed Up and Go Test (TUGT), Glittre ADL test, stair ascent, and stair descent, while Oxygen consumption was measured using the COSMED K5 system. For each task, average oxygen consumption was computed as the total oxygen uptake during activity and recovery (EPOC) divided by total time, and relative aerobic load was defined as percentage of first ventilatory threshold (%$\dot{V}O_2$-VT1). Data analysis involved descriptive feasibility assessment and intraclass correlation to examine consistency of relative aerobic load across tasks.

FINDINGS: The protocol showed to be feasible and no (serious) adverse events occurred during the study and 5 out of 6 participants were able to complete the protocol, demonstrating its practicality. The EPOC method was successfully applied to both short and longer-duration ADL tasks. The results showed relative aerobic loads exceeding 100% $\dot{V}O_2$-VT1 for most ADL tasks, indicating substantial physical effort. Agreement of the rankings of the different tasks between participants was observed (intraclass correlation = 0.73, 95%Confidence interval = 0.01-0.97) , although the wide confidence interval indicates considerable uncertainty.

CONCLUSION: This protocol enables the assessment of relative aerobic load in a heterogeneous group of individuals with LLA and highlights the importance of individual assessment. Given the large variability in $\dot{V}O_2$peak and $\dot{V}O_2$-VT_1 between participants, a generic level of physiological burden for each task cannot be given, instead individualized assessment is crucial to accurately determine physiological burden and avoid under- or overestimation of exercise intensity. The findings support the development of personalized rehabilitation programs tailored to individual capabilities and limitations, potentially improving participation and quality of life. Additionally, future studies with larger cohorts are needed to provide more robust reliability estimates and strengthen the generalizability of these findings.

Keywords:

Relative aerobic load, lower limb amputation, activities of daily living, first ventilatory threshold.

INTRODUCTION

Participation in societal activities requires a certain level of physical capacity to perform activities of daily living (ADL). Individuals with lower limb amputation (LLA) typically exhibit reduced physical capacity compared to able-bodied controls [1,2] and walking with a prosthesis requires more energy, resulting in a higher relative aerobic load [3–5]. A higher relative aerobic load indicates that an activity demands a greater proportion of a person's aerobic capacity, which may lead to increased fatigue and reduced tolerance for sustained activity. This elevated aerobic load is likely not limited to walking alone, but may also apply to other ADL. Consequently, individuals with LLA may experience increased fatigue, perform at a slower walking pace [6–11], or avoid certain activities altogether, which can negatively impact their ability to perform ADL, their quality of life [12,13] and their societal participation [14,15]. To set realistic rehabilitation goals for individuals with LLA, it is essential to understand the relative aerobic load for various ADL tasks in relation to the individual physical capacity. During a cardiopulmonary exercise test (CPET), peak oxygen uptake ($\dot{V}O_2$peak) can be assessed as an indicator of maximum aerobic capacity [16]. Additionally, oxygen uptake at the first ventilatory threshold ($\dot{V}O_2$-VT1) can be determined as an indication of anaerobic threshold [16]. Previous studies in other populations suggest that ADL with oxygen consumption level below the $\dot{V}O_2$-VT1 can be sustained for longer durations. The relative aerobic load (i.e. the aerobic load as percentage of $\dot{V}O_2$-VT1) can be used to express the degree of effort required per activity[17,18].

While ADL tasks such as stair climbing and meal preparation are important for individuals with LLA [19] the relative aerobic load associated with these activities is largely unexplored, leaving a significant gap in current knowledge. A recent study found that individuals with LLA (21 participants: 14 transtibial and 7 transfemoral) exhibited a higher relative peak oxygen uptake (%$\dot{V}O_2$peak) during in-house walking compared to able-bodied controls (n = 12)[20]. However, the study primarily included high-functioning participants, limiting generalizability. Moreover, data on short-duration ADL beyond walking are lacking, possibly due to methodological challenges in assessing non-steady-state activities. These include ADL tasks such as stair climbing, meal preparation, as well as brief movements like standing up to retrieve an item, carrying something away, or opening a door.

In an effort to address the methodological challenges, the excess post-exercise oxygen consumption (EPOC) method was recently developed and applied in individuals post-stroke [18], offering a way to measure the relative aerobic load of short-duration ADL. This method is capable of measuring the relative aerobic load of short ADL in individuals post-stroke. However, there is currently no standardized protocol to investigate the relative aerobic load in individuals with LLA. The LLA population is highly diverse in terms of general fitness and comorbidity, with comorbid conditions themselves further influencing physical capacity. Given the heterogeneity of the LLA population in the Netherlands, where most people are older adults with multiple comorbidities [21], it is crucial to select ADL tasks that are representative of this group's functional capabilities. However, standardized protocols to evaluate the relative aerobic load of these tasks in this population are lacking.

The aim of this pilot study was to assess the developed protocol based on various criteria related to operability and logistics, as well as its suitability in terms of intensity, ensuring that individuals with LLA can effectively perform and complete the selected ADL. Additionally, the study assessed whether the EPOC method can be effectively applied to determine the relative aerobic load of five different ADL tasks, both short and longer in duration.

METHODOLOGY

This pilot study had an observational design. Informed consent was obtained from each participant prior to testing. The Medical Ethical Committee of the University Medical Centre Groningen (UMCG) has approved this study (METc nr:NL2018000572). This study was performed in accordance with the Declaration of Helsinki [22].

Participants

Six individuals with LLA participated in this study. Participants were recruited through flyers distributed in (the waiting rooms at) the orthopedic center in Haren, the orthopedic center of Roessingh (Enschede), and at the amputation rehabilitation unit at the UMCG Centre for Rehabilitation, location Beatrixoord. Interested people could contacted the researchers (LvS/SH) directly. Recruitment took place from late October 2023 until early February 2024. It is unknown how many individuals took a flyer, but all people who contacted the researchers met the inclusion criteria. The study protocol was designed for six participants; however, when one participant withdrew due to illness, a seventh person was recruited as a replacement. After six participants were successfully included and completed the study, recruitment was closed. Inclusion criteria were: (**1**) Participants had undergone unilateral LLA (transtibial, knee disarticulation or transfemoral) over one year prior to participation, (**2**) the causes of LLA to be either vascular, trauma, infection or cancer, (**3**) participants using their own prosthesis for daily functioning and (**4**) had an activity level of K2 (ability to traverse low-level environmental barriers) or K3 (ability for ambulation with variable cadence). Participants were excluded if: **(1)** were not eligible to perform CPET according to the American College of Sports Medicine guidelines [23], (**2**) suffered from severe psychiatric illness, or **(3)** had residual limb problems that limited prosthesis use at the time of inclusion. The researcher (LvS) discussed contraindications for CPET (e.g., recent cardiovascular event, acute pulmonary embolism, systolic blood pressure >200 mmHg or diastolic >120 mmHg) with participants when they expressed interest in joining the study. This was done in accordance with the existing protocol implemented as standard care for screening individuals prior to CPET at UMCG Centre for Rehabilitation, location Beatrixoord.

Five selected ADL tasks

The ADL tasks in this study were chosen based on two criteria: **(1)** standardized tests commonly used in LLA rehabilitation programs and **(2)** priorities identified by individuals with LLA in a previous questionnaire study [19].

The selected tests represent key domains of daily functioning, including standing up and walking short distances, walking longer distances, ascending and descending stairs, and performing complex functional activities that simulate household tasks.

The Timed Up and Go Test (TUGT) was used to assess short-distance walking [24], while the 6-Minute Walk Test (6MWT) evaluated longer-distance walking [25]. Stair ascent and descent were performed by walking through a hallway and then ascending and descending a staircase with 21 steps, ensuring the activity lasted more than three minutes to simulate a realistic ADL scenario. The Glittre ADL test is a widely used timed performance test that evaluates functional capacity through five laps of a 10-meter circuit (total 50 meters). The circuit incorporates multiple functional movements such as sitting and standing from a chair, walking, going up and down a few steps, reaching, squatting, turning, and moving object. This test reflects complex daily activities like tidying up the house or putting away groceries and has been validated in populations with chronic obstructive pulmonary disease and heart failure [26–29].

Cardiopulmonary exercise test

The one-leg ergometer was used for the CPET, which has previously been validated for individuals with LLA[30–32] for determining rest $\dot{V}O_2$, $\dot{V}O_2$-VT1 and $\dot{V}O_2$peak.

PROCEDURES

The participants were tested in the UMCG Centre for Rehabilitation, location Beatrixoord. The sessions were divided over two days within a two-week interval. The first assessment session started with a baseline assessment containing: Medical intake, short physical examination, measuring rest metabolism and performing a CPET[a]. During the CPET a certified clinical exercise physiologist and/or physician was present.

The second assessment session took place within 14 days after first assessment session and began with a short review to check for any physical discomfort or issues following the CPET. Each participant then performed the five ADL tasks in the same order: 6-Minute Walk Test (6MWT), Timed Up and Go Test (TUGT), Glittre ADL test, stair descent, and stair ascent. Participants P01, P03, and P05 completed these tasks in the morning (09:00–12:00), while P02, P04, and P06 performed them in the afternoon (13:00–17:00). Before the first task (6MWT), a 10-minute rest measurement was taken to establish baseline values. After each task, measurements continued for 10 minutes to return to baseline, followed by a 30-minute break. Each subsequent task began with a 2-minute rest measurement. After completing all tasks, participants completed a questionnaire evaluating feasibility and their experience.

During all ADL tasks, breath-by-breath gas exchange was measured using the COSMED K5[b] system. The TUGT was repeated three times to provide a more reliable estimate of the energy requirement for this relatively short test. The duration of the ADL tasks ranged between 3 and 6 minutes, except for the repeated TUGT, which lasted approximately 7–8 minutes due to the additional rest periods.

Study outcomes

Data to determine feasibility of the protocol was collected based on pre-set feasibility criteria as described in Table 1. During the CPET the following data was collected; $\dot{V}O_2$ rest (ml/kg/min), $\dot{V}O_2$-VT1, $\dot{V}O_2$peak (ml/kg/min), maximum heartrate (beats/min), respiratory exchange ratio (RER), maximum power (W) and %predicted heartrate.

Table 1. Feasibility criteria of the protocol

Feasibility criteria	***Outcome (yes/no)***
1. For 5 out of 6 of the participants the breaks are adequate in terms of length and frequency (to return to rest metabolism)	*Yes* (6/6)*
2. 5 out of 6 the participants can complete the entire protocol	*Yes** (5/6)*
3. The logistics are adequate:	
a. 6/6 participants will receive the time schedule at least two weeks in advance	*Yes (6/6)*
b. It is clear for 6/6 participants who he/she can call for questions (e.g. about the schedule)	*Yes* (6/6)*
c.When arriving at UMCG Centre for Rehabilitation location Beatrixoord, it is clear for 6/6 participants how and where he/she can register	*Yes* (6/6)*
d. It is clear for 6/6 participants where they have to wait before the tests	*Yes* (6/6)*
e. No issues with planning to arrange all test moments	*Yes (6/6)*
f. For 6/6 participants there is a clear end of the testing day with a short evaluation moment with the participant and researcher	*Yes (6/6)*
g. The schedule of the test day does not exceed more than 30 minutes due to logistical causes (not based on participant related causes)	*Yes (6/6)*
4. No essential data are missing for the analysis, conform previous described study parameters	*Yes (6/6)*

* Based on responses of participants asked after the second testing day. ** Adjusted version of the Glittre ADL was needed for three participants to ensure everybody could perform the test; participants walked the same distance but on a level surface instead of steps.

Data analysis and statistics

Feasibility was assessed using a pre-defined evaluation form based on the criteria shown in Table 1. Peak aerobic capacity (expressed as $\dot{V}O_2$peak) was determined from the CPET data. The $\dot{V}O_2$peak was considered maximal when the participant reached an RER>1.1 and/or predictive heart rate>85%. The timepoint of $\dot{V}O_2$-VT1 was determined with the V-slope method[33], by two certified clinical exercise physiologists (ML/MH), working independently and not involved in other aspects of the studyconform the method described in a previous study[18]. When the difference of the $\dot{V}O_2$-VT1 between assessors was more than 100mlO_2/min, they conferred for consensus. The average rate of oxygen consumption of each ADL task was calculated as the sum of oxygen consumption (O_2ml/kg) during the ADL tasks and excess post exercise consumption phase, divided by the time to complete the activity as previously outlined in detail by Blokland et al. [18]. The relative aerobic load was defined as the average oxygen consumption divided by $\dot{V}O_2$-VT1, expressed as %$\dot{V}O_{2\text{-}}$VT1.

The intraclass correlation (ICC, two-way mixed design with type consistency) was calculated to assess the correlation of relative aerobic load (%$\dot{V}O_{2\text{-}}$VT1) on different ADL tasks between participants [34], to assess the consistency in ranking of the participants in this heterogeneous group between ADL tasks. Analyses were performed using IBM SPSS Statistics, version 28.

RESULTS

Six participants were included in the study (Table 2). In total, seven individuals contacted the researchers and were screened; all met the inclusion criteria, but one withdrew due to illness, resulting in the inclusion of 6 participants. This number was sufficient, as only six participants were required for the study. Mean age was 58.8 ± 9.0 years, five males, one female. Three participants with transtibial amputations (TTA), one with knee disarticulation and two participants with transfemoral amputations (TFA) were included. Four participants with LLA due to vascular reasons, the other two due to infections of total knee prosthesis. Within this group, a range of comorbidities was present.

Table 2. Participant characteristics

Participant #	01	02	03	04	05	06
Amputation level	TTA	TTA	TFA	TTA	KD	TFA
Age (y)	61.3	45.6	57.7	53.5	71.8	64.7
Sex (m/f)	M	M	M	M	M	F
Years since amputation (y)	1.3	5.9	3.2	1.1	12	2.7
Walking aids, besides prosthesis	No	Yes, walker and AFO	No	No	Yes, two crutches	Yes, walker and AFO
Type of prosthesis	(Passive) vacuum sleeve, Taleo foot, and Össur liner	Shuttle lock (pin system), Proflex XC foot, Össur Synergy liner	(Passive) vacuum seal and anatomically shaped socket with Seal-In, C-Leg (microprocessor knee), Flex-Foot Össur,	Passive vacuum system with sleeve, Taleo foot (OTB), and Össur Dermo liner	Femoral condyl fit socket with a polyform insert; Össur Total Knee 1900; Foot: Ottobock Trias.	IRC socket with (passive) vacuum suspension and movable Seal-In ring (Össur liner); Össur Total Knee 2100; Foot: Össur Variflex.
Height (cm)	182	165	185	185	172	173
Weight (kg)*	85	79	91	94	88	122
K- level	K3	K2	K3	K3	K2	K2
Cause of amputation	Vascular	Vascular	Infection	Vascular	Vascular	Infection
Comorbidities	CVD	CVD, stroke	CVD, sarcoidosis	CVD, DM2	CVD, COPD, DM2, HTN	Asthma, HNP L4-L5 with dropfoot
Use beta blockers	No	No	No	Yes	Yes	No
Smoke	No	No	No	Yes	Yes	No
Berg Balance scale	56	48	53	56	48	44

TTA= Transtibial Amputation; KD = Knee Disarticulation ; TFA = Transfemoral Amputation; AFO = Ankle Foot Orthosis; CVD = Cardio Vascular Disease ; DM2 = Diabetes Mellitus Type 2; COPD = Chronic Obstructive Pulmonary Disease; HTN = Hypertension; HNP = Herniated Nucleus Pulposus. * Weight is without prosthesis

Feasibility

All feasibility criteria of the protocol were met. Of the six participants, five successfully completed all tasks. Participant 06 did not complete all tasks.

Modifications to the Glittre ADL test were required for three participants (P03, P05, and P06) due to the use of walking aids and the absence of support bars (i.e., railings or other stable structures for hand support) to enhance stability. These adaptations were necessary because the steps could not be safely combined with the participants' own walking aids, and no railings or walls were available for additional support. To ensure safety and create a testing environment that felt secure for participants, while simulating a realistic daily situation using their own walking aid, the protocol was adjusted. In the modified version, participants walked the same distance on a level surface instead of steps. One participant (P06) was unable to complete the stair tasks due to fear of the unfamiliar staircase and therefore did not complete the full protocol. All participants reported that the breaks were sufficient and that the logistics were well organized, with clear instructions and communication. All necessary data for analysis were successfully collected.

Relative aerobic load for ADL tasks

The CPET data are presented in Table 3. One participant stopped the CPET during warming up, because this participant couldn't cycle well with one leg due to coordination problems, therefore this participant was excluded from further analysis. Of the remaining five participants, only one person achieved a maximum CPET based on RER and/or predicted heart rate. The mean $\dot{V}O_2$ at rest was 4.1±0.5ml/kg/min, mean $\dot{V}O_2$-VT1 was 10.0±2.4ml/kg/min. Stop reasons were because of fatigue in the leg and/or shortness of breath.

Table. 3. Cardiopulmonary exercise test (CPET) data for each participant.

Participant	**01**	**02**	**03**	**04**	**05**	**06**
$\dot{V}O_2$ in rest (ml/kg/min)	4.7	4.7	3.5	3.5	4.1	n.a.
$\dot{V}O_2$ at VT1 (ml/kg/min)	7.9	10.0	13.3	7.6	11.3	n.a.
$\dot{V}O_2$ peak during test (ml/kg/min)	16.6*	11.5	17.0	8.5	12.1	n.a.
RER	1.27	0.94	1.01	0.99	0.95	n.a.
Watt peak (W/kg)	1.1	0.4	1.0	0.3	0.6	n.a.
Heart rate peak	148	122	98	95	92	n.a.
% predicted HR	93	70	60	57	62	n.a.

* maximal CPET based on RER. N.a. not applicable.

The results for the relative aerobic load of the five ADL are presented in Table 4. With the exception of P02 for descending stairs, all the ADL tasks in all participants are performed at relative aerobic load levels > 100%$\dot{V}O_2$-VT1. The relative aerobic load (%$\dot{V}O_2$-VT1) was highest in the Glittre ADL test and the TUGT. The Glittre ADL test evaluates functional capacity through a circuit of daily activities, including walking, going up and down a few steps, and moving objects. The modified version is identical but excludes the step component. In this study, there seems to be a difference in %$\dot{V}O_2$–VT_1 between participants performing the standard version and those completing the adjusted version without steps.

Table 4. % $\dot{V}O_2$-VT1 for the different ADL tasks**.**

Participant	01	02	03	04	05
6MWT %$\dot{V}O_2$-VT1	147	130	141	121	137
TUGT %$\dot{V}O_2$-VT1	237	150	202	278	168
Glittre ADL test %$\dot{V}O_2$-VT1	240	162*	166	225	157*
Descending stairs %$\dot{V}O_2$-VT1	123	93	124	111	155
Ascending stairs %$\dot{V}O_2$-VT1	170	105	137	174	118

* Adjusted Glittre ADL task without steps. Participant 06 is excluded.

To illustrate the $\dot{V}O_2$ per ADL, Figure 1 shows the measured $\dot{V}O_2$ curves per ADL task for, randomly chosen, participant 03. Data for the other participants are presented in Appendix 1-4.

Figure 2 shows the relative aerobic load (%$\dot{V}O_2$-VT1) of each participant for each task to illustrate the ranking of the participants for each task. The ranking appears quite consistent over all tests. Variation between participants seems highest for the TUGT and lowest for the 6MWT. Using an ICC, the agreement in the ranking of the different tasks between participants was quantified (ICC = 0.73; 95% CI: 0.01–0.97).

Figure 1. $\dot{V}O_2$ curve for each ADL task for Participant 03. The dotted horizontal line is de $\dot{V}O_2$-VT1 of P03. The solid vertical lines represent the start and stop of the ADL task, respectively. In the TUGT the vertical solid line indicates moment of starting TUGT and the dashed vertical line is the end of the TUGT cycle. For both ascending and descending the stairs, the vertical dashed line indicates the moment of starting to climb the stairs.

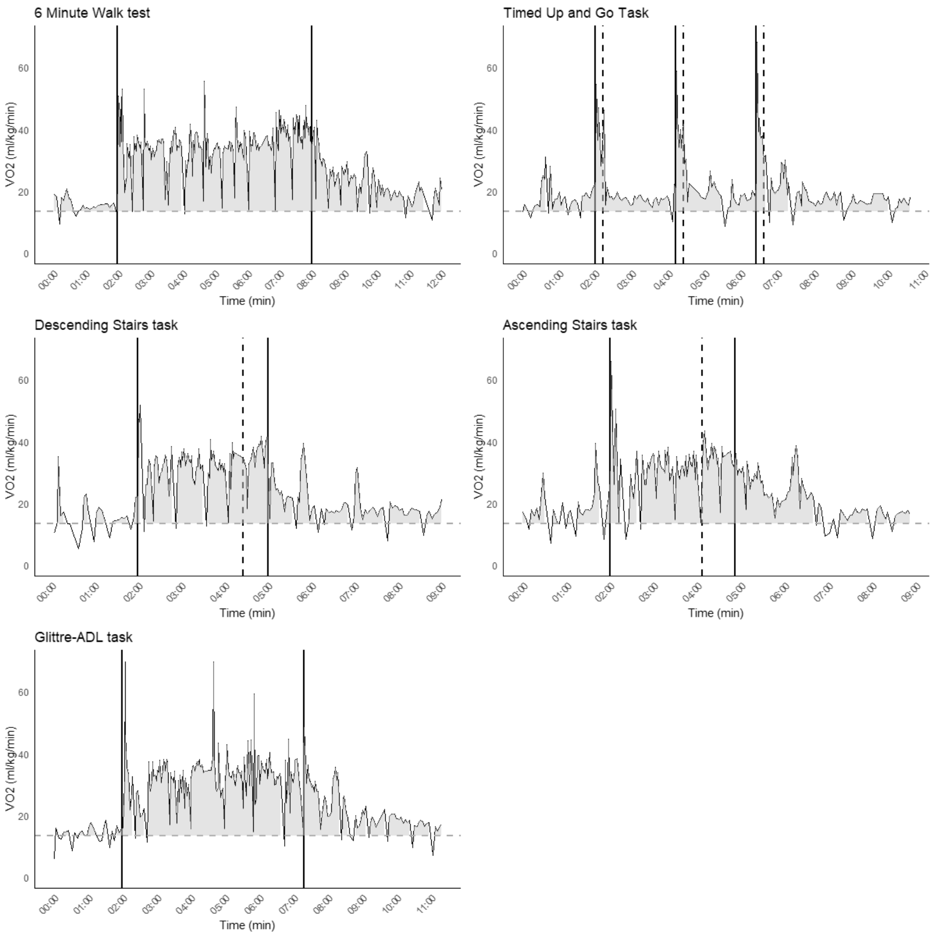
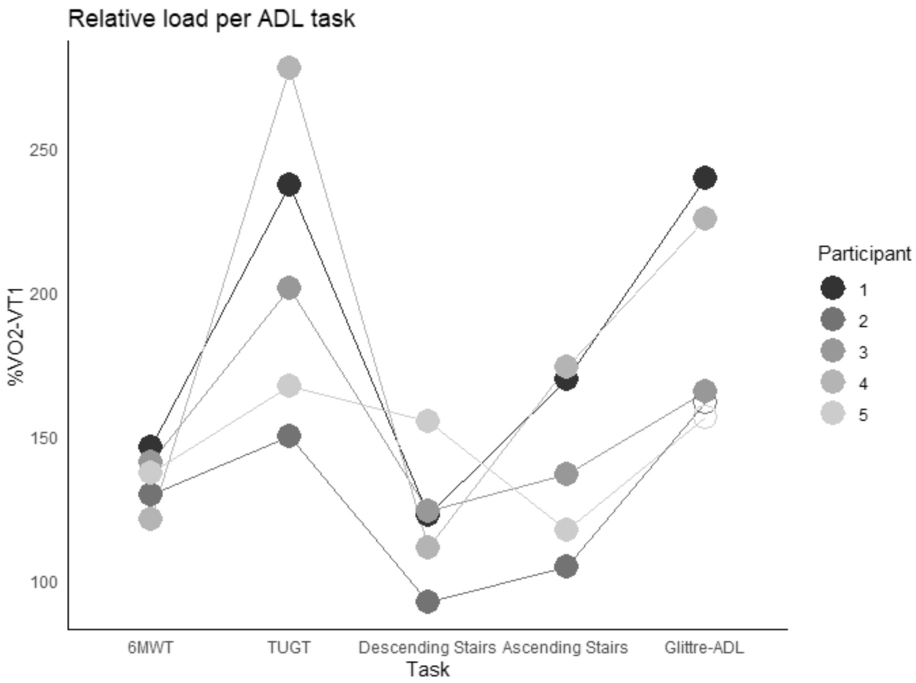


Figure 2. Relative aerobic load per ADL task. Scatterplot of the relative aerobic load for each participant on each test. Unfilled datapoints: Performed the adjusted version of the Glittre ADL test.



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DISCUSSION

This study had two main objectives. First, we aimed to evaluate the developed protocol based on criteria related to operability, logistics, and suitability of intensity. Second, we examined whether the EPOC method, previously applied in individuals after stroke [18], can be used to determine the relative load of five ADL tasks of varying duration in individuals with LLA. The findings indicate that the protocol was feasible, demonstrated by successful implementation in five of six participants, with only minor adjustments required and one participant unable to complete the full protocol. These results suggest that the protocol was operable and logistically manageable within the planned timeframe, and that the intensity of the tasks was appropriate for the target population. The need for small modifications, such as adapting Glittre ADL test for safety, highlights practical considerations for applying the protocol in clinical or research settings. Overall, the findings support the applicability of the protocol and confirm that the EPOC method can be used to quantify relative load during ADL tasks of varying duration in this population.

The Dutch population of individuals with LLA is highly heterogeneous, encompassing a wide range of comorbidities that may influence cardiorespiratory fitness. The participants in this study were a fair representation of this population [21], reflecting substantial variability in amputation level, etiology, and comorbid conditions. This diversity highlights the need for individualized assessment, as comorbidities such as cardiovascular disease, diabetes mellitus, and balance impairments can independently affect both cardiorespiratory fitness and functional capacity. For example, one participant was unable to perform the CPET due to difficulties in maintaining posture and movement on the one-legged cycling test, likely resulting from imbalance associated with LLA or comorbidities.

In terms of task intensity, the protocol was appropriate for most participants (5 out of 6). However, adaptations to the Glittre ADL test were necessary for three participants due to balance limitations and the use of walking aids to ensure safety. These adaptations involved replacing stair climbing with level walking over the same distance. This highlights the need for selecting functional ADL tests that can be uniformly administered across a diverse LLA population, particularly in research settings.

Regarding CPET outcomes, only one participant achieved a maximal effort as indicated by a respiratory exchange ratio (RER) > 1.1. The remaining participants did not achieve an RER>1.1, suggesting that fatigue may have been driven by factors other than cardiopulmonary limitations. Five participants reached their first ventilatory threshold, supporting its use as a reliable reference point for determining relative aerobic load in this population. The mean $\dot{V}O_2$-VT1 (n=5) was 10.0±2.4 ml/kg/min. This is comparable to previously described $\dot{V}O_2$-VT1 in individuals with stroke [18] with respective means (±SD) of 9.7 (±2.4) ml/kg/min for functional ambulation category (FAC) 3, 9.9 (±2.7) ml/kg/min for FAC 4, and 10.9 (±2.8) ml/kg/min for FAC 5. The mean $\dot{V}O_2$peak achieved by the five participants was 13.1ml/kg/min (range 8.5-17.0). Note that this is the $\dot{V}O_2$peak obtained during the test, which was not considered a maximal test for 4 out of the 5 participants. Possibly these $\dot{V}O_2$peak values are therefore somewhat lower to those that were considered maximal in previous studies in dysvascular group of individuals with LLA, where mean $\dot{V}O_2$peak of 17.1±4.1 ml/kg/min was reported. In individuals with traumatic LLA, the $\dot{V}O_2$peak values are reported to be higher (resp. 28.1±6.7 ml/kg/min) [2]. In the study by Mellema et al.[20], the mean $\dot{V}O_2$peak was 21.8 ± 6.8 ml/kg/min, which falls between these previously reported ranges; however, this value was obtained using an arm-crank ergometer. Although differences in $\dot{V}O_2$peak likely reflect age, baseline fitness, and comorbidities, we did not analyze the association between aerobic capacity and functional performance (e.g., 6MWT distance). Future research should examine these relationships to clarify whether lower $\dot{V}O_2$peak corresponds to reduced mobility and endurance.

The ADL tasks in this study were selected to simulate ADL used in daily functioning and were aligned with previous findings on the ADL deemed most important by individuals with LLA[19]. The Glittre ADL test which has recently been validated for individuals with LLA[35], served as a comprehensive measure of functional capacity. The relative aerobic load for the TUGT is challenging to interpret using the EPOC method as the time of action is quite short and error in the resting oxygen uptake level and the proportional impact of EPOC might have a large effect on the outcome (Figure 2). Consequently, it may require alternative methods or analyses for accurate assessment in these short-lasting ADL tasks.

In the remaining ADL tasks, the relative aerobic load determined with the EPOC method ranged between 100-200% of $\dot{V}O_2$-VT1, with the exception of p02 in de ADL descending stairs. These values are not unrealistic compared to data from Blokland et al. [18] who applied the EPOC method in individuals post-stroke for tasks such as cycling, 5-minute walking, an obstacle course, sweeping leaves, and stair ambulation, reporting relative loads of 55–61% $\dot{V}O_2$peak for walking. This comparison suggests that the EPOC method provides realistic estimates of aerobic demand in individuals with LLA. Mellema et al. [20] reported VO_2 values of 11.4 ± 2.1 ml/kg/min for in-house walking and 22.5 ± 3.3 ml/kg/min for stair negotiation in 21 high-functioning individuals with LLA (14 transtibial and 7 transfemoral).

Stair negotiation was performed at a self-selected speed of 0.55 ± 0.17 m/s compared to 0.69 ± 0.09 m/s in controls, despite similar VO_2 values (22.5 ± 3.3 vs. 24.9 ± 3.4 ml/kg/min), illustrating that individuals with LLA expend nearly the same oxygen at a slower pace, indicating reduced gait economy. Importantly, the relative aerobic load was high: %$\dot{V}O_2$peak averaged 55 ± 13% for in-house walking and exceeded 100% (102 ± 21%) for stair negotiation. With $\dot{V}O_2$-VT_1 typically around 40-60% of $\dot{V}O_2$peak [36], these results align with our findings of 100–200% $\dot{V}O_2$-VT_1 during the ADL tasks. Furthermore, the absolute VO_2 values reported by Mellema et al. would translate into an even higher relative aerobic load in people with lower $\dot{V}O_2$peak, such as older adults or those with comorbidities, meaning that these activities could impose a substantially greater physiological burden. These findings highlight that the physiological burden during ADL is highly dependent on individual capacity. Since $\dot{V}O_2$peak and $\dot{V}O_2$-VT_1 vary considerably between individuals with LLA, a generic level of physiological burden for each task cannot be given, instead it is essential to measure these parameters on an individual level to accurately determine relative load. Without such individualized assessment, there is a risk of underestimating or overestimating the actual exercise intensity, which has direct implications for rehabilitation planning and safety recommendations.

Interestingly, agreement in the ranking of relative aerobic load across ADL tasks among participants was observed (Figure 2). The point estimate of the ICC suggested moderate to good agreement (ICC = 0.73), but the very wide confidence interval (95% CI: 0.01–0.97) indicates substantial uncertainty around this estimate. Therefore, while the observed pattern may suggest that performance on one task could be indicative of aerobic demand in others, this finding should be interpreted cautiously and confirmed in a larger and more diverse sample.

Strength and limitations and future research

This study is one of the first to apply the EPOC method to assess the relative aerobic load of functional ADL tasks in individuals with LLA. The inclusion of both short and longer-duration tasks, such as stair climbing and the Glittre ADL test, demonstrates the method's applicability to non-steady-state activities that reflect daily functioning.

This study included individuals with K2–K3 ambulatory levels and reflected the clinical heterogeneity of the LLA population, including variation in amputation level, cause, and comorbidities. Although this variation underscores the importance of individualized assessment, since comorbidities and other factors may independently influence cardiorespiratory fitness and functional performance, the small sample size in this pilot study (six participants, five completed all tasks) limits generalizability.

These findings should therefore be interpreted with caution, but they provide an initial indication of the importance of individualized testing.

Limitations include the small sample size, which restricts generalizability and subgroup analysis. Task feasibility was occasionally affected by environmental factors and individual safety concerns, requiring protocol adaptations. In addition, the wide confidence interval for the ICC (0.01–0.97) reflects the limited sample size and heterogeneity of participants, resulting in considerable uncertainty in this estimate. Therefore, these findings should be interpreted with caution, and future studies with larger cohorts are needed to provide more robust reliability estimates.

Future research should validate these findings in larger, more diverse samples and explore how rehabilitation interventions influence aerobic load and functional capacity. The use of wearable technology may further enable real-time, personalized monitoring of aerobic demand during ADL in daily life.

Conclusion

The described protocol and selected functional ADL appear feasible for logistics and planning for K2-K3 individuals with LLA. This study demonstrates that shorter, non–steady-state ADL tasks can be measured in this population using the EPOC method. The protocol can be applied to estimate the relative aerobic load of functional ADL, offering preliminary insights into the capabilities and challenges faced by individuals with LLA. However, these findings should be interpreted with caution due to the small sample size and the need for task adaptations in some participants. While the EPOC method shows promise, its suitability for very short-burst activities remains uncertain, as these may not allow sufficient time for accurate measurement. Further research is needed to confirm its applicability in such contexts and to validate the protocol in larger and more diverse cohorts before broader generalization. Importantly, the observed variability in amputation level, physical capacity, and comorbidities underscores the importance of individualized assessment. Identifying the specific aerobic demands of ADL at the individual level may support the development of personalized rehabilitation programs tailored to each person's capabilities and limitations. Such an approach could facilitate more realistic goal-setting, improve fatigue management, and ultimately enhance participation and quality of life for individuals with LLA.

[a]Ergometer: ergoselect 200 (Ergoline); CPX: Vyntus CPX Professional (Vyaire); ECG: Cardiosoft 6; Blood pressure monitor: Tango M2 (Suntech).

[b] COSMED K5 spirometer (K5, COSMED, Rome, Italy) (CE MED-9811)

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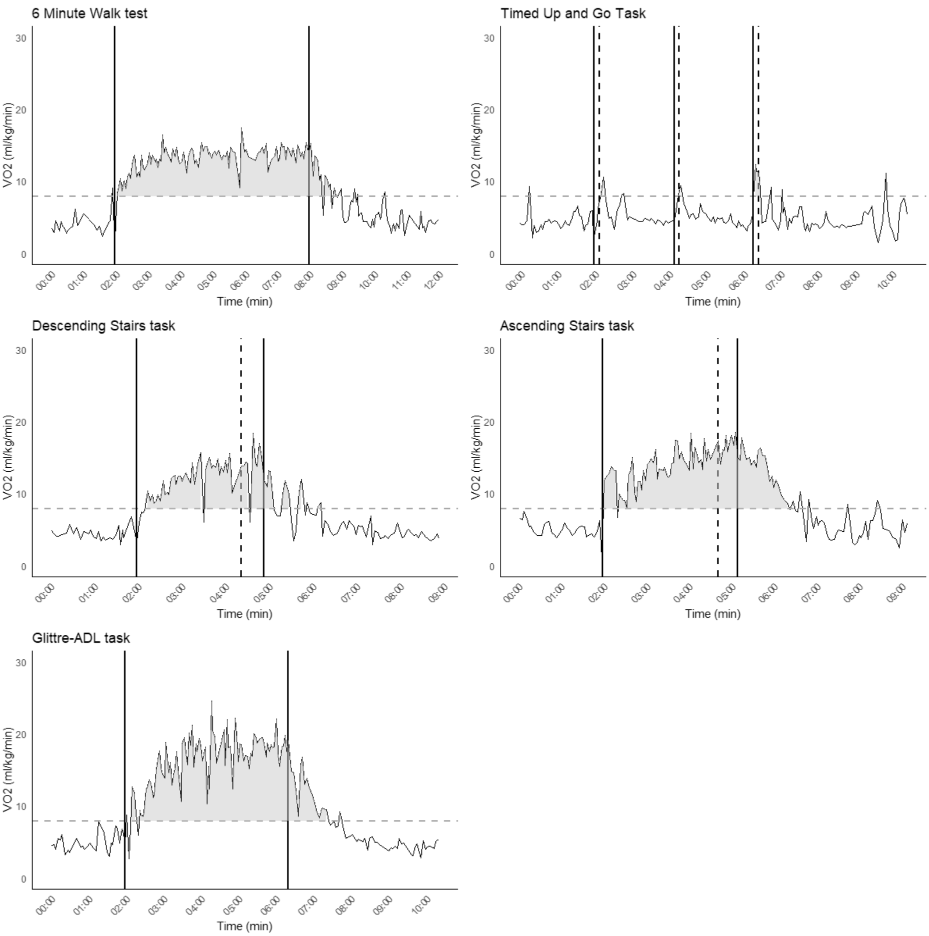
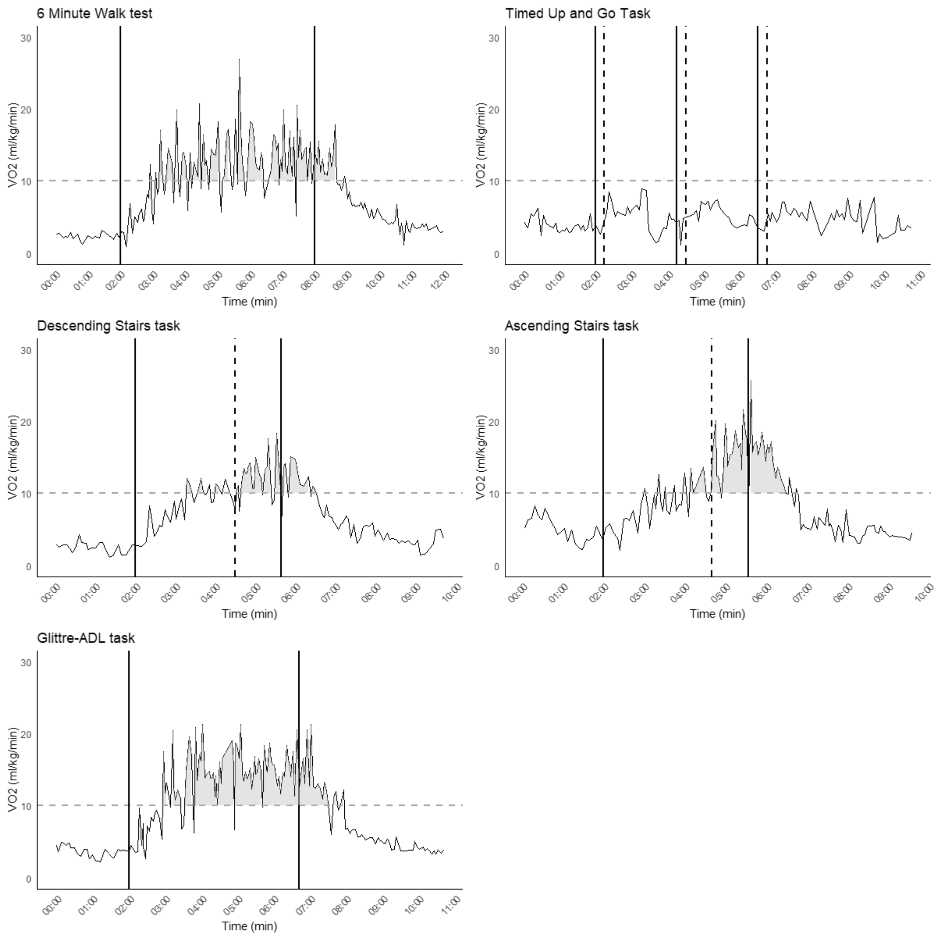
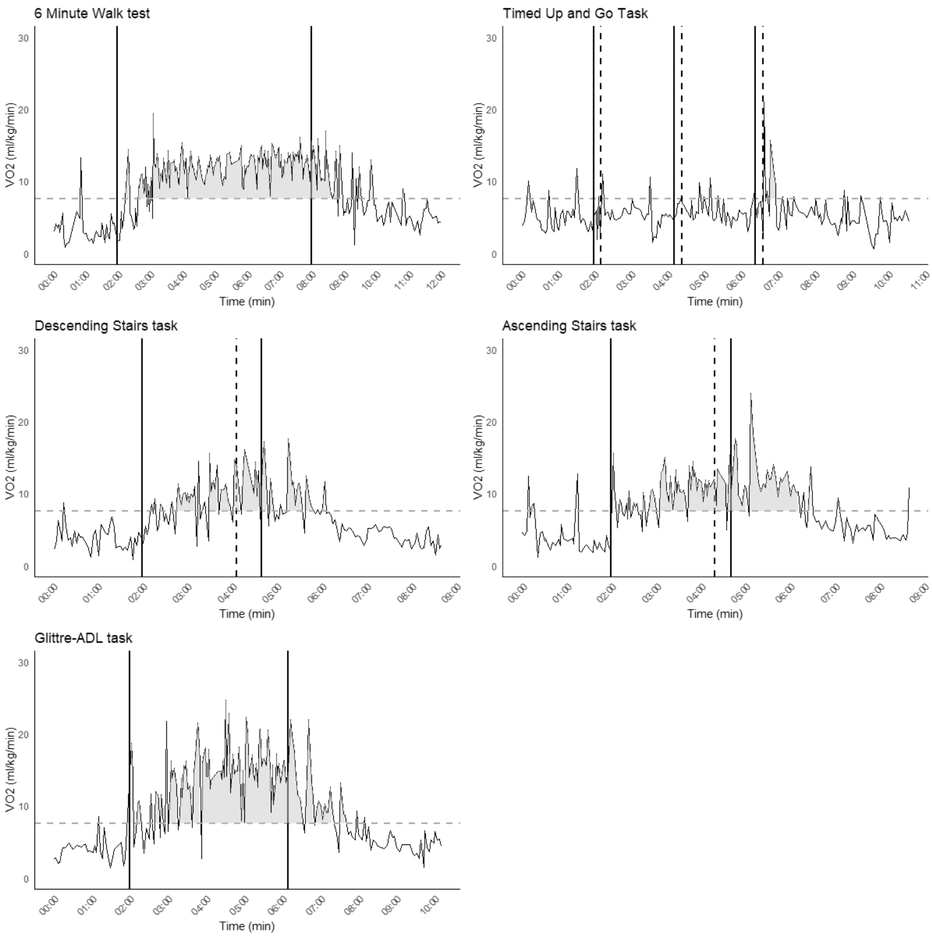
Appendix 1. $\dot{V}O_2$ curve for each ADL task for Participant 01. The dotted horizontal line is the $\dot{V}O_2$-VT1 of P01. The solid vertical lines represent the start and stop of the ADL task, respectively. In the TUGT the vertical solid line indicates moment of starting TUGT and the dashed vertical line is the end of the TUGT cycle. For both ascending and descending the stairs, the vertical dashed line indicates the moment of starting to climb the stairs.



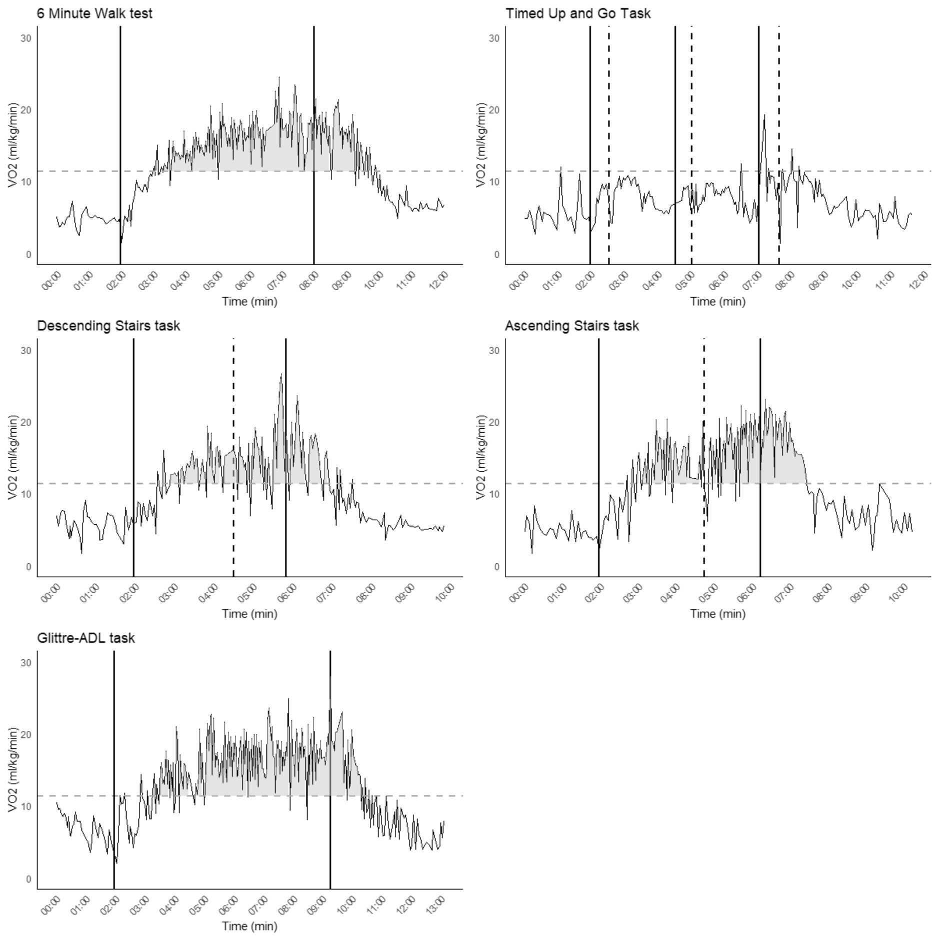
Appendix 2. $\dot{V}O_2$ curve for each ADL task for Participant 02. The dotted horizontal line is the $\dot{V}O_2$-VT1 of P02. The solid vertical lines represent the start and stop of the ADL task, respectively. In the TUGT the vertical solid line indicates moment of starting TUGT and the dashed vertical line is the end of the TUGT cycle. For both ascending and descending the stairs, the vertical dashed line indicates the moment of starting to climb the stairs.



Appendix 3. $\dot{V}O_2$ curve for each ADL task for Participant 04. The dotted horizontal line is the $\dot{V}O_2$-VT1 of P04. The solid vertical lines represent the start and stop of the ADL task, respectively. In the TUGT the vertical solid line indicates moment of starting TUGT and the dashed vertical line is the end of the TUGT cycle. For both ascending and descending the stairs, the vertical dashed line indicates the moment of starting to climb the stairs.



Appendix 4. $\dot{V}O_2$ curve for each ADL task for Participant 05. The dotted horizontal line is the $\dot{V}O2$-VT1 of P05. The solid vertical lines represent the start and stop of the ADL task, respectively. In the TUGT the vertical solid line indicates moment of starting TUGT and the dashed vertical line is the end of the TUGT cycle. For both ascending and descending the stairs, the vertical dashed line indicates the moment of starting to climb the stairs.



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Chapter 6

General discussion

GENERAL DISCUSSION

The importance of physical fitness in persons with lower limb amputation (LLA) cannot be overstated, particularly given the increased physiological demands associated with prosthetic use and daily functioning.

The overarching aim of this thesis was to investigate the metabolic costs and physiological demands of activities of daily living (ADLs) in persons with LLA. The first part of the thesis comprised a systematic review of existing literature, the variables reported, and the specific ADL tasks studied. It also explored which ADLs are considered most important by persons with LLA and healthcare professionals, highlighting discrepancies in perceived relevance. The second part of the thesis focused on assessing cardiorespiratory fitness, specifically $\dot{V}O_2$peak, in persons with LLA, and examined the relative aerobic load of selected ADLs. This dual approach provided insight into both the physiological demands of ADLs and the individual physical capacity to meet those demands, offering a foundation for developing more personalized rehabilitation strategies.

Mr. X is a 66-year old man with type 2 diabetes and peripheral arterial disease who underwent a transtibial amputation due to chronic ulceration. Prior to surgery, he was physically inactive and deconditioned. After LLA he was discharged home with outpatient rehabilitation. His rehabilitation goals included regaining independence in self-care, walking short distances with a prosthesis, and participating in social activities. However, during the initial rehabilitation phase, he experienced severe fatigue and slower-than-expected progress, leading to frustration, as his physical condition was worse than expected.

MAIN FINDINGS

The first part of this thesis focused on reviewing existing literature about metabolic costs in ADL and identifying which ADLs are generally considered important to persons with LLA. **Chapter 2** examined the metabolic costs of walking in persons with LLA, showed that both oxygen consumption and heart rate were significantly higher compared to able-bodied controls, especially at higher walking speeds and in those with transfemoral amputations. Amputation level and walking speed were the strongest predictors of metabolic cost, while the cause of amputation was not statistically significantly related. However, **Chapter 2** also revealed considerable heterogeneity across studies in terms of participant characteristics and measurement methods, which limited generalizability and highlighted the need for more standardized research in persons with LLA. Additionally, data on other ADLs beyond walking were scarce.

Chapter 3 explored the perspectives of persons with LLA and healthcare professionals regarding the importance of various ADLs. A ranked questionnaire completed by 125 persons with LLA and 44 healthcare professionals revealed differing priorities: persons with LLA emphasized mobility-related tasks such as driving, bicycling, and stair navigation, while professionals focused more on basic self-care activities like toileting and indoor walking. These findings underscore the importance of shared decision-making and tailoring rehabilitation goals to the individual's lived experience and personal preferences.

Together, **Chapter 2 and 3** highlight the need for rehabilitation approaches that address both the physiological demands of mobility and the personal relevance of ADLs.
The second part of the thesis addressed cardiorespiratory fitness ($\dot{V}O_2$peak) in persons with LLA and the relative aerobic load of relevant ADLs. **Chapter 4** analyzed cardiorespiratory exercise test (CPET) data from 74 participants and found that cardiorespiratory fitness in persons with LLA is significantly lower than in age- and gender-matched able-bodied controls, with a mean $\dot{V}O_2$peak of 14.6 ml/kg/min. Age was the only significant predictor of cardiorespiratory fitness, while other factors such as gender, amputation level, cause of amputation, and type of ergometry showed no significant association. These results suggest that cardiorespiratory fitness is highly individual and cannot be reliably predicted from demographic or clinical characteristics alone, reinforcing the need for individualized fitness assessments during rehabilitation.
Chapter 5, a pilot study, tested the feasibility of using the excess post-exercise oxygen consumption (EPOC) method to measure the relative aerobic load of five daily activities in persons with LLA. Six participants with moderate ambulatory levels (K2–K3) performed tasks such as walking, stair climbing, and household chores. The study found that most ADL tasks exceeded 100% of the first ventilatory threshold ($\dot{V}O_2$-VT1), indicating high physiological demand. The protocol was feasible and safe, and the EPOC method proved suitable for assessing short, non-steady-state ADLs. These findings suggest that measuring relative aerobic load can help tailor rehabilitation and improve understanding of fatigue and functional limitations.

Combined, the studies presented in this thesis provide a comprehensive picture of the physiological challenges faced by persons with LLA in daily life. They consistently show that walking and other ADLs require significantly more energy, and that cardiorespiratory fitness is often low and difficult to predict. The use of individualized assessments can inform more tailored rehabilitation strategies. Moreover, aligning rehabilitation goals with personal priorities is essential for improving participation, independence, and quality of life.

CHALLENGES IN TRANSLATING CURRENT EVIDENCE TO PERSONALIZED REHABILITATION IN LLA

As outlined in the general introduction, the population of persons with LLA is highly heterogeneous. In the Netherlands, the majority of LLAs are caused by vascular disease and/or diabetes mellitus, resulting in an older population with multiple comorbidities that can by itself influence cardiorespiratory fitness [1,2]. This contrasts with persons who undergo LLA due to trauma, who tend to be younger and in better overall health. Despite these differences, many studies investigating outcomes such as metabolic costs during (prosthetic) walking group persons with varying amputation levels and etiologies into a single cohort. This methodological approach complicates the interpretation of results and limits the applicability of findings to specific subgroups within the LLA population. This issue is further underlined by the findings in **Chapter 2**, which systematically reviewed 61 studies and revealed substantial heterogeneity in study populations, including variation in amputation level, reason for amputation, and time since surgery. Moreover, many studies pooled participants with different clinical profiles into single cohorts and often lacked detailed reporting on comorbidities or use of walking aids. These methodological inconsistencies limited subgroup analysis and reduced the generalizability of findings. Such limitations underscore the need for more rigorous study designs that account for clinical diversity and provide transparent reporting, to enhance the interpretability and applicability of future research.

In addition, **Chapter 2** demonstrated that most studies on metabolic costs in persons with LLA focus primarily on walking. Walking with a prosthesis generally requires significantly more energy than walking in able-bodied controls, with persons with transfemoral LLA showing the highest metabolic demands. These studies often include relatively healthy and fit participants, which may contribute to the frequent lack of statistical significance for predictors such as age, BMI, amputation level, and etiology in relation to oxygen consumption. Due to the heterogeneity within the LLA population, translating existing findings on cardiorespiratory fitness to individual cases, particularly those with vascular LLA, remains challenging. Comorbidities such as chronic obstructive pulmonary disease (COPD), stroke, and heart disease independently reduce physical capacity and further impact cardiorespiratory fitness. Given that cardiorespiratory fitness is a key determinant of the ability to perform ADLs, its relevance is even greater for persons with LLA, who face additional physiological demands during rehabilitation.

Moreover, the lack of data on metabolic costs for ADLs beyond walking, such as stair climbing, household tasks, and community participation, limits the ability to tailor rehabilitation programs effectively.

FUNCTIONAL GOALS AND THE ROLE OF CARDIORESPIRATORY FITNESS IN LLA REHABILITATION

The rehabilitation process following LLA always takes the person's personal goals into account. In clinical practice, it is evident that certain goals are common to most, such as regaining independence in dressing, bathing, and toileting. However, goals related to walking and functioning with a prosthesis can vary significantly. For older adults who were already less mobile and less active prior to the LLA, these goals often differ from those of persons who were physically fit and active before their LLA. In the Netherlands, the International Classification of Functioning, Disability and Health (ICF) [3] serves as a basis for developing personalized rehabilitation programs, including the programs for persons with LLA.

To better understand which goals persons with LLA consider important, and how these align with the perspectives of healthcare professionals, **Chapter 3** addressed goal-setting in rehabilitation, revealing both shared priorities and notable differences between persons with LLA and healthcare professionals. While persons with LLA emphasized mobility-related tasks, professionals focused more on basic self-care. The feasibility of achieving functional goals, such as independent toileting or dressing, is determined by factors like strength, balance, coordination, and motor control. While physical fitness contributes to these abilities, tasks such as independent toileting or dressing are typically short in duration and rely primarily on anaerobic energy systems. Therefore, aerobic capacity is unlikely to be the limiting factor for these specific activities. However, aerobic fitness may still influence overall endurance and recovery, particularly when such tasks are repeated throughout the day or combined with other functional efforts. In contrast, goals that involve sustained physical activity such as prolonged walking, outdoor mobility, or participation in (adapted) sports, as deemed important by persons with LLA in **Chapter 3**, are more dependent on aerobic endurance. For these types of goals, cardiorespiratory fitness becomes a critical factor in determining their feasibility.

To design a personalized and effective rehabilitation and training program, tailored to the person's current cardiorespiratory fitness and goals, it is crucial to have detailed information about their maximal aerobic capacity ($\dot{V}O_2peak$), as well as submaximal thresholds such as the first ventilatory threshold (VT1) and the corresponding heart rate or power output. Ideally, these parameters should be assessed using a cardiopulmonary exercise test (CPET), which is the golden standard, and provides objective and individual data to guide personalized rehabilitation programs [4].

6

CARDIORESPIRATORY FITNESS IN PERSONS WITH LLA IN REHABILITATION SETTING

The results presented in **Chapter 4** demonstrate that cardiorespiratory fitness in persons with LLA is generally low. Among the 74 persons with LLA who underwent CPET in a rehabilitation setting, $\dot{V}O_2$peak values ranged from 6.8 to 26.3 ml/kg/min, with a group average of 14.6 ± 4.1 ml/kg/min.

To interpret these findings, comparisons can be made with several reference standards. When benchmarked against the LowLands Fitness Registry, which includes age- and gender-matched able-bodied controls in the Dutch/Flemish population, the $\dot{V}O_2$peak values of persons with LLA were substantially lower [5]. The average found for $\dot{V}O_2$peak for Dutch/Flemish males is 38.5 ± 9.0 ml/kg/min, and 29.5 ± 7.8 ml/kg/min for females. These comparisons clearly illustrate the reduced aerobic capacity in persons with LLA, even when considering the highest values within the observed range (i.e. 26.3 ml/kg/min). Consistent with previous studies our findings confirm that cardiorespiratory fitness in persons with LLA is significantly reduced compared to able-bodied reference values [6].

To gain better insight into Mr. X's cardiorespiratory fitness, specifically his $\dot{V}O_2$peak and $\dot{V}O_2$-VT1, a CPET was performed. The results showed a $\dot{V}O_2$peak of 15.1 ml/kg/min and a $\dot{V}O_2$-VT1 9.8 ml/kg/min. Using the ACSM reference values, his $\dot{V}O_2$peak fall within the 'very poor' group.

These results indicate a severely reduced aerobic capacity and an early onset of ventilatory limitation, which likely contribute to his fatigue and limited functional progress. This objective information is essential for aligning rehabilitation goals with his physiological capacity and setting realistic expectations for recovery.

PREDICTORS OF CARDIORESPIRATORY FITNESS

Identifying predictors of cardiorespiratory fitness in persons with LLA can help improve rehabilitation outcomes and personalize interventions. Given the diversity within the LLA population, understanding which factors influence cardiorespiratory fitness is key to targeting support effectively. As presented in **Chapter 4,** age was the only significant predictor of reduced cardiorespiratory fitness following LLA. Consistent with previous literature, our findings indicated that specific amputation-related characteristics such as amputation level, etiology, and body mass index (BMI) did not significantly explain the variation in cardiorespiratory fitness [7,8]. This may be due to the heterogeneity within the LLA population, for example in terms of comorbidities, and the relatively small sample size. Consistent with the findings presented in **Chapter 2,** these results further underscore the importance of identifying and analyzing subgroups within the LLA population, along with potential predictors of cardiorespiratory fitness.

In contrast, studies involving other diagnostic groups, such as persons post-stroke, often benefit from larger sample sizes. Within the stroke population, female gender and higher BMI have been identified in addition to older age as predictors of lower peak oxygen uptake ($\dot{V}O_2$peak) [9]. These findings may be relevant to the LLA population, given the overlap in comorbidities and demographic characteristics. This suggests that future research involving larger cohorts may reveal additional predictors of reduced cardiorespiratory fitness in persons with LLA.

RELATIVE AEROBIC LOAD AND ITS IMPACT ON ADL IN PERSONS WITH LLA

Understanding the relative aerobic load during ADLs provides essential insight into the physiological capabilities and limitations of persons, particularly those with LLA. The relative aerobic load refers to the oxygen consumption during an ADL, expressed relative to a person's VT1 or $\dot{V}O_2$peak [10]. The VT1 marks the point during physical exertion where lactate begins to accumulate in the blood, indicating a shift from primarily aerobic to increasingly anaerobic metabolism [10]. ADLs performed below VT1 are generally sustainable over longer periods with minimal fatigue, while those above VT1 become progressively more fatiguing and can only be maintained for shorter durations [10]. In able-bodied persons, most basic ADLs such as indoor walking, dressing are performed well below VT1, making them relatively effortless.

However, as illustrated in **Chapter 2 and 4**, cardiorespiratory fitness is often significantly reduced in persons with LLA, which relates to both lower $\dot{V}O_2$peak and VT1. As a result, even basic ADLs may require oxygen consumption above VT1, turning tasks that are light-intensity for able-bodied persons into moderate- to high-intensity efforts. This increased physiological demand can lead to fatigue, reduced quality of life, and limited participation in daily and social activities.

Despite its clinical relevance, data on VT1 in persons with LLA remains limited. In **Chapter 5**, VT1 was assessed in five participants, with a mean $\dot{V}O_2$-VT1 of 10.0 ± 2.5 mL/kg/min. For comparison, reported $\dot{V}O_2$-VT1 values of 11.9 ± 2.8 mL/kg/min in persons with cardiovascular disease, 17.8 ± 4.4 mL/kg/min in healthy sedentary persons, and 26.2 ± 7.6 mL/kg/min in endurance athletes [11]. In healthy populations, VT1 is typically expressed as a relative percentage of $\dot{V}O_2$peak (approximately 50–75%) [10], with absolute values varying based on fitness level, gender, and body composition.

When combining the VT1 with reduced $\dot{V}O_2$peak, this suggests that even routine ADLs may require effort levels that exceed sustainable capacity. This is confirmed in **Chapter 5**, showing that with one exception, all tested ADLs required oxygen consumption above the participants' VT1. These results are consistent with those of Mellema et al. [12], who observed that persons with LLA performed ADLs such as indoor walking, shopping, vacuuming, and stair climbing at similar absolute VO_2 levels as able-bodied controls, but at significantly lower self-selected walking speeds. Despite the comparable oxygen consumption, persons with LLA exhibited higher percentages of $\dot{V}O_2$peak during these ADLs and reported greater perceived exertion, particularly during vacuuming and shopping. It is important to note that the participants in the study of Mellema et al. [12]were relatively high-functioning. For persons with LLA who are less fit, use walking aids, or experience other limitations, such as those included in **Chapter 5**, the oxygen cost of ADLs may be even higher, while their $\dot{V}O_2$peak is likely lower, further increasing the relative aerobic load and the risk of fatigue.

Although persons with LLA may reduce their walking speed as a compensatory strategy [13–15], this may not be sufficient to remain below VT1. By combining assessments of VT1, $\dot{V}O_2$peak, and personal goals related to daily functioning, healthcare professionals can better evaluate whether targeted interventions are needed. These may include cardiorespiratory training, strength and balance exercises, gait optimization, or prosthetic adjustments. Such strategies aim to either increase $\dot{V}O_2$peak or reduce the oxygen cost of ADLs, thereby lowering the relative aerobic load and improving functional independence.

MET-based activity classification in persons with LLA

In able-bodied populations, the intensity of ADLs is commonly classified using metabolic equivalent of task (MET) values, where 1 MET represents resting metabolism and is defined as 3.5 ml O_2/kg/min [16]. While this value is widely accepted as a standard, the actual resting metabolic rate can vary between persons, and therefore the true representation of 1 MET should ideally be individually measured [17]. MET values are based on the oxygen consumption required to perform specific ADLs and are frequently used in both clinical and research settings to estimate physical activity intensity. However, research has shown that these MET values of the able-bodied population are not valid for elderly or patient populations [17–19], including persons with LLA.

Persons with LLA often experience substantially higher relative aerobic loads when performing the same ADL tasks at the same speed as able-bodied controls, as demonstrated in **Chapter 5**. For example, walking indoors at a comfortable pace, typically rated at 2.5 METs [16], would represent only 25% of $\dot{V}O_2$peak for an able-bodied person with a $\dot{V}O_2$peak of 35 ml/kg/min, but nearly 90% for someone with a $\dot{V}O_2$peak of 10 ml/kg/min. Vacuuming, rated at 3.5 METs, may exceed the $\dot{V}O_2$peak of a person with LLA whose $\dot{V}O_2$peak is limited to 12 ml/kg/min, turning a routine chore into an unsustainable and potentially unsafe effort. These examples illustrate how using MET values derived from able-bodied populations can lead to a significant underestimation of the actual physiological strain experienced by persons with LLA. Moreover, using MET values to prescribe training intensity without considering a person's cardiorespiratory fitness can result in overtraining or undertraining. The American College of Sports Medicine defines high-intensity exercise as activities exceeding 6 METs [4] . However, as shown in **Chapters 4 and 5**, for many participants with LLA, this threshold would exceed their $\dot{V}O_2$peak entirely, making such training intensities unfeasible. In **Chapter 4**, the average $\dot{V}O_2$peak among 74 persons with LLA was 14.6 ± 4.1 ml/kg/min, with the lowest value recorded at just 6.8 ml/kg/min. A $\dot{V}O_2$peak of 6.8 ml O_2/kg/min, compared to the standard 3.5 ml O_2/kg/min for 1 MET, corresponds to approximately 1.9 METs, comparable to slow indoor walking or light housework in able-bodied persons [16]. These findings underscore the importance of individualized fitness assessment and personalized prescription based on objective CPET, including $\dot{V}O_2$peak and VT1. Tailoring rehabilitation programs in this way ensures that training is both safe and effective, particularly for persons with very low cardiorespiratory fitness.

Mr. X. his rehabilitation goals included self-care activities such as toileting, bathing, and cooking, performing household chores, walking short distances with a prosthesis in and around the house, doing groceries independently, and driving a car to maintain social engagement. These activities are typically classified as light-intensity ADLs in able-bodied populations, with estimated metabolic equivalents (METs) ranging from approximately 1.5 METs for driving, 2.0–3.0 METs for bathing, cooking, and slow indoor walking, to over 4.0 METs for stair climbing or walking at 3 mph [16].

However, Mr. X's CPET has a $\dot{V}O_2$peak of 15 ml/kg/min (≈ 4.3 METs) and a $\dot{V}O_2$-VT1 of 9.8 ml/kg/min (≈ 2.8 METs). These values indicate that even relatively light-intensity tasks, such as cooking or walking indoors, approach or exceed his $\dot{V}O_2$-VT1, meaning they are not physiologically sustainable over longer durations without inducing fatigue. Tasks rated above 4.0 METs, such as stair climbing or brisk walking, would likely exceed his $\dot{V}O_2$peak entirely, making them not only exhausting but potentially unsafe.

CLINICAL IMPLICATIONS

Recommendations for daily practice:

Incorporate CPET whenever feasible: Use CPET as the preferred method to assess $\dot{V}O_2$peak and ventilatory thresholds (e.g., VT1) in persons with LLA. This allows for accurate, individualized assessment of cardiorespiratory fitness, which is essential for safe, effective and personalized rehabilitation programs and training.

Avoid sole reliance on predictive models or MET values: Be cautious when using prediction equations, MET values or submaximal tests (e.g., walking tests, heart rate estimations), as these are often based on able-bodied populations, may overestimate fitness in persons with LLA, especially those with comorbidities or vascular aetiologies and do not reliably offer risk stratification.

Tailor training programs to individual capacity: Design personalized exercise programs based on individually determined VO_2peak and VT1 to ensure appropriate intensity. For persons with very low aerobic capacity, start with low-intensity, closely monitored training to avoid overexertion and promote gradual improvement.

Monitor progress and adjust interventions: Reassess cardiorespiratory fitness periodically to evaluate the effectiveness of training interventions using CPET. Use this data to refine rehabilitation goals and adapt exercise prescriptions over time.

Support research on functional thresholds: Encourage further research to define the minimum levels of aerobic capacity, strength, and endurance required for functional prosthetic ambulation. This includes identifying walking speed and distance thresholds relevant to daily life participation.

GENERAL CONSIDERATIONS

Integrating measurements of cardiorespiratory fitness in rehabilitation setting for persons with LLA

CPET is considered the gold standard for assessing maximal oxygen uptake ($\dot{V}O_2$peak) [4], yet its implementation in clinical rehabilitation remains limited due to the need for specialized equipment, trained personnel, and standardized protocols. Availability varies across rehabilitation centres. Most studies involving persons with LLA use a one-leg cycling ergometry protocol, though many participants report difficulties due to reduced residual limb strength, balance issues, or discomfort. Alternative modalities such as arm ergometry or combined arm-leg ergometry (e.g., the Cruiser [20]) have shown promise in improving feasibility and comfort, though technical challenges, particularly with ECG monitoring, must be considered. In response to the limited accessibility of CPET, more practical alternatives have been explored, such as walking tests, the Physiological Cost Index (PCI), and heart rate-based estimations [21–23]. However, these methods are typically based on data from able-bodied populations and may not accurately reflect the physiological profile of persons with LLA. Furthermore, predictive models often overestimate $\dot{V}O_2$peak due to unaccounted factors like altered biomechanics, reduced muscle mass, and comorbidities [24]. Additionally, heart rate-based methods may be unreliable due to medication use, such as beta-blockers. While tests like the 6MWT and Incremental Shuttle Walk Test correlate well with $\dot{V}O_2$peak in COPD populations, their validity in LLA remains insufficiently studied.

To accurately assess the physical strain of ADLs, it is essential to measure $\dot{V}O_2$peak. Additionally, the first ventilatory threshold (VT1) provides valuable insight into the transition from aerobic to anaerobic metabolism, indicating the point at which ADLs may become more fatiguing and less sustainable. Portable spirometry enables real-time measurement of oxygen consumption during standardized ADL tasks, particularly those representative of home-based functioning, as illustrated in **Chapter 5**. This facilitates meaningful comparisons between persons with LLA and helps identify strategies to reduce relative aerobic load, especially in those with low physical resilience. Interventions may include aerobic training, strength and balance exercises, gait retraining, or prosthetic optimization. Linking these physiological parameters to participation goals and quality of life is essential for developing meaningful, personalized rehabilitation programs.

When CPET is available, integrating results into rehabilitation planning can enhance safety, efficiency, and outcomes. Periodic reassessment allows for monitoring progress and adjusting goals based on ventilatory thresholds such as $\dot{V}O_2$peak and VT1. Structured data collection across centres could support the development of reference values and predictive models for each specific diagnostic group. In the future, simpler and more accessible tests that correlate strongly with $\dot{V}O_2$peak or VT1 may facilitate broader implementation. Importantly, CPET data may also inform discharge planning and rehabilitation potential.

A clinical example: an older adult with a transtibial amputation was initially referred to a geriatric facility due to low mobility scores and comorbidities. However, after a short inpatient rehabilitation stay focused on nutrition, early mobilization, and psychological support, the patient regained sufficient strength and balance to walk independently with a prosthesis. This allowed for discharge to his home setting with outpatient follow-up, rather than long-term institutional care. This example highlights the potential for recovery when assessments are dynamic and person-centered. Simple fitness assessments, such as short walking tests, grip strength, or portable metabolic measurements, may help predict prosthetic ambulation potential and guide personalized rehabilitation strategies. However, the predictive value and clinical applicability of these tools in persons with LLA require further investigation to ensure their reliability and effectiveness in diverse rehabilitation settings.

Prerehabilitation and preoperative fitness in persons at risk of LLA

Although this thesis primarily focuses on rehabilitation following LLA, it is reasonable to assume that better physical fitness prior to surgery may positively influence postoperative recovery and rehabilitation outcomes, as observed in other patient populations. Entering surgery in a more favorable physiological state may enhance functional progress and improve tolerance to rehabilitation efforts. However, evidence specific to the LLA population remains limited [25].

Strengths and limitations

A common limitation in research involving persons with LLA is the consistently small sample sizes, which, combined with person-specific variability, restrict robust statistical analysis and weaken the generalizability of findings. This makes it difficult to translate results into clinical practice or tailor them to the person. As discussed in **Chapter 3**, selection bias, such as low response rates and limited willingness to participate, further reduces both the size and representativeness of study populations. These methodological issues were also evident in **Chapter 2**, where poor quality of the included studies and inconsistent reporting complicated analysis. Many studies lacked detailed descriptions of participant characteristics and key predictors of metabolic cost, such as age and comorbidities. Combined with heterogeneity in study designs and outcome measures, these limitations made conventional meta-analysis unfeasible, leading to the use of a linear mixed model based on reported means, which limits both precision and generalizability.

To enhance clinical relevance, **Chapter 4** interpreted CPET outcomes using reference values from the Dutch, Flemish Lowlands Fitness Registry rather than international standards [5]. This choice was made due to the limited applicability of norms from sources like ACSM and Wasserman [4,26], which are based on American populations and may not reflect Dutch characteristics, such as average body weight, activity levels, and general health. While the Lowlands Registry offers a more contextually appropriate benchmark, it is important to note that these reference values are derived from healthy, able-bodied persons and are not specific to those with physical impairments. This highlights the need for LLA-specific reference values to enable more accurate assessments and support individualized rehabilitation strategies.

In **Chapter 5**, the Timed Up and Go Test (TUGT) was used as a functional assessment. Due to its short duration, the EPOC method is less suitable, as energy expenditure in such tasks is primarily anaerobic. This underscores the importance of selecting physiological assessment methods that match the nature and duration of the ADL. For brief, high-intensity tasks like the TUGT, alternatives such as heart rate recovery, lactate measurements, or wearable accelerometry may offer more accurate insights. The Wingate Anaerobic Test (WAnT) [27] could also be considered for high-functioning persons with LLA to assess anaerobic power, though its high physical load and limited functional relevance mean it should be weighed against simpler alternatives, such as sit-to-stand or short walking tests.

A key strength of this thesis lies in its focus on individualized cardiorespiratory fitness data in relation to personal rehabilitation goals and ADLs considered important by the target population, as illustrated in **Chapters 3 and 5**. The study population reflects the diversity of persons with LLA in the Netherlands, with a predominance of vascular cases. This work marks an important step in demonstrating the value of personalized goal-setting based on physiological capacity and lays a foundation for training programs guided by ventilatory thresholds, such as $\dot{V}O_2$peak and VT1.

The ADL tasks selected in **Chapter 5** were based on validated functional assessments commonly used in clinical rehabilitation, enhancing ecological validity and facilitating comparison with routine practice. For persons with LLA, who often have reduced cardiorespiratory fitness, altered movement patterns, and additional health conditions, standard exercise guidelines may not be appropriate. Instead, using data that reflect the actual physiological demands of ADLs allows clinicians to design safe, tailored training programs. This approach emphasizes the need for rehabilitation strategies that are both evidence-based and tailored to the person's unique situation and goals.

Generalization of results

This thesis primarily focuses on cardiorespiratory fitness and relative aerobic load in persons with LLA. While these physiological parameters are central to understanding physical functioning, other factors, such as balance, muscular strength, motivation, and the ability to adapt to prosthetic use, also play a critical role in achieving rehabilitation goals. These aspects, not extensively addressed in this work, need further investigation.

The importance of individualized assessment and training extends beyond the LLA population. It is equally relevant for other diagnostic groups commonly encountered in rehabilitation medicine, such as persons post-stroke or those with neuromuscular or cardiopulmonary conditions. Across all populations, there exists a physiological ceiling to cardiorespiratory fitness. For instance, persons with LLA, stroke, or chronic obstructive pulmonary disease (COPD) may be limited at the pulmonary or muscular (myogenic) level, while those with cardiac conditions may reach their limit at the cardiovascular level [26]. Applying CPETs will increase understanding these limitations, which is essential for tailoring rehabilitation strategies to the individual's physiological profile.

FUTURE RESEARCH

To improve rehabilitation outcomes, future research should examine the minimum levels of cardiorespiratory fitness, strength, and endurance needed for safe and effective prosthetic ambulation. While benchmarks such as walking 100 meters continuously, or reaching a speed of 1.0 m/s mobility [28], are commonly used, they may be unrealistic for some persons with LLA, especially those with vascular causes or multiple comorbidities. Understanding the physiological demands behind these goals is key to developing personalized rehabilitation plans. These challenges are not limited to persons with LLA, as similar mobility limitations affect those with neurological or cardiopulmonary conditions. Insights from future research may therefore inform rehabilitation strategies across a broader range of populations.

A central focus of future research should be the definition of functional thresholds for prosthetic ambulation, by investigating $\dot{V}O_2$peak, muscular strength, and balance, along with walking speed and endurance. Large-scale CPET data collection across diverse LLA subgroups is needed to establish reference values for VT1 and $\dot{V}O_2$peak, adjusted for demographic and clinical factors. A shared CPET database would help identify physiological predictors and support evidence-based modeling.

Given the value of CPET, all rehabilitation centers should ideally have access to such facilities. Where this is not feasible, structured implementation protocols should guide the setup, including patient selection criteria, equipment needs, and staffing requirements. In the meantime, alternative assessments or referral pathways should be available. Portable spirometry during standardized ADLs can also provide insight into task-specific aerobic demands, supporting more tailored rehabilitation planning.

Understanding these physiological demands is essential for linking physical fitness to broader ICF outcomes, such as autonomy, participation, and quality of life. Research should explore whether improvements in $\dot{V}O_2$peak and VT1 lead to better social reintegration and mental well-being. For persons with low fitness, optimizing training, through comparisons of interval versus continuous, and home-based versus center-based programs, is crucial. Finally, wearable technologies offer promising tools for monitoring ADL performance, metabolic cost, and recovery, potentially enhancing feedback, self-management, and adherence. Together, these research directions aim to build a more personalized, data-driven, and functionally meaningful rehabilitation framework for persons with LLA.

CONCLUSION

This thesis highlights the critical role of cardiorespiratory fitness in the rehabilitation of persons with LLA, particularly in relation to the performance of ADLs. Across multiple studies, it was demonstrated that persons with LLA often exhibit significantly reduced $\dot{V}O_2$peak values compared to able-bodied reference populations, with many persons with LLA operating near or above their ventilatory threshold (VT1) during basic ADLs. These findings underscore the disproportionate physiological strain experienced by this population during ADLs typically considered light intensity.

The concept of relative aerobic load emerged as a key framework for understanding functional limitations in persons with LLA. By expressing oxygen consumption during ADLs relative to $\dot{V}O_2$peak or VT1, healthcare professionals can better assess the sustainability of ADLs and identify persons at risk of fatigue, reduced participation, or unsafe exertion. This approach also provides a physiological rationale for tailoring rehabilitation interventions, such as aerobic training, gait optimization, or prosthetic adjustments, to reduce relative load and improve functional outcomes.

Importantly, the heterogeneity of the LLA population, particularly the differences between vascular and traumatic etiologies, necessitates individualized assessment and goal-setting. Standardized reference values derived from able-bodied populations are insufficient for guiding rehabilitation in this group. Therefore, the use of cardiopulmonary exercise testing (CPET) is strongly recommended whenever feasible, as it provides objective, reliable and person-specific data on $\dot{V}O_2$peak and VT1. These parameters are essential for designing safe and effective training programs, especially for persons with LLA with low physical resilience, but also for other populations within rehabilitation setting.

To advance clinical practice and research, this thesis advocates for the development of a shared CPET database across rehabilitation centers. Such a resource would enable the establishment of population-specific reference values, support the identification of physiological predictors of functional outcomes, and facilitate the creation of predictive models. Additionally, future research should focus on validating simpler field-based tests and wearable technologies to estimate cardiorespiratory fitness and monitor ADL performance in real-world settings.

In conclusion, integrating individualized physiological assessment into rehabilitation programs offer a promising path toward more personalized, evidence-based care for persons with LLA. By aligning training intensity with actual physical capacity and functional goals, rehabilitation programs can become more effective, safer, and better suited to the diverse needs of this population.

Future case:

Mr. Y. a 66-year old man with diabetes mellitus type 2 and peripheral arterial disease, underwent a transtibial amputation due to chronic foot ulceration. Prior to surgery, prolonged inactivity had led to significant deconditioning. At home, he managed short distances using a wheelchair and crutches, supported by family.

Following the amputation, Mr. Y was referred to outpatient rehabilitation. During intake, he expressed goals of regaining independence in self-care (e.g., toileting, bathing, cooking), walking short distances with a prosthesis, and resuming driving to maintain social participation.

To assess his physical capacity, a CPET was performed. Mr. Y reached a $\dot{V}O_2$*peak of 13.2 ml/kg/min and a* $\dot{V}O_2$*-VT1 of 9.1 ml/kg/min (approx. 3.8 and 2.6 METs, respectively), indicating markedly reduced aerobic capacity with early onset of ventilatory threshold.*

Based on these results, a tailored rehabilitation program was developed. The program focused on low-intensity aerobic training below $\dot{V}O_2$*-VT1 to improve endurance without inducing excessive fatigue. Strength and balance exercises were executed to support safe transfers and prosthetic ambulation as well as gait training with a focus on energy efficiency and prosthetic alignment. Functional task practice (e.g., kitchen and bathroom activities) and pacing strategies were included to enhance daily functioning and energy management.*

Progress was monitored through periodic reassessment of $\dot{V}O_2$*peak with CPET and functional performance. After 12 weeks, Mr. Y demonstrated improved walking distance and reduced perceived exertion during ADLs. Although his* $\dot{V}O_2$*peak remained below normative values, the relative aerobic load during key ADLs had decreased, enabling him to perform these activities more sustainably and contributing meaningfully to the achievement of his rehabilitation goals.*

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Appendices

SAMENVATTING

Dit proefschrift, *Het beoordelen van de fysiologische belasting van dagelijkse activiteiten bij mensen met een beenamputatie*, richtte zich op de cardiorespiratoire fitheid en de fysiologische belasting van dagelijkse activiteiten bij mensen met een beenamputatie.

Een beenamputatie beperkt de mobiliteit en het uitvoeren van dagelijkse activiteiten aanzienlijk, vooral bij ouderen met comorbiditeiten. Deze groep heeft vaak al een lage cardiorespiratoire fitheid. Tegelijkertijd kosten activiteiten zoals lopen en traplopen veel energie. Generieke intensiteitsclassificaties, zoals Metabolic Equivalent of Task (MET) waarden worden vaak gebruikt om de energiebelasting van activiteiten te schatten. Deze waarden zijn echter gebaseerd op gezonde personen en geven geen realistische weergave van de werkelijke belasting bij mensen met een beenamputatie. Voor hen zijn dagelijkse activiteiten vaak veel zwaarder, waardoor de standaard MET-schattingen de inspanning aanzienlijk onderschatten.

Om de belasting van dagelijkse activiteiten bij mensen met een beenamputatie beter te begrijpen, is het belangrijk om niet alleen het absolute energieverbruik te meten, maar ook de relatieve belasting ten opzichte van de individuele capaciteit. Parameters zoals $\dot{V}O_2$peak (maximale zuurstofopname) en de eerste ventilatoire drempel (VT1) geven inzicht in de maximale aerobe capaciteit en het omslagpunt waarbij inspanning merkbaar zwaarder wordt. Er is echter weinig kennis over VT1, relatieve aerobe belasting en hun relatie tot dagelijkse activiteiten bij mensen met een beenamputatie. Dit gebrek aan kennis, in combinatie met interindividuele variatie, bemoeilijkt het ontwikkelen van gepersonaliseerde trainingsprogramma's. Het kan bovendien leiden tot onrealistische revalidatiedoelen en maakt een adequate evaluatie van trainingsinterventies lastig.

Dit promotieonderzoek bestond uit twee delen. Het eerste deel had als doel om inzicht te krijgen in wat er in de literatuur bekend is over de metabole kosten en de (relatieve) belasting van verschillende dagelijkse activiteiten bij mensen met een beenamputatie. Daarnaast werd onderzocht welke activiteiten volgens mensen met een beenamputatie en professionals het belangrijkst zijn. Het tweede deel richtte zich op het in kaart brengen van de cardiorespiratoire fitheid van mensen met een beenamputatie en een methode te ontwikkelen om de relatieve aerobe belasting bij verschillende activiteiten te meten, zodat de individuele relatieve aerobe belasting van een activiteit nauwkeurig kan worden vastgesteld.

In hoofdstuk 2 '*Metabole kosten van dagelijkse activiteiten bij mensen met een beenamputatie: een systematische review en meta-analyse*' werd een systematische review en meta-analyse uitgevoerd naar de metabole kosten van dagelijkse activiteiten bij mensen met een beenamputatie. In totaal werden 61 studies met 1.912 deelnemers geïncludeerd, waarbij de meeste onderzoeken zich richtten op lopen met een prothese. De resultaten toonden aan dat zuurstofverbruik en hartslag tijdens het lopen hoger waren bij mensen met een beenamputatie dan bij controles. Het effect van loopsnelheid was duidelijk: hoe sneller men loopt, hoe hoger het zuurstofverbruik, met een sterker effect bij mensen met een transfemorale amputatie. De reden van beenamputatie bleek geen significante voorspeller van energieverbruik, mogelijk door beperkte beschikbare data in de literatuur of het niet goed beschrijven van subgroepen. Over andere activiteiten dan lopen is nauwelijks literatuur beschikbaar. De kwaliteit van de studies was laag en deelnemers waren relatief gezond, waardoor de generaliseerbaarheid naar de mensen met comorbiditeit en oudere leeftijd beperkt is. De review laat zien dat meer onderzoek naar andere dagelijkse activiteiten, met name bij oudere mensen met comorbiditeit, noodzakelijk is om revalidatieprogramma's te optimaliseren.

In Hoofdstuk 3 '*De belangrijkste dagelijkse activiteiten: de mening van mensen met een beenamputatie en zorgprofessionals verschilt aanzienlijk*' werd onderzocht welke dagelijkse activiteiten volgens mensen met een beenamputatie het belangrijkst waren om zelfstandig uit te voeren, in vergelijking met de perceptie van zorgprofessionals. Een totaal van 125 mensen met een beenamputatie en 44 zorgprofessionals selecteerden en rangschikten tien activiteiten uit een lijst van veertig. Er bleken significante verschillen in de rangorde van de belangrijkste activiteiten tussen beide groepen. Mensen met een beenamputatie vonden autorijden, fietsen, traplopen, zware inspanning en maaltijden bereiden belangrijker, terwijl professionals meer nadruk legden op basisactiviteiten zoals naar het toilet gaan, in en uit bed komen en binnenshuis lopen. Subgroep-analyses lieten bovendien zien dat leeftijd en reden van beenamputatie invloed hebben op prioriteiten. Deze resultaten benadrukken het belang van gedeelde besluitvorming en communicatie in het revalidatieproces.

Hoofdstuk 4 '*Cardiorespiratoire fitheid bij mensen met een beenamputatie*' analyseerde cardiorespiratoire fitheid bij mensen met een beenamputatie op basis van cardiopulmonale inspanningstesten (CPET) bij 74 mensen in een revalidatiecentrum. De $\dot{V}O_2$peak was gemiddeld 14,6 ml/kg/min, ruim lager dan referentiewaarden voor mensen zonder beenamputatie (circa 30–40 ml/kg/min). Oudere leeftijd bleek de enige significante voorspeller voor lagere $\dot{V}O_2$peak; andere factoren zoals amputatieniveau, reden van amputatie, geslacht en type ergometer hadden geen significante invloed op

$\dot{V}O_2$peak. Het objectief vaststellen van de individuele fitheid is van groot belang, omdat er aanzienlijke verschillen tussen mensen kunnen bestaan. Zonder een individuele meting is het vaak niet mogelijk om de werkelijke capaciteit en belastbaarheid van een persoon goed in te schatten, zeker bij mensen met comorbiditeit. Schattingen op basis van generieke intensiteitsclassificaties, algoritmes of submaximale testen kunnen leiden tot onrealistische revalidatiedoelen of trainingsprogramma's die te licht of juist te zwaar zijn. Dit vergroot het risico op onvoldoende vooruitgang of overbelasting. CPET bleek veilig en haalbaar en wordt daarom aanbevolen om de cardiorespiratoire fitheid objectief vast te stellen en gepersonaliseerde trainingsprogramma's te ondersteunen.

Hoofdstuk 5 '*Relatieve aerobe belasting van dagelijkse activiteiten bij mensen met een beenamputatie: een pilotstudie* ' beschrijft een protocol dat werd toegepast om de relatieve aerobe belasting van dagelijkse activiteiten bij personen met een beenamputatie te bepalen. Vijf gestandaardiseerde testen, variërend van korte tot langere activiteiten zoals de 6-minutenlooptest, traplopen en de Glittre ADL-test, werden uitgevoerd. Met behulp van de methode voor extra zuurstofverbruik na inspanning (Excess Post-exercise Oxygen Consumption, EPOC) en CPET werd de belasting uitgedrukt als percentage van de VT1. De EPOC-methode maakt gebruik van het verhoogde zuurstofverbruik na inspanning om de totale inspanningsbelasting te bepalen, wat een nauwkeuriger beeld geeft van de fysiologische belasting van een activiteit dan enkel meten tijdens de activiteit. Het protocol bleek haalbaar en veilig, hoewel kleine aanpassingen nodig waren om de Glittre ADL-test geschikt te maken voor deelnemers met loophulpmiddelen. De resultaten toonden aan dat vrijwel alle geteste activiteiten meer dan 100% van $\dot{V}O_2$-VT1 vereisten, wat duidt op een aanzienlijke fysiologische belasting. Er was echter grote variatie tussen deelnemers, wat het belang van individuele beoordeling benadrukt. Deze bevindingen onderstrepen dat generieke intensiteitsclassificaties onvoldoende zijn voor deze populatie. Individuele metingen van $\dot{V}O_2$peak en VT1 zijn belangrijk om over- of onderschatting van inspanning te voorkomen. Het identificeren van deze verschillen is daarom van belang voor het opstellen van gepersonaliseerde revalidatieprogramma's. Verdere studies met grotere groepen zijn nodig om de betrouwbaarheid en generaliseerbaarheid van deze methode te bevestigen.

De *algemene discussie* benadrukt dat lopen en andere dagelijkse activiteiten bij mensen met een beenamputatie aanzienlijk meer fysiologische belasting vergen dan bij gezonde mensen, vooral bij hogere loopsnelheden en een proximaler amputatieniveau. Cardiorespiratoire fitheid in de onderzochte populatie was laag en moeilijk te voorspellen, waarbij leeftijd de enige significante factor was. Activiteiten die mensen met een beenamputatie doen, liggen mogelijk vaak boven VT1, wat wijst op hoge inspanning en risico op vermoeidheid. De resultaten benadrukken het belang van individuele beoordeling van fitheid met CPET en gepersonaliseerde revalidatieprogramma's, afgestemd op fysiologische capaciteit en persoonlijke doelen. Voor de klinische praktijk is toekomstig onderzoek nodig om specifieke referentiewaarden vast te stellen voor mensen met een beenamputatie, praktische en valide functionele testen te ontwikkelen die eenvoudig in een revalidatiesetting kunnen worden toegepast, en draagbare technologie te integreren voor het monitoren van inspanningsbelasting tijdens dagelijkse activiteiten. Deze stappen ondersteunen gepersonaliseerde revalidatie en verbeteren zowel veiligheid als effectiviteit van interventies. Door deze inzichten kunnen revalidatieprogramma's realistischer, veiliger en effectiever worden ingericht, wat uiteindelijk kan bijdragen aan een betere participatie en kwaliteit van leven voor mensen met een beenamputatie.

SUMMARY

This thesis, *Assessing the physiological demands of daily life in persons with lower limb amputation*, focused on cardiorespiratory fitness and the physiological demands associated with activities of daily living (ADL) in persons with a lower limb amputation (LLA). LLA leads to significant limitations in mobility and daily functioning, particularly in older persons with comorbidities. These persons often have low cardiorespiratory fitness, while activities such as walking and stair climbing require more energy. Standard intensity classifications, such as Metabolic Equivalent of Task (MET) values, are commonly used to estimate the energy cost of activities. However, as these values are based on healthy persons, they do not accurately reflect the actual load for persons with LLA.

To better understand the physiological load of daily activities in persons with LLA, it is important not only to measure absolute oxygen consumption, but also to determine the relative aerobic load compared to individual capacity. Parameters such as $\dot{V}O_2$peak (maximum oxygen uptake) and the first ventilatory threshold (VT1) provide insight into aerobic capacity and indicate the point at which exertion becomes noticeably harder. However, little is known about VT1, relative aerobic load, and their relationship to daily activities in persons with LLA. This knowledge gap, combined with interindividual variability, complicates the development of personalized training programs. It can also lead to unrealistic rehabilitation goals and complicates adequate evaluation of training interventions.

This dissertation consisted of two parts. The first part aimed to review the current literature on the metabolic cost and (relative) load of various daily activities in persons with LLA. It also explored which activities were considered most important by persons with LLA and by professionals. The second part focused on mapping cardiorespiratory fitness in this population and on developing a method to measure the relative aerobic load of different ADL tasks, allowing accurate assessment of individual relative load.

Chapter 2 presented a systematic review and meta-analysis of metabolic costs during ADL in persons with LLA. Sixty-one studies involving 1,912 participants were included, most focusing on walking with a prosthesis. Results showed that oxygen consumption and heart rate during walking were significantly higher in persons with LLA compared to able-bodied controls, especially at higher walking speeds. The effect of walking speed was clear: the faster the pace, the higher the oxygen consumption. Additionally, persons with transfemoral amputations showed substantially higher metabolic costs compared to those with more distal amputations. The reason for LLA was not a

significant predictor, possibly due to limited data or poor subgroup descriptions. Data on activities other than walking were scarce. Study quality was low, and participants were relatively healthy, which limited generalizability of the findings to older persons with comorbidities. More research on other ADL and more diverse groups is needed to optimize rehabilitation programs.

Chapter 3 investigated which daily activities persons with LLA considered most important to perform independently and compared these priorities with the views of healthcare professionals. A total of 125 persons with LLA and 44 healthcare professionals ranked ten activities from a list of forty. Significant differences were found between groups: persons with LLA prioritized driving, cycling, stair climbing, heavy exertion, and meal preparation, while professionals emphasized basic activities such as toileting, getting in and out of bed, and indoor walking. Subgroup analyses showed that age, amputation level, and cause of LLA influenced priorities. These findings highlighted the importance of shared decision-making and communication in rehabilitation.

Chapter 4 analyzed cardiorespiratory fitness determined with cardiopulmonary exercise testing (CPET) in 74 persons with LLA in a rehabilitation setting. The mean peak oxygen uptake ($\dot{V}O_2$peak) was 14.6 ml/kg/min, which was substantially lower than reference values for able-bodied controls (approximately 30–40 ml/kg/min). Older age was the only significant predictor of lower $\dot{V}O_2$peak; other factors such as amputation level, cause of LLA, gender, and type of ergometer showed no significant association. Due to the large variability observed, objective assessment of individual fitness seemed essential. Without individual measurement, true capacity and aerobic load tolerance could not be accurately estimated, especially in those with comorbidities. Relying on generalized reference values or submaximal tests could lead to setting unrealistic goals or prescribing inappropriate training loads. CPET proved to be safe and feasible and was recommended as a standard assessment to tailor personalized training programs.

Chapter 5 introduced a protocol designed to determine relative aerobic load during standardized tests representing daily activities. Five standardized tests were conducted, including the 6-minute walk test, stair climbing, and the Glittre ADL test. Using the Excess Post-exercise Oxygen Consumption (EPOC) method and CPET, the load was expressed as a percentage of VT1. The EPOC method utilized elevated post-exercise oxygen consumption to estimate total exertion, providing a more accurate representation of physiological load than measuring during the activity alone. The protocol proved feasible and safe, although minor adjustments were needed for participants using walking aids. Results showed that nearly all tested activities exceeded 100% of $\dot{V}O_2$-VT1, indicating substantial physiological load. The large interindividual variation underscored the need for individual assessment. Generic intensity classifications were inadequate for this population. Individual $\dot{V}O_2$peak and VT1 measurements are essential to avoid over- or underestimation of effort. Further studies with larger samples are needed to confirm reliability and generalizability.

The general discussion emphasized that walking and other ADL in persons with LLA required considerably more physiological effort than in able-bodied controls, particularly at higher speeds and with proximal amputations. Cardiorespiratory fitness was found to be low and difficult to predict, with age as the only significant predictor. Activities often exceeded VT1, indicating high exertion and fatigue risk. These results highlighted the importance of individualized assessment using CPET and personalized rehabilitation programs tailored to physiological capacity and personal goals. Future research should establish reference values for this population, develop practical functional tests for clinical settings, and integrate wearable technology to monitor exertion during daily activities. These steps would support personalized rehabilitation and improve safety and effectiveness, ultimately enhancing participation and quality of life.

APPENDIX B

Author contribution using the Contributor Role Taxonomy (CRediT)

Contribution of the PhD Candidate The contributions of the PhD candidate, **Loeke van Schaik**, to this thesis are detailed below for each chapter, using the Contributor Role Taxonomy (CRediT). Contributions are listed according to role definitions as established by the CRediT system.

Chapter 2: Metabolic costs of activities of daily living in persons with a lower limb amputation: A systematic review and meta-analysis.

- Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.
- Investigation: conducted literature search in 5 databases and performed screening title/abstract and articles for eligibility. Responsible for collecting, organizing, and storing research data extracted from included articles, including cleaning and structuring datasets, and maintaining associated files to ensure data integrity, accessibility, and long-term usability.
- Project Administration: Responsible for planning and organization of the study.
- Methodology: Designed the protocol following PRISMA guidelines for systematic review.
- Formal Analysis: Conducted statistical analyses using SPSS.
- Validation: Assessed the quality of included studies using AHRQ checklist.
- Visualization: Created the PRISMA flowchart and meta-analysis results, tables with data of the included studies.
- Writing – Original draft preparation: Wrote initial draft, revised content following feedback from co-authors and supervisory team.
- Writing – Review & Editing: Revised content following feedback editor and reviewers, with co-authors and the supervisory team.

Chapter 3: The most important activities of daily functioning; the opinion of persons with lower limb amputation and healthcare professionals differ considerably.

- Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team.
- Investigation: Responsible for participant recruitment, data collection, and storing research data, including cleaning and structuring datasets, and maintaining associated files to ensure data integrity, accessibility, and long-term usability.
- Project Administration: Responsible for planning and organization of the study.
- Methodology: Developed the questionnaire and study design in collaboration with the supervisory team and students.

- Formal Analysis: Conducted statistical analyses using SPSS.
- Visualization: Created the figures and tables with data of the results.
- Writing – Original draft preparation: Wrote initial draft, revised content following feedback from co-authors and supervisory team.
- Writing – Review & Editing: Revised content following feedback editor and reviewers, with co-authors and the supervisory team.

Chapter 4: Cardiorespiratory fitness in persons with lower limb amputation.

- Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team and co-authors.
- Investigation: Responsible for participant recruitment, data collection, and storing research data, including cleaning and structuring datasets, and maintaining associated files to ensure data integrity, accessibility, and long-term usability.
- Project Administration: Responsible for planning and organization of the study.
- Formal Analysis: Conducted statistical analyses using SPSS.
- Visualization: Created the figures and tables with data of the results.
- Writing – Original draft preparation: Wrote initial draft, revised content following feedback from co-authors and supervisory team.
- Writing – Review & Editing: Revised content following feedback editor and reviewers, with co-authors and the supervisory team.

Chapter 5: Relative aerobic load of daily activities in persons with lower limb amputation; a pilot study.

- Conceptualization: Conceived the research questions and study design in collaboration with the supervisory team and co-authors.
- Investigation: Responsible for participant recruitment, data collection, and storing research data, including cleaning and structuring datasets, and maintaining associated files to ensure data integrity, accessibility, and long-term usability.
- Project Administration: Responsible for planning and organization of the study.
- Formal Analysis: Conducted statistical analyses using SPSS.
- Supervision: Supervised student while participating in data collection and data analysis.
- Writing – Original draft preparation: Wrote initial draft, revised content following feedback from co-authors and supervisory team.
- Writing – Review & Editing: Revised content following feedback editor and reviewers, with co-authors and the supervisory team.

General Contributions (Applicable to Entire Thesis)

- Funding Acquisition: Application for funding to cover expenses for Chapter 5, including materials, staff time, and participant-related costs.
- Writing – Review & Editing: Performed final review and editing of all thesis chapters based on committee feedback.

A

DANKWOORD

Hoewel mijn naam op de kaft staat, wil ik beginnen met iedereen te bedanken die heeft bijgedragen. Dit werk heb ik zeker niet alleen gedaan. Het samenwerken met zoveel verschillende mensen maakte het niet alleen mogelijk, maar vooral ook ontzettend leuk! Dank aan alle deelnemers die bereid waren mee te doen.

Natuurlijk ging het niet altijd van een leien dakje. Soms zat het even tegen, soms zat het wat langer tegen.. Maar samen hebben we het toch maar mooi voor elkaar gekregen en daar ben ik ontzettend trots op!

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A