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DOI:
10.1002/pmrj.12944

Received: 13 October 2021 | Revised: 30 November 2022 | Accepted: 27 December 2022

DOI: 10.1002/pmrj.12944

ORIGINAL ARTICLE—CME

PM&R

Influence of traumatic lower-limb amputation on physical activity, body composition, and cardiometabolic risks: A descriptive preliminary study

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Abstract

Background: Following traumatic lower-limb amputation (LLA), humans are predisposed to numerous unfavorable changes in health, including the development of secondary chronic health conditions such as metabolic disorders and cardiovascular disease.

Objective: To determine within and between group differences in cardiometabolic component risks, body composition, and physical activity (PA) in individuals with traumatic unilateral and bilateral LLA, compared to noninjured controls.

Design: Prospective observational cohort study.

Setting: A military complex trauma rehabilitation center.

Participants: Sixteen males with traumatic LLA (8 unilateral, mean age 30 ± 5 years and 8 bilateral, mean age 29 ± 3 years). Thirteen active age-matched males with no LLA (28 ± 5 years) acted as controls and performed habitual activities of daily living.

Intervention: Participants with LLA attended two 4-week periods of inpatient rehabilitation, separated by two 6-week periods of home-based recovery.

Main Outcome Measures: Venous blood samples were taken prior to and following a 75 g oral glucose load, for determination of biomarkers, including insulin and glucose, at baseline and 20 weeks. Body composition (dual X-ray absorptiometry) was measured at baseline, 10 weeks, and 20 weeks. Daily PA was recorded using a triaxial accelerometer for 7 days during inpatient rehabilitation and while at home. Energy expenditure was estimated using population-specific equations.

Results: Individuals with bilateral LLA demonstrated more unfavorable mean body composition values, lower PA, and increased cardiometabolic health risk compared to controls. Cardiometabolic syndrome was identified in 63% of individuals with bilateral LLA. No statistically significant differences in cardiometabolic component risk factors, body composition, and estimated daily PA were reported between unilateral LLA and control groups ($p > .05$). While at home, mean PA counts.day^{-1} reduced by 17% ($p = .018$) and 42% ($p = .001$) in the unilateral and bilateral LLA groups, respectively.

Conclusions: Despite extensive inpatient rehabilitation, cardiometabolic component risks are elevated in individuals with bilateral LLA but are comparable between unilateral LLA and active noninjured control groups. Innovative strategies that improve/support the long-term PA and cardiometabolic health of severely injured individuals with bilateral LLA are warranted.

INTRODUCTION

Severe traumatic injuries, such as lower-limb amputation (LLA), can result in extensive long-term health care and rehabilitation needs. The restoration of physical function and maintenance of physical activity (PA) are considered vital therapeutic component in the short-term rehabilitation and long-term recovery of individuals following LLA.[1] Current evidence suggests an increased prevalence of physical inactivity and reduced functional status in individuals with LLA.[2] Despite advanced prosthetic technology and rehabilitative care, current efforts have been unsuccessful in mitigating the effects of severe traumatic injury.

Following traumatic LLA, humans are predisposed to numerous unfavorable changes in health and well-being.[3] These include changes in body composition, characterized by lower-limb skeletal muscle atrophy and the development of central and peripheral adiposity.[4] Such adaptations are commonly associated with, and thought to lead to, the development of secondary chronic health conditions, including cardiovascular disease and type 2 diabetes mellitus.[5] Changes in clinically relevant systemic biomarkers of these conditions, including changes in blood lipid profiles, inflammatory cytokines, and insulin and glucose concentrations/sensitivity, might provide insight into the early development and ensuing risk of chronic disease in this population.[5–7]

Unfortunately, the majority of studies investigating cardiometabolic component risks following traumatic LLA are now over 20 years old,[8–11] which predates many recent developments in prosthetic design/technology and multidisciplinary rehabilitation care. It therefore remains unclear if previously physically active and healthy individuals with LLA have compromised cardiometabolic health following intensive exercise-based rehabilitation. The aim of this longitudinal cohort study was therefore to determine whether (1) cardiometabolic component risks are elevated among the more severely injured individuals with bilateral LLA, compared to those with unilateral LLA and healthy age-matched noninjured controls; (2) body fat, particularly visceral adipose tissue (VAT), is greater among those with bilateral LLA compared to those with unilateral LLA and controls; (3) estimates of PA energy expenditure would be lower in those with LLA compared to controls; and (4) PA energy expenditure is further compromised when individuals with LLA are at home compared to inpatient rehabilitation.

METHODS

Study design

A descriptive 20-week longitudinal observational cohort study design was used to compare the effect of two 4-week inpatient admissions interspersed by two 6-week blocks of active recovery at home. PA behavior, body composition, and cardiometabolic component risks in individuals with traumatic unilateral LLA and bilateral LLA compared to an active control group without LLA were assessed. The trial protocol was approved by the UK Ministry of Defence Research Ethics Committee (Reference number: 512/MOD-REC/14) and conforms to Helsinki Declaration. All participants provided written informed consent. Figure 1 provides a schematic representation of the study design detailing the measurements taken over the 20-week observation period. The complex trauma rehabilitation care pathway at the UK Defence Medical Rehabilitation Centre (DMRC) has been described previously.[12] While at home, patients were provided with an individualized exercise program and encouraged to participate in regular activities of daily living (ADL) while wearing their prosthetic limb(s).[12]

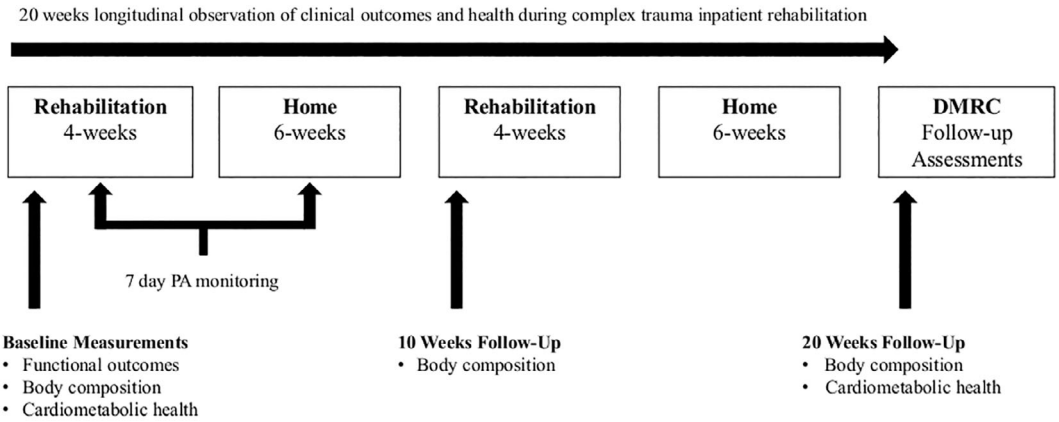

FIGURE 1 Schematic description of the longitudinal observational cohort study design. Abbreviations: DMRC, Defence Medical Rehabilitation Centre; PA, physical activity.

Study participants

Participant characteristics are provided in Table 1. Participants who met the following eligibility criteria were included in the study: male, aged 18–50 years, with traumatic unilateral or bilateral LLA, and known to require a further three inpatient rehabilitation admissions at DMRC (enabling the monitoring of the final 20 weeks of the rehabilitation care pathway). Exclusion criteria included known medical discharge/last admission date that did not allow for three inpatient admissions to DMRC, planned surgery during the data

TABLE 1 Baseline participant characteristics: injury and functional status

	Unilateral LLA group	Bilateral LLA group	Normative controls
Number	8	8	13
Age (years)	30 ± 5	29 ± 3	28 ± 5
Injury Characteristics			
Time since amputation			
<1 year	3 (37.5)	-	-
1 to 2 years	4 (50)	2 (25)	-
2 to 3 years	1 (12.5)	2 (25)	-
3 to 4 years	-	2 (25)	-
>4 years	-	2 (25)	-
Level of amputation			
Below knee	6 (75)	-	-
Through knee	1 (12.5)	-	-
Above knee	1(12.5)	-	-
Bilateral - below knee	-	1 (12.5)	-
Bilateral - below/above knee	-	1 (12.5)	-
Bilateral - through knee	-	2 (25)	-
Bilateral - above knee	-	4 (50)	-
Secondary injuries			
Fractures	3 (37.5)	8 (100)	-
Nerve damage	1 (12.5)	2 (25)	-
Soft tissue or vascular trauma	6 (75)	8 (100)	-
Location of secondary injuries			
Head/neck/face	1 (12.5)	5 (62.5)	-
Chest/upper back	1 (12.5)	5 (62.5)	-
Upper limbs	1 (12.5)	8 (100)	-
Spine	-	3 (37.5)	-
Abdomen	1 (12.5)	4 (50)	-
Pelvis	2 (25)	6 (75)	-
Lower limbs	7 (87.5)	8 (100)	-
Functional Outcomes			
Physical function			
6-MWD (m) *	574 ± 66	337 ± 85	705 ± 32
AMP†	46 ± 1	40 ± 4	-
DMRC - mobility			
Able to run independently	1 (12.5%)	0 (0%)	13 (100%)
Able to walk independently	8 (100%)	5 (62.5%)	13 (100%)
Requires a walking aid / adaptation	0 (0%)	3 (37.5%)	0 (0%)

Note: Data are presented as mean ± SD for continuous variables or as number of participants (%) for categorical variables.
Abbreviations: 6-MWD, six-minute walk distance; AMP, amputee mobility predictor; DMRC, Defence Medical Rehabilitation Centre; LLA, lower-limb amputation.
*Significant differences between individuals with unilateral and bilateral amputation, unilateral amputation and normative controls, and bilateral amputation and normative controls ($p < .001$).
†Significant difference between individuals with unilateral and bilateral amputation ($p < .05$).

collection study period (potential risk of systemic inflammatory response and interrupted progression of physical rehabilitation), severe traumatic brain injury, insufficient wound healing around the residuum (screened by physician), or unable to ambulate using a prosthesis (screened by physiotherapist). Ninety-seven percent of UK military service personnel admitted to DMRC with traumatic LLA are men.[12] At the time of recruitment, no women were attending the DMRC complex trauma rehabilitation care pathway with an LLA who had multiple inpatient admissions remaining. Retrospectively, no females were admitted to DMRC who met the eligibility criteria during the data collection period.

A convenient sample of age-matched, noninjured active males, employed within physically active roles in the UK Ministry of Defence (ie, physiotherapists and exercise rehabilitation instructors), who engaged in aerobic or resistance-based training at least three times per week, were recruited to act as normative controls. Being employed in physically active roles, the control group is more likely to resemble the PA status demonstrated preinjury in both LLA groups (front-line infantry roles), allowing us to consider the impact of traumatic limb loss in a previously physical active population. Owing to their physically demanding job roles and regular engagement in structured physical exercise, the control group is not representative of the wider general population.

OUTCOME MEASURES

Biomarkers of cardiometabolic component risk

Blood sampling and oral glucose tolerance test

Given that skeletal muscle is an important glucose disposal site during postprandial conditions,[5] it is currently unclear what impact the effects of muscle atrophy and/or diminished lower-limb muscle strength following LLA may have on metabolic health. Blood sampling occurred on two separate occasions during the study; within 3 days of commencing inpatient rehabilitation (baseline admission) and at the 20-week follow-up (Figure 1). All participants reported to the laboratory in the morning following an overnight fast (≥10 hours). A cannula was inserted into the antecubital vein and a 25-mL blood sample drawn. Within 5 minutes of the baseline blood sample being drawn, participants consumed 140 g of a carbohydrate supplement equivalent to 75 g of glucose. Blood samples were then obtained every 15 minutes for the first hour and every 30 minutes during the second hour. Following centrifugation of whole blood, plasma and serum samples were subsequently dispensed into 0.5-mL aliquots using a pipette and immediately stored in a freezer at −80°C.

Blood analyses

All blood analyses were performed in duplicate using a batch analysis. Concentrations of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triacylglycerol, nonesterified fatty acids (NEFA), plasma glucose, and C-reactive protein (CRP) were conducted on a Daytona analyzer, according to manufacturer instructions, using commercially available assays. Enzyme-linked immunosorbent assays (ELISA) were used to measure serum insulin concentrations. Absorption was determined using a microplate reader at the wavelengths specified by the manufacturer.

Derived indices

In order to simplify data analyses and facilitate the interpretation of complex data,[13,14] serial measurements of glucose and insulin responses following oral glucose tolerance test were converted into simple summary statistics,[15] such as incremental area under the curve (iAUC)[16] and insulin sensitivity index (ISI-Matsuda).[17] The homeostasis model assessment (HOMA) calculator, incorporating the updated HOMA-2 model,[18] was also used to derive fasting estimates of pancreatic β-cell function, insulin resistance, and sensitivity, both at rest and post exercise. Metabolic syndrome was determined using established cut-point criteria from the International Diabetes Foundation.[19] These criteria (for men) include increased "abdominal" obesity (waist circumference ≥ 94 cm), hypertriglyceridemia (≥1.7 mmol/L), reduced HDL cholesterol (<1.03 mmol/L), hyperglycemia (fasted plasma glucose ≥5.6 mmol/L), and hypertension (blood pressure ≥ 130/85 mm Hg).

Body composition

Body composition was determined using a dual-energy X-ray absorptiometry (DXA) and administered at three time points; baseline, 10 weeks, and 20 weeks. DXA was performed within 3 days of arriving at DMRC for each respective inpatient admission and time matched for controls. Scans were analyzed for total mass, fat mass, lean mass, percentage body fat, android/gynoid fat percentage, and VAT area following the guidelines described in the user manual. The android region represents the proportion of fat around the abdomen, and the gynoid region represents the gluteofemoral fat depot. Android and gynoid fat distribution is commonly estimated via the anthropometric assessment of waist-

to-hip ratio. Body height was measured and recorded to the nearest centimeter using a stadiometer. For individuals with bilateral LLA, preinjury body height was used. Waist and hip circumference were taken at baseline only. Waist measurements were taken at the midway point between the lowest rib and the top of the iliac crest, with hip circumference taken as the widest part of the buttocks. The mean of three measurements was used.

Estimating daily ambulatory physical activity parameters

Participants wore an Actigraph GT3X+ triaxial accelerometer on the hip of their shortest residual limb (right hip for controls) using an elasticated belt, which has previously been validated as an accurate method for estimating ambulatory PA energy expenditure with population-specific LLA equations.[20] Individuals with LLA wore the device for 7 continuous days during inpatient rehabilitation at DMRC and 7 continuous days during active recovery at home. Control participants wore their device for 7 continuous days during a normal week of employment. All participants were told to remove the monitor before participating in any water-based activity (ie, hydrotherapy, showering) and during sleeping hours. After 7 days the participants returned the device and the data were downloaded onto the ActiLife version 6 software for subsequent analyses. Wear time validation analysis, an integral part of the ActiLife software, was performed using the Troiano equation prior to converting to an Excel file for analysis.[21] The ActiLife software defined nonwear time by an interval of at least 60 consecutive min whereby vector magnitude values remained constantly at zero. Based on a typical 8-hour sleep pattern and making allowances for water-based activities, >14 hours (87.5% of potentially available data) from a 16-hour waking day was considered an appropriate cut-point for a valid day. Vector magnitude data from the Actigraph was plotted against the corresponding 24-hour timestamp and visually inspected. Nonwear time vector magnitude data were excluded from the daily averages. An arbitrary unit called a physical activity count (PAC), calculated through summing the change in raw acceleration values measured during a specific interval of time or "epoch" was used as a surrogate marker of PA levels per day.

Functional outcomes

To provide an insight into the physical functional status of the LLA participants, a variety of functional outcomes were captured at baseline. These variables were: 6-minute walk distance,[22] amputee mobility predictor,[23] and a DMRC-specific question relating to mobility.[24]

Statistical analysis

Mixed model analysis of variance (ANOVA) tests with Bonferroni post hoc analysis were performed to assess differences between the three groups (unilateral LLA, bilateral LLA, control) at baseline and over time for cardiometabolic component risk biomarkers and body composition outcomes. In order to simplify data analysis and facilitate the interpretation of a complex data set, serial measurements of glucose and insulin responses to the oral glucose tolerance test at baseline and follow-up were converted into simple summary statistics (ie., fasting and peak concentrations, time to peak, iAUC, and estimates of insulin resistance and sensitivity[15]). ANOVA were performed irrespective of any minor deviations from a normal distribution but with Greenhouse–Geisser corrections applied to intraindividual contrasts where $\epsilon < 0.75$ and the Huynh-Feldt corrections applied for less severe asphericity.[25] Where significant interactions were observed, one-way ANOVAs (for three group or time-point comparisons) with Bonferroni post hoc analysis or multiple *t*-tests were applied to determine the location of variance both between time points within each group relative to baseline.

PACs and PA energy expenditure responses within and between amputation groups were determined by a two-way (group [unilateral, bilateral] × environment [rehabilitation, home]) mixed-model ANOVA. Where significant interactions were observed between the two amputation groups, multiple *t*-tests were applied to determine differences between groups and/or environments. As the control group wore the device in one environment only (during employment), a one-way ANOVA was used to determine the differences in PA between the three groups (ie, both amputation groups during a week of rehabilitation vs. control participants at work; and both amputation groups during a week at home versus controls at work). All data are presented in text and tables as mean ± SD, whereas error bars on figures represent SEM. Mean and the lower and upper 95% confidence interval (CI) of the change (Δ) were calculated for all biomarkers of cardiometabolic health and PA measures between environments. Statistical significance was set at a priori of $\alpha \leq .05$. All analyses were performed using IBM® SPSS® Statistics 22 for Windows. Standardized effect sizes (Cohen's *d*) were also calculated to facilitate the interpretation of the substantive significance within groups, with thresholds of >0.2 (small), >0.5 (moderate) and >0.8 (large) used.[26]

RESULTS

Participant characteristics

Table 1 describes the injury characteristics of the LLA groups, highlighting differences in injury severity. All participants with a through and/or above knee LLA, in

TABLE 2 Cardiometabolic component risk markers for unilateral and bilateral lower-limb amputees (LLA) and normative controls at baseline and change score after 20 weeks

	Unilateral LLA group (n = 8)		Bilateral LLA group (n = 8)		Controls (n = 13)	
Marker	**Baseline**	**Δ (95% CI)**	**Baseline**	**Δ (95% CI)**	**Baseline**	**Δ (95% CI)**
Total cholesterol, mmol·L^{-1}	3.1 ± 1.1	−0.1 (−0.8 to 0.6)	3.6 ± 0.4	−0.7 (−1.3 to − 0.1)*	3.2 ± 0.9	−0.2 (−0.5 to 0.2)
HDL cholesterol, mmol·L^{-1}	0.9 ± 0.3	−0.0 (−0.3 to 0.2)	0.8 ± 0.1	−0.1 (−0.3 to 0.0)	1.1 ± 0.4	−0.1 (−0.2 to 0.1)
LDL cholesterol, mmol·L^{-1}[a]	1.9 ± 1.0	−0.1 (−0.6 to 0.4)	2.6 ± 0.4	−0.6 (−1.0 to − 0.2)*	2.0 ± 0.6	−0.2 (0.4 to 0.1)
TC:HDL ratio	3.3 ± 0.6[§]	0.1 (−0.1 to 0.4)	4.8 ± 0.9[‡,§]	−0.1 (−0.4 to 0.2)	3.2 ± 0.8[‡]	0.0 (−0.3 to 0.3)
Triacylglycerol, mmol·L^{-1}	0.7 ± 0.3[§]	0.2 (0.0 to 0.3)	1.8 ± 1.0[‡,§]	−0.1 (−0.8 to 0.5)	0.7 ± 0.3[‡]	0.2 (0.0 to 0.4)
NEFA, mmol·L^{-1}	0.3 ± 0.2[§]	0.1 (−0.1 to 0.3)	0.6 ± 0.3[§]	−0.1 (−0.4 to 0.1)	0.4 ± 0.1	0.1 (−0.2 to 0.1)
C-reactive protein, mg.L^{-1}	0.40 ± 0.28[§]	0.3 (−0.2 to 0.7)	2.85 ± 2.56[‡,§]	−0.4 (−2.8 to 2.1)	0.40 ± 0.48[‡]	0.2 (−0.4 to 0.8)
Systolic BP (mm Hg)	125 ± 6[§]	−7 (−11 to − 3)[†]	137 ± 8[§]	−4 (−8 to 0)	118 ± 2	−1 (−2 to 0)
Diastolic BP (mm Hg)	69 ± 10	−3 (−11 to 6)	78 ± 9	−2 (−8 to 5)	63 ± 7	1 (−2 to −2)
Fasted glucose, mmol·L^{-1}	5.7 ± 0.4	−0.1 (−0.4 to 0.2)	5.5 ± 0.6	0.1 (−0.2 to 0.5)	5.5 ± 0.4	0.0 (−0.2 to 0.3)
Peak glucose, mmol·L^{-1}	9.9 ± 1.5	−0.6 (−1.8 to 0.6)	10.1 ± 1.5	−0.1 (−2 to 1.9)	9.4 ± 1.4	0.1 (−1.0 to 1.2)
Time to peak glucose (min)	35.6 ± 11.2	1.9 (−12.2 to 16.0)	45.0 ± 8.1[‡]	−9.4 (−22.7 to 4.0)	33.5 ± 6.6[‡]	0.0 (−7.4 to 7.4)
Fasted insulin, pmol·L^{-1}	30.5 ± 25.4	2.1 (−4.4 to 8.7)	49.2 ± 36.3	−7.5 (−30.9 to 15.9)	22.4 ± 9.4	0.7 (−6.1 to 7.5)
Peak insulin, pmol·L^{-1}	282.2 ± 99.3	−27.7 (−84.3 to 29.0)	482.5 ± 254.2[‡]	−38.3 (−133.6 to 56.9)	258.7 ± 116.1[‡]	3.6 (−49.4 to 56.5)
Time to peak insulin (min)	43.1 ± 12.5	0.0 (−11.6 to 11.6)	48.8 ± 13.3	−7.5 (−25.2 to 10.2)	39.2 ± 9.8	−2.3 (−8.6 to 3.9)

Note: Data presented as mean ± SD and mean change Δ (95% lower and upper CI).
Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NEFA, nonesterified fatty acid; TC:HDL, total cholesterol: high-density lipoprotein.
*Significant difference between baseline and follow-up in individuals with bilateral LLA ($p < .05$).
[§]Significant difference between individuals with baseline bilateral LLA and unilateral LLA ($p < .05$).
[‡]Significant difference between individuals with baseline bilateral LLA and normative controls ($p < .05$).
[a]Calculated with the use of the Friedwald equation [LDL cholesterol = total cholesterol - HDL cholesterol - (triacylglycerol/2.2)].
[†]Significant difference between baseline and follow-up in individuals with unilateral LLA ($p < .05$).

both groups, wore a Genium prosthetic device. At baseline, individuals with bilateral LLA had received a significantly greater total length of rehabilitation (39 ± 15 versus 14 ± 8 months, $d = 2.08$, $p < .05$) and number of admissions (15 ± 15 versus 6 ± 3, $d = 0.83$, $p < .001$) compared to those with unilateral LLA, respectively.

Cardiometabolic component risk biomarkers

Lipid profile, inflammation, and blood pressure

Individuals with bilateral LLA demonstrated significantly greater TC:HDL ratio ($d = 1.88$, $p < .001$), triacylglycerol ($d = 1.49$, $p = .001$), CRP ($d = 1.33$, $p = .002$), systolic blood pressure (BP; $p < .001$), and diastolic BP ($d = 3.26$, $p = .002$) compared to controls (Table 2). The bilateral LLA group also demonstrated significant greater TC:HDL ratio ($d = 1.96$, $p = .002$), triacylglycerol ($d = 1.49$, $p = .003$), NEFA ($d = 1.18$, $p = .030$), CRP ($d = 1.35$, $p = .004$), and systolic BP ($d = 1.70$, $p = .001$) compared to the unilateral LLA group (Table 2). No statistically significant differences in lipid profile or inflammation were reported between the unilateral LLA group and active normative controls ($p > .05$). Although systolic BP ($d = 1.57$, $p = .020$) was significantly greater in the unilateral LLA group, values were within the normal range. There were no significant interaction effects or main effects of time for any lipid profile or inflammatory biomarker ($p > .05$).

Fasted blood insulin and glucose levels and oral glucose tolerance test

No significant main effect of group was demonstrated for fasted serum insulin concentrations at baseline ($p > .05$). A significantly greater insulinemic response following a

75 g glucose load was demonstrated in the bilateral LLA group compared to controls at 45 minutes ($d = 1.06$, $p = .024$), 60 minutes ($d = 1.37$, $p = .017$), 90 minutes ($d = 1.98$, $p < .001$) and 120 minutes ($d = 1.50$, $p = .001$) with greater peak insulin values ($d = 1.13$, $p = .015$) and iAUC ($d = 1.61$, $p = .002$) (Figure 2). The bilateral LLA group demonstrated significantly greater iAUC ($d = 1.43$, $p = .017$) compared to individuals with unilateral LLA. No statistically significant differences in insulinemic response to the oral glucose tolerance test were demonstrated between the unilateral LLA group and controls ($d < 0.05$, $p > .05$). There was no interaction effect on serum insulin responses during the oral glucose tolerance test ($p > .05$).

No significant main effect of group was demonstrated at baseline for fasting concentrations of plasma glucose ($p > .05$) (Table 2). Following a 75 g oral glucose tolerance test challenge, significantly greater plasma glucose concentrations were demonstrated in individuals with bilateral LLA at 60 minutes post glucose ingestion ($d = 1.74$, $p = .010$) and greater mean time to peak glucose ($d = 1.56$, $p = .016$) when compared to controls (Figure 2). No statistically significant differences in glycemic response to the oral glucose tolerance test were observed between the unilateral LLA group and controls ($d < 0.05$, $p > .05$). No interaction effects were apparent for plasma glucose response to the oral glucose tolerance test after 20 weeks ($p > .05$).

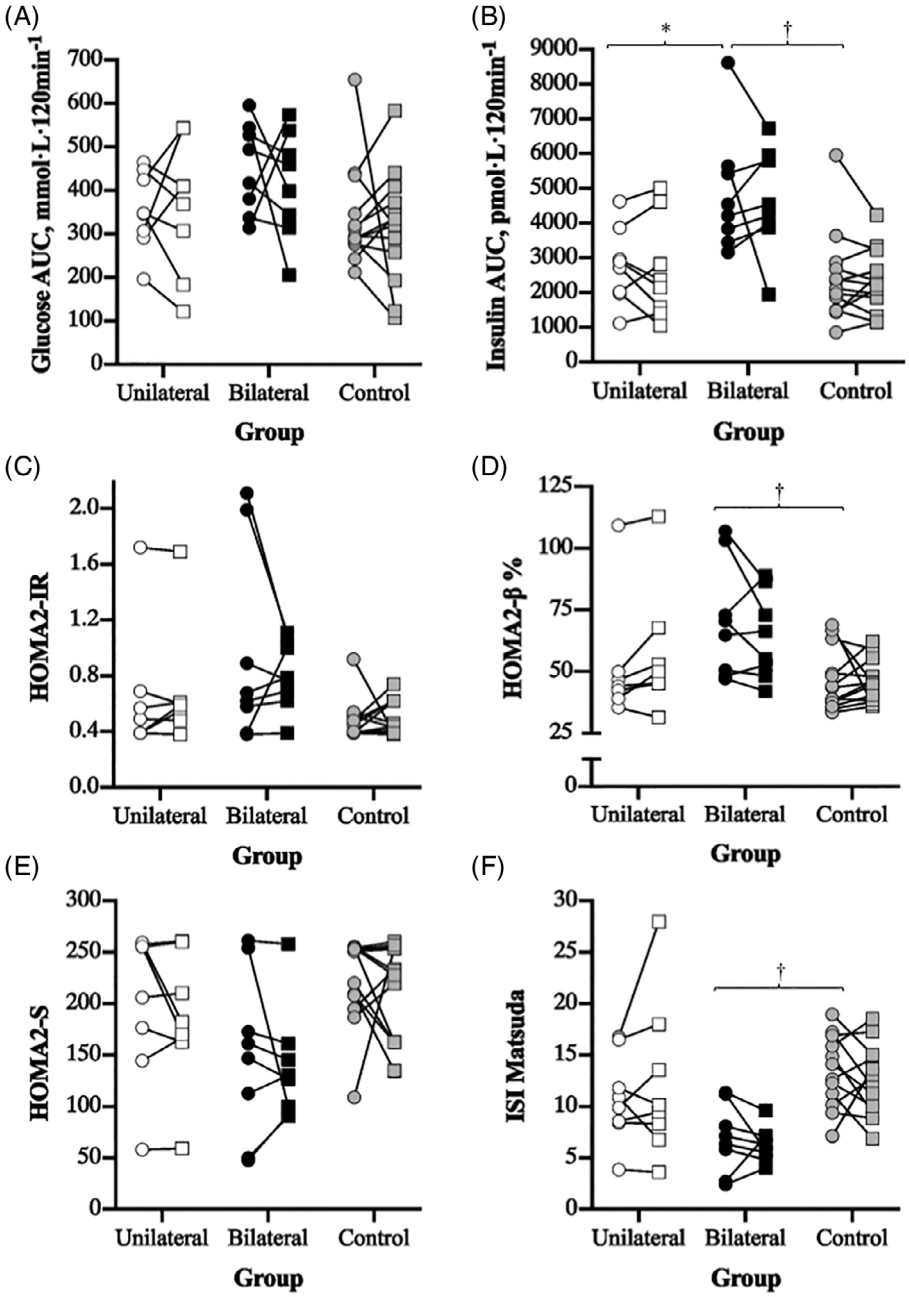

FIGURE 2 Summary of indices of metabolic health derived using plasma glucose and serum insulin during an oral glucose tolerance test. Mean glucose area under curve (AUC) values (A), mean insulin AUC values (B), mean values of insulin resistance (C), mean values indicating pancreatic β-cell function (D), mean insulin sensitivity (E), mean Matsuda insulin sensitivity index (F). Circles represent values recorded at baseline. Squares represent values recorded at 20-week follow-up. White shapes represent unilateral amputees, black shapes represent bilateral amputees, and gray shapes represent normative controls. *Significant difference between unilateral amputation and bilateral amputation ($p < .05$). †Significant difference between bilateral amputation and control ($p < .05$). Abbreviations: HOMA2, homeostasis model assessment; IR, insulin resistance; ISI, insulin sensitivity index.

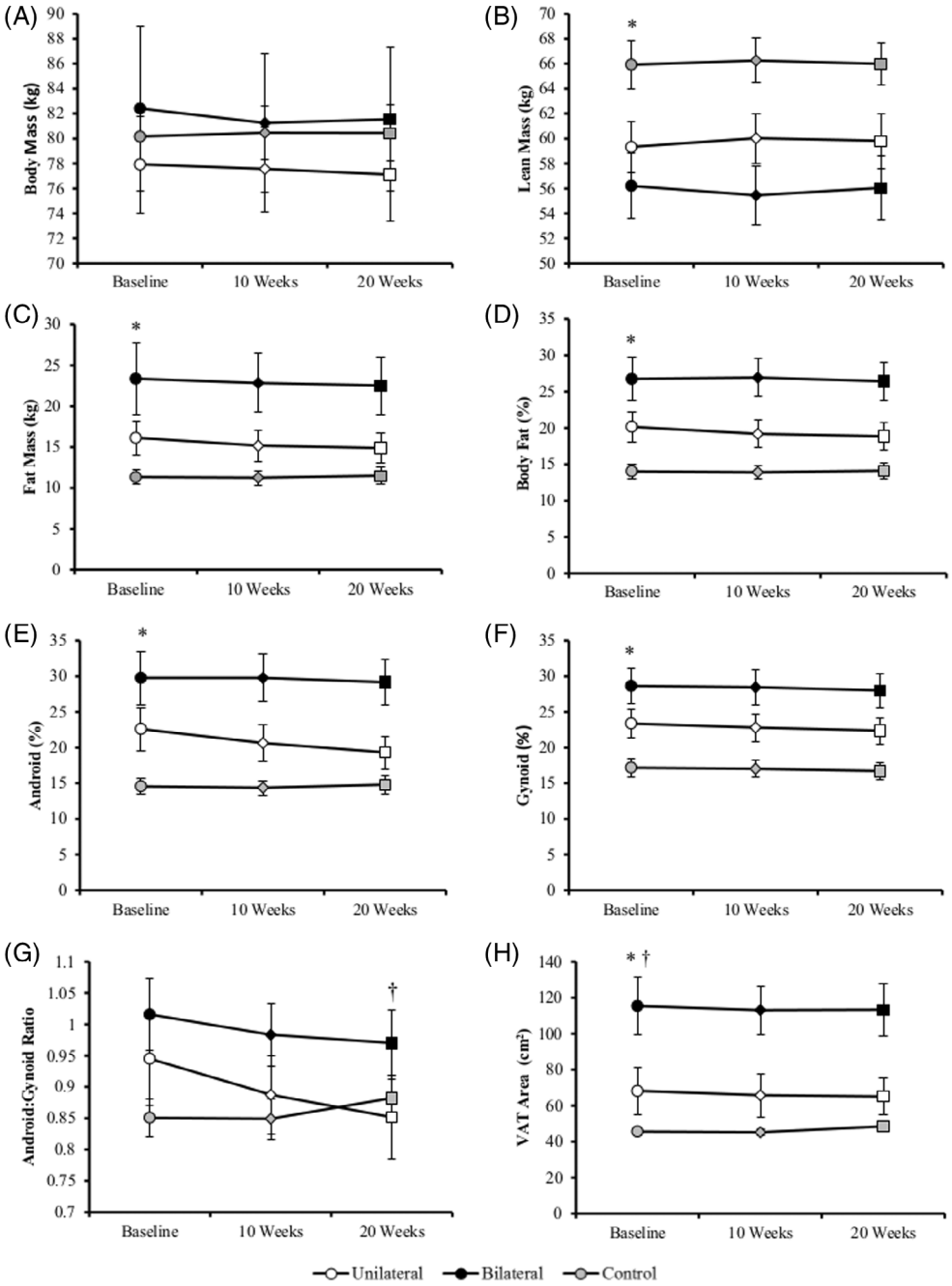

FIGURE 3 Body composition at baseline, 10-week, and 20-weeks follow-up in individuals with unilateral (n = 8) and bilateral (n = 8) lower-limb amputation and normative controls (n = 13). Body mass (kg) (A), lean muscle mass (kg) (B), fat mass (kg) (C), percentage body fat (D), percentage android fat (E), percentage gynoid fat (F), android: gynoid ratio (G), visceral adipose tissue (VAT) area (cm^2) (H). Black dots represent individuals with bilateral amputation, white dots represent individuals with unilateral amputation, gray dots represent normative controls. Data are presented as mean and SE. *Significant difference between individuals with bilateral amputation and controls ($p < .05$). †Significant difference between individuals with bilateral amputation and unilateral amputation ($p < .05$).

Cardiometabolic syndrome

Cardiometabolic syndrome was identified in 63% of those with bilateral LLA. Cardiometabolic syndrome was not demonstrated in any individuals with unilateral LLA or the normative control group.

Indices of insulin sensitivity/resistance

The bilateral LLA group demonstrated significantly greater fasted estimates of pancreatic β-cell function (HOMA2-β, $d = 1.29$, $p = .030$), and significantly less insulin sensitivity (ISI-Matsuda, $d = 1.68$, $p = .005$) compared to controls (Figure 2). No significant differences were observed between the unilateral LLA and control groups ($p > .05$). No significant interaction effects were demonstrated for any indices of insulin sensitivity or resistance ($p > .05$) (Figure 2).

Body composition

Waist circumference and waist-to-hip ratio values for each group were as follows: unilateral LLA, 84 ± 6 cm and 0.87 ± 0.04; bilateral LLA, 101 ± 22 cm and 0.93

± 0.10; control, 83 ± 5 cm and 0.83 ± 0.03, respectively. At baseline, the bilateral LLA group demonstrated significantly greater fat mass ($d = 1.27$, $p = .005$), percentage of body fat ($d = 1.94$, $p < .001$), android fat percentage ($d = 1.82$, $p < .001$), gynoid fat percentage ($d = 1.92$, $p < .001$), VAT area (2.11, $p < .001$), waist circumference ($d = 1.13$, $p = .010$), and waist-to-hip ratio ($d = 1.35$, $p = .001$) and lower lean mass ($d = 1.18$, $p = .026$) compared to controls. The bilateral LLA group also demonstrated significantly larger waist circumference ($d = 1.05$, $p = .014$) and VAT area ($d = 1.67$, $p = .046$) compared to the unilateral LLA group. There were no statistically significant differences reported between unilateral LLA and control groups on any measure of body composition at baseline ($p > .05$). Despite varying levels (transtibial and transfemoral) and numbers of amputation(s) there were no significant differences in total body mass between groups (Figure 3a). However, Figure 3b and c clearly demonstrate a different regional distribution of tissues (fat and muscle) between the three groups. There was a significant interaction effect ($F = 2.949$, $p = .029$) for android:gynoid ratio. This was caused by a significant difference in android fat percentage change over time between unilateral LLA and control groups ($p = .015$), where android fat percentage reduced over time in the unilateral LLA group.

Physical activity

There were no differences in the number of valid days (>14 hours) recorded or mean wear time between groups or environments (ie, rehabilitation versus home) ($p > .05$). Unilateral LLA group recorded 5 ± 1 valid days in each environment with mean daily wear times of 918 ± 41 minutes during rehabilitation and 916 ± 55 minutes while at home. The bilateral LLA group recorded 6 ± 1 valid days in each environment with mean daily wear times of 918 ± 45 minutes during rehabilitation and 904 ± 42 minutes while at home. The control group recorded 5 ± 1 valid days with mean daily wear times of 934 ± 40 minutes during work.

During inpatient rehabilitation, post hoc analyses revealed significantly lower PAC. day^{-1} ($d = 1.44$, $p = .009$) and estimated daily PA energy expenditure ($d = 4.50$, $p < .001$) in the bilateral LLA group when compared to controls (Figure 4). Individuals with bilateral LLA also demonstrated significantly lower estimated daily PA energy expenditure compared to those with unilateral LLA ($d = 5.4$, $p < .001$), but no significant difference in mean PAC.day^{-1} ($p = .142$). No statistically significant differences in mean PAC.day^{-1} and estimated daily PA energy expenditure were demonstrated between unilateral LLA and control groups ($p > .05$).

During time spent at home, post hoc analyses revealed significantly reduced PAC.day^{-1} ($d = 2.75$, $p < .001$) and estimated daily PA energy expenditure ($d = 5.85$, The $p < .001$) in the bilateral LLA compared to control group (at work) (Figure 4). The unilateral LLA group also demonstrated significantly reduced PAC. day^{-1} ($d = 1.13$, $p = .049$) and estimated daily PA energy expenditure ($d = 1.71$, $p = .002$) compared to controls. The bilateral LLA group recorded significantly reduced PAC.day^{-1} ($d = 2.76$, $p = .008$) and estimated daily PA energy expenditure ($d = 6.00$, $p < .001$) compared to the unilateral LLA group.

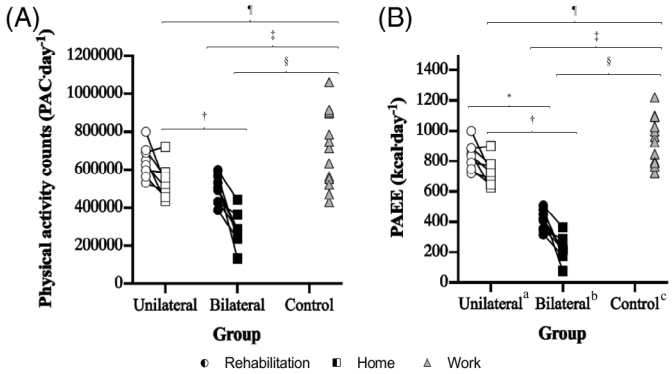

FIGURE 4 Estimated daily physical activity (PA) levels of individuals with unilateral and bilateral lower-limb amputation (LLA) during inpatient rehabilitation and while at home and uninjured normative controls during work. Daily physical activity counts (PAC) (A); estimated physical activity energy expenditure (PAEE) (B). Circles represent values during rehabilitation. Squares represent values at home. White circles/squares represent values of PA within unilateral LLA. Black circles/squares represent values of PA within bilateral LLA. Gray triangles represent values of PA for normative controls during a working week. Individual data points reflect mean scores for each participant. Mean ± SD data for daily PAC are as follows: individuals with unilateral LLA 645,084 ± 86,078 during rehabilitation and 534,248 ± 90,125 while at home; individuals with bilateral LLA, 492,569 ± 72,750 during rehabilitation and 283,357 ± 91,406 while at home; controls, 707,632 ± 197,909 during work. Mean ± SD data for daily physical activity energy expenditure are as follows: individuals with unilateral LLA, 839 ± 88 kcal during rehabilitation and 733 ± 87 kcal while at home; individuals with bilateral LLA, 410 ± 68 kcal during rehabilitation and 217 ± 85 kcal while at home; controls, 948 ± 155 during a working week. The cross-validated population specific prediction models developed for estimating physical activity energy expenditure (22) in Figure 4B are [a]individuals with unilateral LLA physical activity energy expenditure = (0.000979 × PAC·min^{-1}) + 0.225548; [b]individuals with bilateral LLA physical activity energy expenditure = (0.000929 × PAC·min^{-1}) – 0.051541; and [c]normative control physical activity energy expenditure = (0.000776 × PAC·min^{-1}) + 0.427097. *Significant difference between individuals with unilateral amputation and bilateral amputation during rehabilitation ($p < .05$). †Significant difference between individuals with unilateral amputation and bilateral amputation while at home ($p < .05$). ‡Significant difference between individuals with bilateral amputation during rehabilitation and normative controls ($p < .05$). §Significant difference between individuals with bilateral amputation at home and normative controls ($p < .05$). ¶Significant difference between individuals with unilateral amputation at home and normative controls ($p < .05$).

There was a reduction in PAC.day^{-1} and mean daily PA energy expenditure (kcal.d^{-1}) during habitual free-living at home in both LLA groups. However, the difference demonstrated between these two environments was greatest for bilateral LLA. The unilateral LLA group reduced their daily PAC while at home by 17% ($d = 1.26$, $p = .018$) and their physical activity energy expenditure by 13% ($d = 1.21$, $p = .019$). The bilateral LLA group reduced their mean PAC.day^{-1} by 42% ($d = 2.53$, $p = .001$) and their daily PA energy expenditure by 47% ($d = 2.51$, $p = .001$). There were no significant interaction effects demonstrated between any PA measurements.

DISCUSSION

This study investigated the influence of LLA severity (unilateral versus bilateral LLA) on cardiometabolic component risk, PA, and body composition in UK military personnel at the end of their complex trauma rehabilitation care pathway. Individuals with bilateral LLA demonstrated lower ambulatory PA and elevated cardiometabolic component risks compared to controls, including higher waist circumference, VAT area, percentage of body fat, TC:HDL cholesterol, triacylglycerol concentrations, systemic inflammation (CRP), systolic BP, insulin iAUC, and fasting estimates of β-cell function and reduced lean muscle mass and insulin sensitivity. The bilateral LLA group also had lower ambulatory PA and demonstrated elevated cardiometabolic component risks when compared to the unilateral LLA group, including greater waist circumference, VAT, TC:HDL ratio, triacylglycerol concentration, NEFA, CRP, and insulin iAUC. These are particularly compelling findings considering the relatively short duration (39 ± 15 months) since their injuries occurred. Individuals with unilateral LLA demonstrated low effect size ($d < 0.05$) and no statistically significant differences in any cardiometabolic risk profile to healthy active age-matched controls, which may reflect a positive adaptation to physical rehabilitation. To our knowledge this is the first study to demonstrate comparable health outcomes between individuals with unilateral LLA and physically active healthy adults.

Mechanisms likely to be contributing toward the elevated cardiometabolic component risks in bilateral LLA could be the less favorable body composition values and lower free-living PA, particularly while at home. It is well documented that skeletal muscle atrophy, diminished muscle strength, and increased visceral fat mass commonly occur following LLA.[4,27,28] Despite losing healthy tissue from both lower limbs, the total body mass of individuals with bilateral LLA recorded at baseline is comparable to the control group; however, their body fat content was >2-fold greater (24 versus 11 kg, respectively). Of concern, the location of this higher body fat content appears to be central (waist circumference: 101 ± 22 cm, android fat percentage: 30% ± 11%, and VAT area 117 ± 47 cm^2), which is a known risk factor for future cardiovascular and metabolic related disorders[29] and prosthetic mobility.[30,31] The majority of participants with bilateral LLA were transfemoral (above knee) amputees (Table 1); the level of amputation and length of the residual limb are significant factors not only in the severity of muscle atrophy[28] but also in the loss of functional performance.[24] Although it is not obvious from the results of this study how much muscle mass each participant lost following their bilateral injury and subsequent surgery, using control as a reference, we estimate that the bilateral LLA group lost a mean 9 kg (or 14%) of metabolically active tissue (66 versus 57 kg, respectively). Skeletal muscle is a critical glucose and fat disposal site during postprandial conditions.[5,32] Therefore the reduced amount of whole body lean muscle tissue evident among individuals with bilateral LLA may have considerable implications for their short- to long-term metabolic health. Significant muscle atrophy and diminished muscle strength following amputation will not only reduce resting metabolic rate but also reduce physical function, engagement in ADL, and overall PA energy expenditure,[33] as was demonstrated in this study.

The elevated cardiometabolic component risks evident in the bilateral LLA group could be a consequence of their increased injury severity (see list of secondary injuries in Table 1). Stewart et al.[34] predicted each 5-point increment in injury severity score was associated with a 6%, 13%, and 13% increase in incidence rates of hypertension, diabetes mellitus, and coronary artery disease, respectively. The estimated incidence rates of hypertension, diabetes mellitus, and coronary artery diseases for the most severely injured patients (injury severity score > 25) were 2.5- to 4-fold higher than published rates for the overall U.S. military population, respectively.[35,36] Similar to our own study, these projected outcomes were observed in as little as 1–3 years following injury.

We found a reduction in PAC.day^{-1} of 42% ($d = 2.53$) and PA energy expenditure by 47% ($d = 2.51$) when individuals with bilateral LLA were at home compared to inpatient rehabilitation. This discrepancy was less pronounced in those with unilateral LLA with PAC.day^{-1} and PA energy expenditure reductions of 17% ($d = 1.26$) and 13% ($d = 1.21$), respectively. This confirms that recovery environment (ie, rehabilitation versus home) and injury severity (number of amputations) both affect daily PAC and PA energy expenditure in individuals with LLA. Another recent study in UK military LLA supports these observations, with mean daily step count significantly reduced (39%) from 2258 ± 192 steps.d^{-1} during inpatient rehabilitation to 1387 ± 363 steps.d^{-}1 while at home.[37] One

reason the authors provided for this discrepancy between environments is there may be more occasions at home when it is considered more appropriate for an individual with a LLA to use a wheelchair to mobilize as oppose to ambulating in their prosthesis.[37]

Access to advanced prosthetic technology in combination with prolonged interdisciplinary rehabilitation is likely to have supported the positive outcomes demonstrated by those with unilateral LLA. Maintaining higher levels of PA and associated energy expenditure may have helped to elicit their favorable body composition values. As cardiometabolic health is, in part, regulated by lean muscle and adipose tissue, and these body composition values remained unchanged in all three groups throughout the 20 weeks observation, it is not surprising that no significant time-related changes in components of cardiometabolic risk occurred during this study.

LIMITATIONS

An unavoidable limitation of the study design was the inability to standardize the length of time since injury, the amount of rehabilitation exposure prior to participating in the trial, and the homogeneity within the LLA groups (ie, below versus above knee amputation). This was due to the availability of eligible participants at the time of recruitment. However, by recruiting participants with three admissions remaining prior to their discharge from inpatient care, we were able to comment on the health and well-being of severely injured military personnel with LLA at the end of their rehabilitation care pathway. In the context of measuring the impact of traumatic LLA on objective markers of cardiometabolic risk, the current study is one of the largest, although the sample size of individuals with LLA remains relatively small ($n = 16$). Despite the small sample size and the large variance in lower-limb injury severity within groups, significant differences were still demonstrated between groups. This heterogeneity of injury may be considered beneficial as the range of functional abilities improves the external validity of the findings, making them more relevant to the wider LLA population. Due to the multiple outcome measures and analysis performed, there is an elevated risk of type 1 error. However, this was an exploratory/descriptive study that aimed to facilitate better understanding of health determinants of LLA at the end of the complex trauma care pathway and is balanced by the comprehensive assessment of cardiometabolic component risk completed with every participant. Positioning the accelerometer at the hip captured changes in ambulatory-based PA (a primary goal of rehabilitation). However, PA energy expenditure values may have been underestimated using this anatomical location in the bilateral LLA group as the device would be unable to accurately capture PA energy expenditure during time spent performing wheelchair propulsion or upper-limb resistance exercise. Military personnel are predominantly male, aged 20 to 40 years old, and have undergone extensive physical training in the course of their career. As a higher functioning LLA group, with access to advance rehabilitation and prosthetic provision, these finding may not be immediately applicable to the wider LLA population.

CLINICAL IMPLICATIONS

These findings highlight the importance of long-term monitoring of the most severely injured military personnel, especially those with bilateral LLA. Despite access to advance prosthetic provision and prolonged rehabilitative care (15 ± 15 inpatient admissions over 39 ± 15 months), the bilateral LLA group demonstrated unfavorable body composition and elevated biomarkers of cardiometabolic risk compared to the unilateral LLA and control groups. Large differences occurred in PA levels between inpatient rehabilitation and home. These data emphasize the importance of maintaining an active lifestyle in the home environment. To facilitate this, a home-based exercise/nutritional intervention is perhaps the most likely approach to ensure a longer term maintenance or improvement in cardiometabolic component risks, body composition, and physical function. The results presented in this study reflect the health and well-being status of UK military personnel at the end of the complex trauma rehabilitation pathway. The longer term impacts of transitioning away from a structured defense rehabilitation care pathway to independent care remain unknown and warrant further investigation.[38]

CONCLUSION

Despite extensive inpatient rehabilitation, cardiometabolic component risk biomarkers are elevated in individuals with traumatic bilateral LLA, but considered "healthy/normal" for those with unilateral LLA and active healthy controls. This increased risk among people with bilateral LLA was characterized by higher total body fat content, visceral and gynoid fat tissue, impaired systemic lipid profile, systemic inflammation, and impaired post-load insulin sensitivity. Interestingly, this unfavorable cardiometabolic risk profile was accompanied by lower PA and associated energy expenditure, which was even further reduced when recovering at home compared to the inpatient rehabilitation environment. Strategies that improve/support the long-term health and well-being of severely injured

individuals with bilateral LLA are necessary, with a particular focus on long-term healthy and active aging.

ACKNOWLEDGMENTS

The authors would like to thank all staff and participants from the Complex Trauma Department at the Defence Medical Rehabilitation Centre (DMRC) for their individual and joint efforts supporting this research program.

DISCLOSURES

No conflicts are declared by the authorship.

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How to cite this article: Ladlow P, Nightingale TE, McGuigan MP, et al. Influence of traumatic lower-limb amputation on physical activity, body composition, and cardiometabolic risks: A descriptive preliminary study. *PM&R*. 2023;15(4):413-425. doi:10.1002/pmrj.12944

CME Question

According to this study, individuals with traumatic lower-limb amputation (LLA) have the following cardiometabolic component risks:

a. Favorable for unilateral LLA compared to age matched male controls
b. Unfavorable for unilateral LLA compared to age matched male controls
c. Favorable for bilateral LLA compared to unilateral LLA
d. Unfavorable for bilateral LLA compared to unilateral LLA

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