Original Article

Physical activity decreases in patients on the liver transplant waiting list and influences postoperative outcome—a prospective cohort study

Christian T. J. Magyar#^, Lea Bühlmann#, Chiara Becchetti^, Lara Beekman, Daniel Candinas^, Guido Beldi^, Corina Kim-Fuchs^, Annalisa Berzigotti^, Vanessa Banz^

Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Contributions: (I) Conception and design: CTJ Magyar, C Becchetti, L Beekman, V Banz; (II) Administrative support: C Becchetti, L Beekman, V Banz; (III) Provision of study materials or patients: L Bühlmann; (IV) Collection and assembly of data: L Bühlmann, L Beekman; (V) Data analysis and interpretation: CTJ Magyar; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

Correspondence to: Vanessa Banz, MD, PhD. Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Freiburgstrase 18, 3010 Bern, Switzerland. Email: vanessa.banz@insel.ch.

Background: Physical deconditioning affects patients suffering from end-stage liver disease (ESLD). Liver transplantation (LT) is the only curative option for ESLD. Growing evidence suggests that pre-habilitation is beneficial in reducing post-surgical morbidity and mortality. We investigated physical activity (PA) in patients awaiting LT in a country with long waiting times.

Methods: Prospective, single center, longitudinal study in Bern, Switzerland between June 2019 and February 2020 (halted due to SARS-CoV-2 pandemic), with follow-up data up to six months post-transplant. Patients were instructed to use a wrist tracker (FitBit) to monitor PA, which was assessed using mixed-effects generalized linear models. The study was approved by the local ethics committee (BASEC ID 2019-00606).

Results: Thirty-five patients were included [71% male, median 59 years, body mass index (BMI) 28 kg/m^2, lab Model End-Stage Liver Disease (MELD) 11], 17 (49%) pre-frail and 5 (14%) frail according to the Liver Frailty Index (LFI). Twenty-eight patients underwent transplantation with 0 ninety-day mortality and 15 (53.6%) composite adverse clinical outcome. Median daily steps were 4,661 [interquartile range (IQR), 1,685–8,609] and weekly moderate PA (MPA) was 41 min (IQR, 0–127 min). Longitudinal analysis showed that female patients and patients on nutritional support had an increase in MPA between weeks 20 and 40. A significant decrease was seen in MPA after week 40, whilst no significant association was seen with age, Child-Pugh Score, LFI or quality of life at time of inclusion. MPA was significantly associated with the occurrence of the composite clinical endpoint after week 30 of waiting time (odds ratio 0.882, P=0.026). World Health Organization (WHO)-recommended MPA was significantly associated with less adverse composite clinical outcomes (P<0.001).

Conclusions: In patients listed for LT, MPA decreased over time, showing a significant association with adverse outcome, specifically after week 30 on the waiting list. Our data support the implementation of routine pre-habilitation in patients awaiting LT.

Keywords: Sarcopenia; liver disease; solid organ transplant; physical activity (PA); outcome

^ ORCID: Christian T. J. Magyar, 0000-0002-4570-949X; Chiara Becchetti, 0000-0002-8262-0304; Daniel Candinas, 0000-0002-9924-1749; Guido Beldi, 0000-0002-9914-3807; Corina Kim-Fuchs, 0000-0002-2237-9432; Annalisa Berzigotti, 0000-0003-4562-9016; Vanessa Banz, 0000-0002-4487-5776.

Introduction

Background

Decreased physical performance or deconditioning [as measured by e.g., skeletal muscle index (1-3), handgrip strength (1), 6-minute walk distance (4)], associated sarcopenia (2,5) and frailty occur in up to 78% of patients (3) with end-stage liver disease (ESLD). They are considered multifactorial and correlate with morbidity and mortality (6-10). Specifically, sarcopenia and frailty have been shown to be associated with increased mortality in patients with ESLD listed for liver transplantation (LT) during the waiting list period (8,11) as well as post-LT (12). A sedentary behavior [<1.5 metabolic equivalents of tasks (METs) daily] is observed in 75.9%±18.9% of patients awaiting LT (8). Moreover, persistent deconditioning post-LT (13) is associated with decreased quality of life (QoL) (14), morbidity and mortality (15). A recent meta-analysis assessing eight randomized control trials, evaluating physical rehabilitation after LT, was able to show improved cardiorespiratory fitness and QoL (16).

Rationale and knowledge gap

In the general population, growing evidence shows that

pre-habilitation can be beneficial, leading to improved stress tolerance (17), and better surgical outcomes (18,19), impacting on tissue regeneration (20) and metabolism (21) as well as mental health (22). However, controversies regarding studied populations exist, resulting in a debate concerning the significance of pre-habilitation (19,23,24). Independent of surgery, the World Health Organization (WHO) recommends 150–300 min of moderate physical activity (MPA) weekly (25). Whilst pre-habilitation before LT is strongly recommended in the 2022 International Liver Transplantation Society consensus guidelines, the quality of evidence remains very low (26).

Objective

We hypothesized that (I) the majority (≥50%) of patients pre-LT do not meet the WHO recommendations of MPA (25), (II) that Liver Frailty Index (LFI) (27) at LT listing is significantly associated with a change of PA over time, and (III) decreased pretransplant MPA is associated with postoperative adverse clinical outcome. With this prospective cohort study, we (I) describe the PA with regard to WHO recommendations in patients wait-listed for LT in a real-life setting, (II) assess factors influencing the PA and its change over time and (III) test the association of pretransplant MPA with postoperative morbidity and mortality. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn. amegroups.com/article/view/10.21037/hbsn-23-399/rc).

Methods

Study design

We conducted a single center prospective observational longitudinal study at the Department of Visceral Surgery and Medicine, Inselspital, University Hospital Bern in Switzerland. All patients included in the present study signed a specific informed consent. The study was approved by the local ethics committee (Kantonale Ethikkommission, Kanton Bern, BASEC ID 2019-00606). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Selection of patients

The consecutive recruitment was initiated in June 2019 and was prematurely halted in February 2020 due to the

---

Highlight box

Key findings
- Over time, there is a significant decrease of moderate physical activity (MPA) after week 40 on wait list for liver transplantation (LT). No association of MPA over time with age, Child-Pugh Score, Liver Frailty Index or quality of life at time of inclusion to study.
- Female patients and patients receiving nutritional support had an increase in MPA (week 20 and 40).
- Reduced MPA is significantly associated with adverse outcome post-LT.

What is known and what is new?
- Evidence in other surgical fields suggests that pre-habilitation is beneficial in reducing post-surgical morbidity and mortality.
- First prospective study evaluating specifically pretransplant physical activity using wearable device demonstrating an association with adverse outcomes in this cohort with a significant sex-related disparity.

What is the implication, and what should change now?
- This study provides evidence for warranted interventional studies on physical activity combined with nutritional support in pre-LT.

SARS-CoV-2 pandemic. Initial planned sample-size was 40 patients. Follow-up ended at six months after LT, whereas patients who had not yet been transplanted, were followed up regularly every six months. Eligible patients included adults (≥18 years) who had been accepted on the waiting list for a liver only or combined liver/kidney transplant. Exclusion criteria were failure to provide oral and written informed consent. Participants could discontinue their enrollment at any time point. Reporting of this observational study was undertaken in accordance with the STROBE guidelines and the flowchart is shown in *Figure 1*.

Activity tracker

For the PA assessment, the patients needed to have access to a cell phone with Bluetooth connection and had to be able to navigate the Fitbit-App. Patients were instructed to continuously wear the activity tracker (Fitbit Charge 2, Fitbit LLC, San Francisco, CA, USA, RRID: non-existant) for the study period. The activity data was downloaded three monthly during the outpatient visits. The automatic stratification of the PA into low, moderate and vigorous occurred according to the wearable trackers' producers coding. The wearable device was funded by the study center from internal funds. A cumulative weekly (seven days) PA was calculated in order to be in line with WHO recommendations and adjust for daily fluctuations.

Clinical definitions

Frailty was assessed every three months using the LFI (27) and QoL using the SF36 questionnaire every six months (28). Nutritional support was defined as receiving regular counseling by a board-certified dietician in an outpatient setting either at our own hospital or in an institution closer to the patient's home and oral supplementation either with branch-chained amino acids or other protein-rich supplement prescriptions and/or placement of a nasojejunal feeding tube. Placement of a nasojejunal feeding tube was usually done as an inpatient procedure with enteral feeding started in a hospital setting and once established a supported by the patient, continued as an outpatient with support from community nurses. Frequency of outpatient consultations was carried out based on the individual needs of each patient.

Outcome

The primary endpoint was to describe the weekly moderate

PA in patients wait-listed for LT in accordance with the WHO recommendations (25). Secondary outcome measures (factors influencing PA and its change over time and association with composite adverse clinical outcome) were assessed in a longitudinal temporo-spatial analysis. The composite adverse clinical outcome endpoint was defined as the need for re-transplantation, emergency hospitalization or occurrence of in-hospital complications during LT as defined per the Dindo-Clavien classification ≥ IIIa (29,30) occurring within the first six months post-LT.

Statistical analysis

Categorical variables were reported as numbers and percentages, continuous variables as medians and interquartile ranges (IQRs). Categorical variables were compared using Fisher's exact test. Continuous variables were assessed using Mann-Whitney *U*-test. A P of 0.05 or less was considered statistically significant. Temporo-spatial data visualization was done using non-parametric LOESS regression and heatmap displaying medians in boxes of 5 weeks and MPA 20 min/week.

Complex statistical analyses were carried out with the help of a biostatistician. Due to the skewed distribution of the weekly moderate PA data, mixed-effects generalized linear models with a gamma distribution and a log link were used. Splines and time periods were used to have more flexibility modelling the data with two knots, one at week 20 and a second at week 40. The estimation of the association was done for these three time periods (0 to 20, 20 to 40 and after 40 weeks onward). Random slope and intercept were included in the model. Robust estimation of the variance was used. Weekly MPA values of zero were excluded from further analysis. First, a mixed-effects generalized linear model with a Gamma distribution and a log link was used to analyze weekly MPA (time included through three splines as dependent variable). Second, the same model was used to analyze the univariate impact of factors (*a priori* per-protocol analysis with variables at time of inclusion: categorical: sex, nutritional support and continuous variables: age, Child-Pugh Score, LFI, SF36 total score) on the spatial weekly moderate PA. Finally, a logistic regression was used to estimate the odds ratio of the occurrence of the composite clinical outcomes in dependence of the weekly moderate PA. Cluster estimation of the variance was performed for each patient.

Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria,
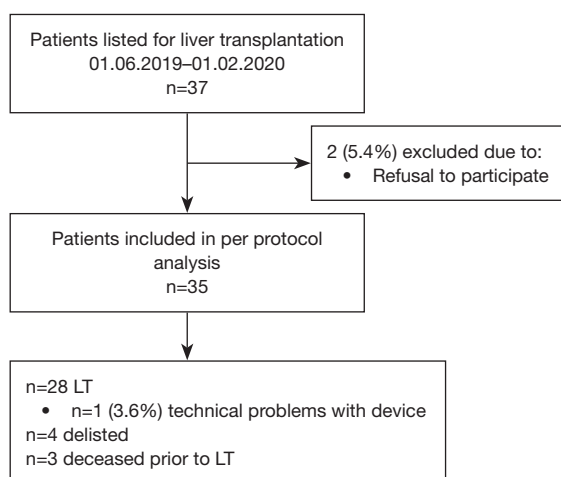
Figure 1 Study flowchart in accordance with STROBE guidelines. LT, liver transplant.

RRID: SCR_001905) with R Studio software (R Studio, Inc, Boston, MA, USA; RRID: SCR_000432) and Stata 17 (Stata Corporation, College Station, TX, USA; RRID: SCR_012763).

Results

Patient population

A total of 37 patients were listed for LT during the study period and after evaluation 35 patients were included (*Figure 1*). Twenty-five (71%) were male with a median age 59 years (IQR, 51.0–63.0 years) (*Table 1*). Most common primary indication for LT was 14 (40%) hepatocellular carcinoma (HCC). At time of inclusion into the study 21 (60%) of patients' liver function was classified as Child-Pugh-Score B, median LFI was 3.4 (IQR, 3.0–3.8; 11 robust, 17 pre-frail and 5 frail). The median handgrip was 32.8 kg (IQR, 22.6–38.6 kg). During the study period 28 (80%) patients underwent LT, three died before LT and four were delisted (two considered too sick for LT and two improved significantly not requiring LT) (*Figure 1*). Ninety-day mortality after LT was 0% and composite adverse clinical outcomes occurred in 15 patients (overall 43%, of transplanted 54%) (*Table 2*).

PA

Daily values were tracked and a weekly activity was composed. Daily activity included steps 4,661 (IQR,

1,685–8,609) (Table S1) whereas weekday stratified analysis revealed significant differences of PA measures (P<0.001) with Sunday being the weekday with the least amount of activity (Table S2). A total of 1,053 patient-weeks in 35 patients were recorded (*Table 3*). The overall median weekly MPA was 41.0 min (IQR, 0.0–127.2 min) with 131 (12%) patient-weeks within the 150–300 min/week category (*Table 3*). A preliminary mixed linear model analysis found a median decrease of MPA of 0.6 min per week on the waiting list (intercept 111.5 min, correlation –0.800). Longitudinal change is displayed in *Figure 2* as a dynamic LOESS regression of all data up until the time of LT. The *a priori* per-protocol analysis (*Table 4*) assessing the impact of factors on the longitudinal association with MPA was performed. Temporo-spatial graphical representation of a MPA over time with regard to these *a priori* factors and stratification per occurrence of the composite adverse clinical endpoint (below) is shown in *Figure 3*. The visual presentation of the median distribution of continuous factors (age, Child-Pugh Score, LFI and QoL) with regard to MPA and temporal changes are shown using heatmaps in Figure S1. In male patients, a significant decrease of MPA over time was detected only after week 40 after inclusion [regression coefficient (RC) 0.952; 95% confidence interval (CI): 0.926–0.979; P<0.001]. In female patients, a significant increase over time between week 20 and 40 was found (RC 1.025; 95% CI: 1.011–1.039; P<0.001) (*Table 4*). Sex-associated interaction was identified after week 40 (P<0.001). Patients receiving nutritional support significantly increased MPA between week 20 and 40 (RC 1.011; 95% CI: 1.000–1.022; P=0.045); this decreased again after week 40 (RC 0.962; 95% CI: 0.950–0.974; P<0.001). No significant association was found between age, Child-Pugh Score, LFI or SF36 at time of inclusion and change of MPA over time. A non-significant tendency was observed for SF36 between week 0 to 20 after inclusion (RC 0.998; 95% CI: 0.997–1.000; P=0.095).

Post-transplant outcome

Events included in the composite clinical endpoint (including Re-LT, post-LT emergency re-hospitalisation or in-hospital complication during LT) were detected in 15 (42.9%) of patients. *Figure 3A,3B* display the temporal changes of MPA for the *a priori* chosen categorical factors sex and nutritional support for stratified outcome. *Figure 4* depicts a univariate logistic regression with subsequent presentation in a Forest Plot to assess for significance. Significant risk of occurrence with regard to MPA (in

Table 1 Patient characteristics

Characteristics	Value (n=35)
Age (years)	59.0 (51.0, 63.0)
Sex	
Male	25 [71]
Weight (kg)	86.0 (71.7, 94.8)
BMI (kg/m^2)	28.0 (25.3, 30.0)
Bilirubin (mcmol/L)	24.0 (14.5, 47.5)
Creatinine (mcmol/L)	78.0 (61.5, 107.5)
Albumin (g/L)	34.0 (26.0, 36.5)
CPS	
CPS A	10 [29]
CPS B	21 [60]
CPS C	4 [11]
Lab MELD at time point study inclusion	11.0 (8.0, 19.0)
Allocation MELD at time point LT	32.0 (25.5, 37.5)
Use of selective beta blocker	21 [60]
History of decompensation	
Ascites	23 [66]
Variceal bleeding	11 [31]
Hepatic encephalopathy	14 [40]
Co-morbidities	
T2DM	12 [34]
CKD	9 [26]
Hypertension	7 [20]
Heart disease	6 [17]
Pulmonary disease	6 [17]
Metabolic syndrome	7 [20]
Malnutrition	8 [23]
Others	13 [37]
Nutritional support prior to LT	10 [29]
Primary/major indication for LT	
Complications of cirrhosis	14 [40]
HCC	14 [40]
Other	5 [14]
Primary liver tumor other than HCC	2 [6]

Table 1 (continued)

Table 1 (continued)

Characteristics	Value (n=35)
Underlying liver pathology	
ALD/ASH	8 [23]
NASH	7 [20]
NASH/MASH	7 [20]
HCV	3 [9]
AIH/PBC/PSC	3 [9]
Other	7 [20]
Handgrip total (kg) at inclusion	32.8 (22.6, 38.6)
Standing (s) at inclusion	8.5 (7.8, 12.1)
Balancing total (s) at inclusion	30 (30, 30)
Liver Frailty Index at inclusion	3.4 (3.0, 3.8)
Liver class of frailty at inclusion	
Robust	11 [31]
Pre-frail	17 [49]
Frail	5 [14]

Values are given in numbers [%] for categorical or medians (interquartile ranges) for continuous variables. BMI, body mass index; CPS, Child-Pugh Score; MELD, Model End-Stage Liver Disease; LT, liver transplantation; T2DM, type 2 diabetes mellitus; CKD, chronic kidney disease; HCC, hepatocellular carcinoma; ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; NASH, non-alcoholic steatohepatitis; MASH, metabolic dysfunction associated fatty liver disease; HCV, hepatitis C virus; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

steps of +10 min) occurred after week 30 [odds ratio (OR) 0.882, 95% CI: 0.790–0.985, P=0.026] and OR sequentially increased to 0.367 (95% CI: 0.213–0.634, P<0.001) at week 70 of listing (*Figure 4*). Dynamic longitudinal temporal stratification is displayed using LOESS regression in *Figure 3* and Figures S1,S2. On crude univariate logistic regression analysis, nutritional support did not significantly reduce the occurrence of adverse clinical endpoints (OR 0.848, 95% CI: 0.179–3.740, P=0.829). Patients achieving WHO-recommended weekly MPA targets showed a lower risk of adverse composite clinical outcomes [endpoint: <150 min/week 350 (84.4%), 150–300 min/week 26 (6.3%), >300 min/week 39 (9.4%) *vs.* no endpoint: <150 min/week 450 (70.5%), 150–300 min/week 105 (16.5%), >300 min/week 83 (13.0%); P<0.001].

Table 2 Clinical outcomes of patients

Characteristics	Value (n=35)
LT	28 (80.0)
Time from listing to study inclusion (days)	88 (11–264)
Time from listing to LT (days)	370 (239–513)
Time from study inclusion to LT (days)	195 (109–350)
Pre-transplant period	
All hospitalizations (elective and emergency)	23 (65.7)
Emergency hospitalizations	18 (51.4)
De-listing for LT	4 (11.4)
Mortality prior to LT	3 (8.6)
Transplant period	
Length of stay (days)	8.5 (6.0–14.3)
ICU length of stay (days)	2.0 (1.0–3.0)
In-hospital complication	
Surgical	13 (37.1)
Non-surgical	1 (2.9)
Severity of complication according to Dindo-Clavien-Classification	
IIIa	2 (5.7)
IIIb	5 (14.3)
IVa	4 (11.4)
Description of complication	
Bleeding	4 (11.4)
Biliary complication	3 (8.6)
Arterial complication	2 (5.7)
PV thrombosis	2 (5.7)
Graft dysfunction	2 (5.7)
Portocaval-shunt-stenosis	1 (2.9)
Post-transplant period	
Emergency re-hospitalization	8 (22.9)
Mortality 90 days after LT	0
Relisting for re-LT	4 (11.4)
Re-LT	4 (11.4)
Indication for re-LT	
PV thrombosis	1 (2.9)
Primary non function	1 (2.9)

Table 2 *(continued)*

Table 2 *(continued)*

Characteristics	Value (n=35)
Biliary complication	1 (2.9)
Other	1 (2.9)
Composite postoperative adverse outcomes (re-LT or post-LT emergency hospitalization or in-hospital complication during LT)	15 (42.9)

Values are given in numbers (%) for categorical or medians (interquartile ranges) for continuous variables accordingly. LT, liver transplant; ICU, intensive care unit; PV, portal vein.

Table 3 Weekly total median physical activity measured by the FitBit®

Characteristics	Value (1,053 datapoints for n=35)
Steps	35,604.0 (17,835.0–59,310.0)
Distance travelled (m)	25,095.0 (11,635.0–42,002.5)
Floors climbed	36.5 (6.0–72.2)
Time spent sitting (min)	6,523.0 (5,190.8–8,532.2)
Energy expenditure total (kcal)	15,370.0 (12,979.8–17,904.2)
Energy expenditure during activities (kcal)	5,451.0 (1,871.5–8,543.8)
Low physical activity (min)	1,220.5 (463.8–1,686.2)
Moderate physical activity (min)	41.0 (0.0–127.2)
Moderate physical activity (min) grouped per WHO recommendation	
<150 min/week	800/1,053 [76]
150–300 min/week	131/1,053 [12]
>300 min/week	122/1,053 [12]
Vigorous physical activity (min)	41.0 (0.0–127.2)
Vigorous physical activity (min) grouped per WHO recommendation	
<75 min/week	636/1,024 [62]
75–150 min/week	164/1,024 [16]
>150 min/week	224/1,024 [22]

Values are given in numbers [%] for categorical or medians (interquartile ranges) for continuous variables accordingly. WHO, World Health Organization.

Discussion

Key findings, explanation and comparison

In our prospective study, we are able to show a clear association between pre-transplant decreased weekly moderate PA, as measured by a wristband activity tracker, and the increased rate of morbidity after LT. This was particularly apparent after a long time (30 weeks) on the waiting list. Importantly, patients achieving the WHO-

Figure 2 Weekly moderate physical activity. Analysis was performed using LOESS regression analysis and 95% confidence interval is shown. Bandwidth of per World Health Organization recommended weekly moderate physical activity using dashed lines.

recommended weekly MPA targets showed a lower risk of adverse composite clinical outcomes after LT. Our findings underline the importance of pre-transplant interventions aimed at improving the physical performance in an often frail and fragile patient population. This becomes even more important as the average age of the organ recipients is increasing and with it, the number of comorbidities the patients have. Achieving the aim of improving pre-transplant fitness within a structured pre-habilitation program, tailored to this patient population as is already recommended by several societies, will be essential to maintain high post-transplant success rates (26,31). Crespo *et al.* identified 4 assessment tools to detect patients suitable for Enhanced Recovery After Surgery (ERAS) protocols in the pre-transplantation period [Karnofsky performance status (KPS), LFI, abdominal muscle mass, cardiopulmonary exercise testing] (32). A recent systematic review on prehabilitation in patients awaiting LT did not detect an impact on adverse clinical outcomes including mortality due to sparse data (33). This lack of findings might also be confounded by not having identified the beneficial exercise intervention or prehabilitation program so far in these patients (34).

Our findings show that a decline in PA is in line with other identified decreasing PA measures (e.g., 6-minute walk, chair stands, hand grip) (4,35,36). De Smet *et al.* (16) and Berben *et al.* (37) have recently performed two separate
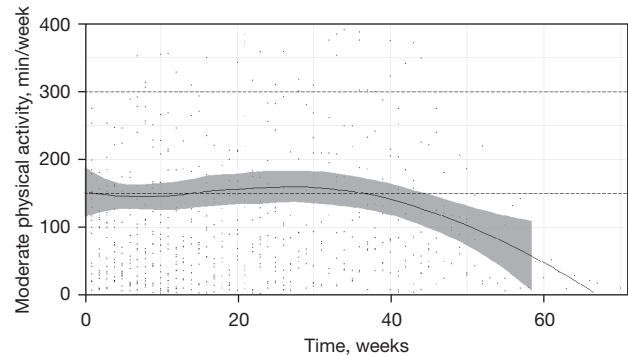
Table 4 Factors associated with weekly moderate physical activity in patients listed for liver transplantation

Variable	From week 0 to 20		From week 20 to 40		After week 40	
	Effect	P value	Effect	P value	Effect	P value
Sex[†]						
Male	1.014 (1.000–1.027)	0.054	1.018 (0.998–1.038)	0.074	0.952 (0.926–0.979)	<0.001
Female	1.001 (0.977–1.027)	0.908	1.025 (1.011–1.039)	<0.001	1.009 (0.995–1.023)	0.202
Relative MR (interaction term)	0.988 (0.961–1.016)	0.405	1.007 (0.983–1.031)	0.580	1.060 (1.027–1.094)	<0.001
Nutritional support before liver transplant[†]						
No	1.009 (0.995–1.023)	0.202	1.023 (1.003–1.042)	0.024	0.970 (0.916–1.027)	0.302
Yes	1.022 (0.995–1.050)	0.106	1.011 (1.000–1.022)	0.045	0.962 (0.950–0.974)	<0.001
Relative MR (interaction term)	1.013 (0.983–1.044)	0.399	0.989 (0.967–1.011)	0.320	0.991 (0.935–1.052)	0.775
Age (years)[‡]	1.000 (1.000–1.001)	0.454	1.000 (0.998–1.001)	0.546	0.997 (0.992–1.002)	0.266
Child-Pugh Score inclusion[‡]	1.001 (0.992–1.009)	0.872	1.011 (0.994–1.029)	0.195	0.983 (0.948–1.019)	0.355
Liver frailty Index at inclusion[‡]	0.998 (0.972–1.025)	0.869	1.001 (0.985–1.017)	0.899	1.021 (0.992–1.052)	0.156
SF36 total score at inclusion[‡]	0.998 (0.997–1.000)	0.095	1.004 (0.999–1.009)	0.105	1.013 (0.994–1.031)	0.180

Analyses were done using a mixed-effects generalized linear model with a Gamma distribution and a log link. [†], regression coefficient (95% CI); [‡], multiplicative change regression coefficient (95% CI). MR, mean ratio; CI, confidence interval.
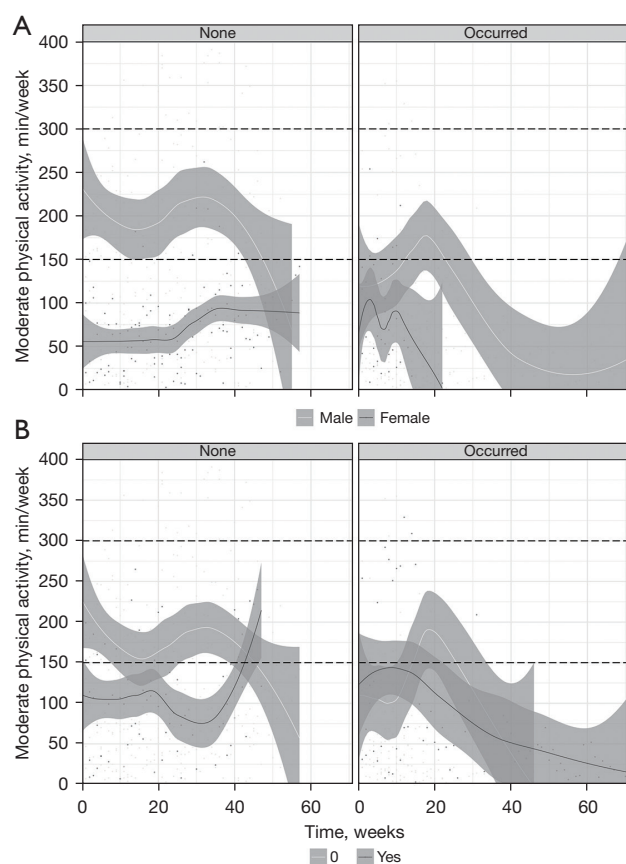
Figure 3 *A priori* factors at inclusion and their respective association with weekly moderate physical activity faceted by occurrence of composite adverse clinical outcome. (A) Sex; (B) nutritional support. Displayed using LOESS regression analysis is shown along with bandwidth of per World Health Organization recommended weekly moderate physical activity using dashed lines.

Figure 4 Forest plot of post-transplant morbidity and mortality association with weekly moderate physical activity in patients waitlisted for liver transplantation at different time points. Composite clinical adverse outcomes (re-LT or post-LT emergency hospitalization or in hospital complication during LT) assessed per marginal increase of 10 min weekly MPA in a logistic regression analysis model. OR, odds ratio; 95% CI, 95% confidence interval; MPA, moderate physical activity; LT, liver transplantation.

meta-analyses on PA in the post-transplantation period, showing improved cardiorespiratory fitness measures and QoL. Subsequent limitations were discussed in detail by Thuluvath *et al.* (38). In a Korean study, declined physical performance (per the KPS) during the early post-transplantation period (one *vs.* six months post-transplant) was associated with increased mortality up to 5 years post-LT (15). Assessing the KPS or Rosow-Breslau Score are quite complex and time-consuming, while downloading data from a wrist-tracking device is not only quick but also objective, combing many different variables.

In our study, we were able to show a significant association between outcomes and decreased PA. Our data show that nutritional supplementation was associated with improved MPA between week 20 and 40 in patients
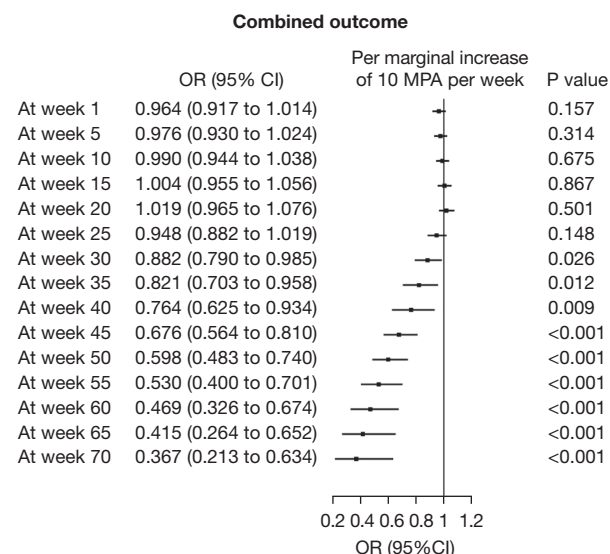
awaiting LT, suggesting a benefit of this intervention. The clinical interpretation is challenging, as there is likely to be a selection bias in as much as that severe sarcopenic patients are typically those receiving nutritional support. Nutritional support may thus be considered a surrogate marker for the extent of the disease severity in waitlisted patients. The interpretation in this sense is comparable to the restrictions of the interpretation of the Model End-Stage Liver Disease in these frail patients.

Our cohort showed a difference in MPA over time, stratified according to the recipient sex, with an increase in MPA at inclusion (P=0.054 and P=0.074) in males (n=25) and a significant decrease (P<0.001) only after week 40 onwards. In females (n=10) on the other hand, there was a significant increase found solely between week 20 and 40 (P<0.001) of inclusion. A significant difference between sexes was identified after week 40 (P<0.001).

Interestingly, both patients with and without nutritional support showed a significant increase of MPA over time between week 20 and 40 after inclusion. After week 40, a significant decrease (P<0.001) of MPA over time in the group receiving nutritional support was noted possibly suggesting

a "point of no return" of malnutrition in this very advanced phase of ESLD as was discussed by Dasarathy (39).

Strengths and limitations

While the majority of the available literature focuses on the post-transplantation period, we present data to support the use of health-prevention measures and implementation of an active pre-habilitation program in patients awaiting LT. This is of particular relevance in countries like Switzerland where patients spend long average times on the waiting list (40-44). The sex discrepancy of MPA over time in our cohort might be due to power, ascertainment bias or insufficient adherence regarding wearing of the tracking device or sex-related differences in underlying pathology and/or co-morbidities. Limitations include the inability to assess who was actually wearing the device and the small patient sample size. Resulting limitations are encountered in subgroup analyses. As such, which type of nutritional support might result in the most benefit for the patient in this setting, could not be assessed. In-depth analysis of adverse outcome endpoints (such as infections) was not feasible due to inadequate power due to the small sample size. The non-significance within the nutritional *vs.* no nutritional support group may be due to under-powering regarding this factor.

Moreover, a Hawthorne effect (45) or corresponding ascertainment bias cannot be ruled out, as no measurements were carried out prior to the study inclusion.

Implications and actions needed

The wristband activity tracking device or other wearable devices allow for a personalized approach, adapted to an individual's possibilities and needs, serving as a telemedicine device to intervene in between the outpatient consultations. The latter aspects are particularly interesting for patients living far away from their transplant center, who are not seen on a regular basis. Home-based exercise has been shown to effectively improve sarcopenia (measured using the skeletal muscle index) and QoL (46) while increasing cardiopulmonary and aerobic capacity (47,48) in ESLD patients, with a wristband tracking device would allow for a closer follow-up (and intervention) in these patients.

The results of our study underline that intervention studies in the field of PA possibly combined with nutritional support are urgently needed to reduce morbidity and mortality before and after LT. Ultimately, pre-habilitation

in combination with nutritional support might help stabilize or even reduce sarcopenia and frailty (49). Furthermore, involving patients in such a program will help to positively influence their sedentary life style as well as improving cardiorespiratory fitness (50) while decreasing postoperative morbidity and mortality. Influencing frailty and sarcopenia are essential, as they impact delisting and post-transplant outcomes (51).

Conclusions

Our findings show a significant association between decreased PA and adverse clinical outcome, especially after week 30 on the waiting list. Collectively, our findings support the implementation of a structured pre-habilitation program for patients awaiting LT.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-399/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-399/dss

Peer Review File: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-399/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-399/coif). C.B. received grant from Stiftung für Leberkrankheiten Bern. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the local ethics committee (Kantonale Ethikkommission, Kanton Bern, BASEC ID 2019-00606). All patients included in the present study signed a specific informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Belarmino G, Gonzalez MC, Sala P, et al. Diagnosing Sarcopenia in Male Patients With Cirrhosis by Dual-Energy X-Ray Absorptiometry Estimates of Appendicular Skeletal Muscle Mass. JPEN J Parenter Enteral Nutr 2018;42:24-36.

2. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2012;10:166-73, 173.e1.

3. Giusto M, Lattanzi B, Albanese C, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. Eur J Gastroenterol Hepatol 2015;27:328-34.

4. Carey EJ, Steidley DE, Aqel BA, et al. Six-minute walk distance predicts mortality in liver transplant candidates. Liver Transpl 2010;16:1373-8.

5. Montano-Loza AJ, Angulo P, Meza-Junco J, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle 2016;7:126-35.

6. Duarte-Rojo A, Ruiz-Margáin A, Montaño-Loza AJ, et al. Exercise and physical activity for patients with end-stage liver disease: Improving functional status and sarcopenia while on the transplant waiting list. Liver Transpl 2018;24:122-39.

7. Allen SL, Quinlan JI, Dhaliwal A, et al. Sarcopenia in chronic liver disease: mechanisms and countermeasures. Am J Physiol Gastrointest Liver Physiol 2021;320:G241-57.

8. Dunn MA, Josbeno DA, Schmotzer AR, et al. The gap between clinically assessed physical performance and objective physical activity in liver transplant candidates. Liver Transpl 2016;22:1324-32.

9. Kumar R, Prakash SS, Priyadarshi RN, et al. Sarcopenia in Chronic Liver Disease: A Metabolic Perspective. J Clin Transl Hepatol 2022;10:1213-22.

10. Kim G, Kang SH, Kim MY, et al. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. PLoS One 2017;12:e0186990.

11. Kardashian A, Ge J, McCulloch CE, et al. Identifying an Optimal Liver Frailty Index Cutoff to Predict Waitlist Mortality in Liver Transplant Candidates. Hepatology 2021;73:1132-9.

12. Tapper EB. Frailty and Outcomes After Liver Transplantation. Curr Transplant Rep 2019;6:1-6.

13. Lai JC, Segev DL, McCulloch CE, et al. Physical frailty after liver transplantation. Am J Transplant 2018;18:1986-94.

14. Pieber K, Crevenna R, Nuhr MJ, et al. Aerobic capacity, muscle strength and health-related quality of life before and after orthotopic liver transplantation: preliminary data of an Austrian transplantation centre. J Rehabil Med 2006;38:322-8.

15. Kim DG, Hwang S, Lee KW, et al. Physical Performance Decline During the Early Posttransplantation Period Affects Survival After Living Donor Liver Transplantation. Transplantation 2023;107:1545-53.

16. De Smet S, O'Donoghue K, Lormans M, et al. Does Exercise Training Improve Physical Fitness and Health in Adult Liver Transplant Recipients? A Systematic Review and Meta-analysis. Transplantation 2023;107:e11-26.

17. Meri C B, Solak S, Aydogdu N, et al. The comparison of endothelial function of moderate intensity interval exercise with continuous exercise in healthy men. Curr Res Physiol 2022;5:338-43.

18. Barberan-Garcia A, Ubré M, Roca J, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery: A Randomized Blinded Controlled Trial. Ann Surg 2018;267:50-6.

19. Jain SR, Kandarpa VL, Yaow CYL, et al. The Role and Effect of Multimodal Prehabilitation Before Major Abdominal Surgery: A Systemic Review and Meta-Analysis. World J Surg 2023;47:86-102.

20. Chen J, Zhou R, Feng Y, et al. Molecular mechanisms of exercise contributing to tissue regeneration. Signal Transduct Target Ther 2022;7:383.

21. Perry AS, Annis JS, Master H, et al. Association of

Longitudinal Activity Measures and Diabetes Risk: An Analysis From the National Institutes of Health All of Us Research Program. J Clin Endocrinol Metab 2023;108:1101-9.

22. Kandola A, Ashdown-Franks G, Hendrikse J, et al. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. Neurosci Biobehav Rev 2019;107:525-39.

23. Gloor S, Misirlic M, Frei-Lanter C, et al. Prehabilitation in patients undergoing colorectal surgery fails to confer reduction in overall morbidity: results of a single-center, blinded, randomized controlled trial. Langenbecks Arch Surg 2022;407:897-907.

24. O'Doherty AF, West M, Jack S, et al. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. Br J Anaesth 2013;110:679-89.

25. WHO. Guidelines on physical activity and sedentary behaviour: at a glance. Vol. 1, 2020:1-17. Available online: https://www.who.int/publications/i/item/9789240015128

26. Pollok JM, Tinguely P, Berenguer M, et al. Enhanced recovery for liver transplantation: recommendations from the 2022 International Liver Transplantation Society consensus conference. Lancet Gastroenterol Hepatol 2023;8:81-94.

27. Functional Assessment in Liver Transplantation. Liver Frailty Index™. 2021. Available online: https://liverfrailtyindex.ucsf.edu

28. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.

30. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.

31. Janaudis-Ferreira T, Mathur S, Deliva R, et al. Exercise for Solid Organ Transplant Candidates and Recipients: A Joint Position Statement of the Canadian Society of Transplantation and CAN-RESTORE. Transplantation 2019;103:e220-38.

32. Crespo G, Hessheimer AJ, Armstrong MJ, et al. Which preoperative assessment modalities best identify patients who are suitable for enhanced recovery after liver transplantation? A systematic review of the literature and expert panel recommendations. Clin Transplant 2022;36:e14644.

33. Jetten WD, Hogenbirk RNM, Van Meeteren NLU, et al. Physical Effects, Safety and Feasibility of Prehabilitation in Patients Awaiting Orthotopic Liver Transplantation, a Systematic Review. Transpl Int 2022;35:10330.

34. Serper M, Jones LS, Clement T, et al. A randomized, controlled, prehabilitation intervention to maximize early recovery (PRIMER) in liver transplantation. Liver Transpl 2024;30:10-9.

35. Lai JC, Dodge JL, Sen S, et al. Functional decline in patients with cirrhosis awaiting liver transplantation: Results from the functional assessment in liver transplantation (FrAILT) study. Hepatology 2016;63:574-80.

36. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14:1870-9.

37. Berben L, Engberg SJ, Rossmeissl A, et al. Correlates and Outcomes of Low Physical Activity Posttransplant: A Systematic Review and Meta-Analysis. Transplantation 2019;103:679-88.

38. Thuluvath AJ, Lai JC. Understanding Current Limitations to Exercise Interventions After Liver Transplantation. Transplantation 2023;107:e1-2.

39. Dasarathy S. Cause and management of muscle wasting in chronic liver disease. Curr Opin Gastroenterol 2016;32:159-65.

40. Steck P, Immer F. Organspende: Lange Wartezeiten für Patientinnen und Patienten. Schweizerische Ärztezeitung 2022;103:589-92.

41. De Geest S, Burkhalter H, Berben L, et al. The Swiss Transplant Cohort Study's framework for assessing lifelong psychosocial factors in solid-organ transplants. Prog Transplant 2013;23:235-46.

42. Koller MT, van Delden C, Müller NJ, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. Eur J Epidemiol 2013;28:347-55.

43. Eden J, Sousa Da Silva R, Cortes-Cerisuelo M, et al. Utilization of livers donated after circulatory death for transplantation - An international comparison. J Hepatol 2023;78:1007-16.

44. Swisstransplant. Abb 4.13 - Wartezeit bis zur Transplantation. 2023. Available online: https://www.swisstransplant.org/de/organ-gewebespende/statistiken/jahreszahlen-1

45. Demetriou C, Hu L, Smith TO, et al. Hawthorne effect on surgical studies. ANZ J Surg 2019;89:1567-76.

46. Sirisunhirun P, Bandidniyamanon W, Jrerattakon Y, et al. Effect of a 12-week home-based exercise training program

on aerobic capacity, muscle mass, liver and spleen stiffness, and quality of life in cirrhotic patients: a randomized controlled clinical trial. BMC Gastroenterol 2022;22:66.

47. Román E, García-Galcerán C, Torrades T, et al. Effects of an Exercise Programme on Functional Capacity, Body Composition and Risk of Falls in Patients with Cirrhosis: A Randomized Clinical Trial. PLoS One 2016;11:e0151652.

48. Chen HW, Ferrando A, White MG, et al. Home-Based Physical Activity and Diet Intervention to Improve Physical Function in Advanced Liver Disease: A Randomized Pilot Trial. Dig Dis Sci 2020;65:3350-9.

49. Lin FP, Visina JM, Bloomer PM, et al. Prehabilitation-Driven Changes in Frailty Metrics Predict Mortality in Patients With Advanced Liver Disease. Am J Gastroenterol 2021;116:2105-17.

50. Debette-Gratien M, Tabouret T, Antonini MT, et al. Personalized adapted physical activity before liver transplantation: acceptability and results. Transplantation 2015;99:145-50.

51. Ferreira AP, Machado MV. Impact of pretransplant frailty and sarcopenia on the post-transplant prognosis of patients with liver cirrhosis: a systematic review. Eur J Gastroenterol Hepatol 2021;33:e883-97.
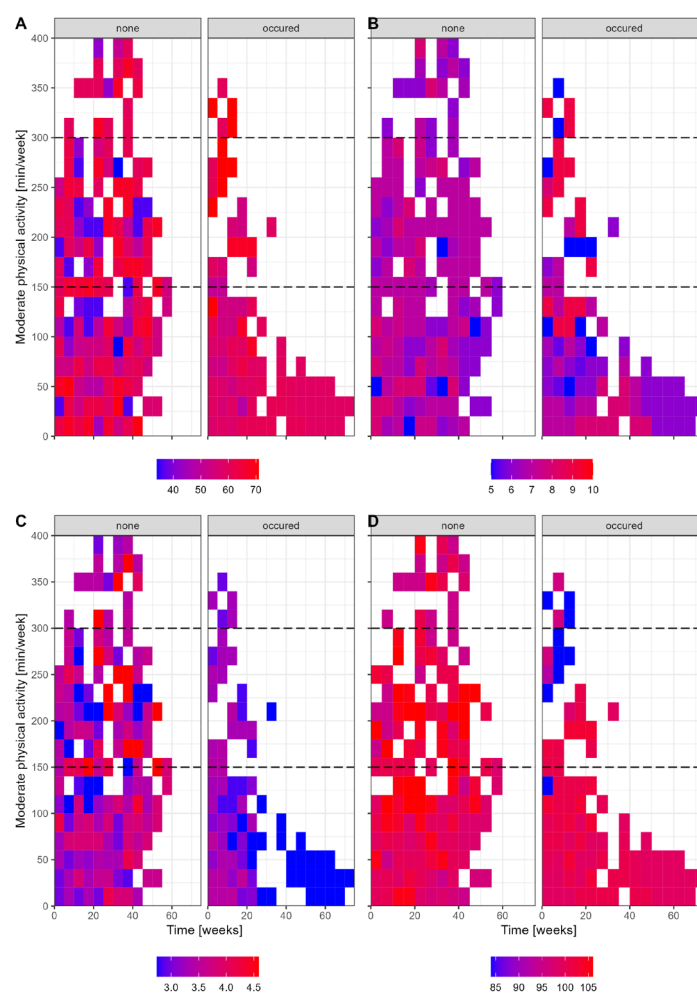
Figure S1 *A priori* factors at inclusion and their respective association with weekly moderate physical activity faceted by occurrence of composite adverse clinical outcome. (A) Age in years, (B) Child-Pugh Score, (C) Liver Frailty Index and (D) quality of life as per SF36 total score. Displayed using heatmap (median per boxes of 5 weeks and MPA 20 min/week) is shown along with bandwidth of per WHO recommended weekly moderate physical activity using dashed lines.
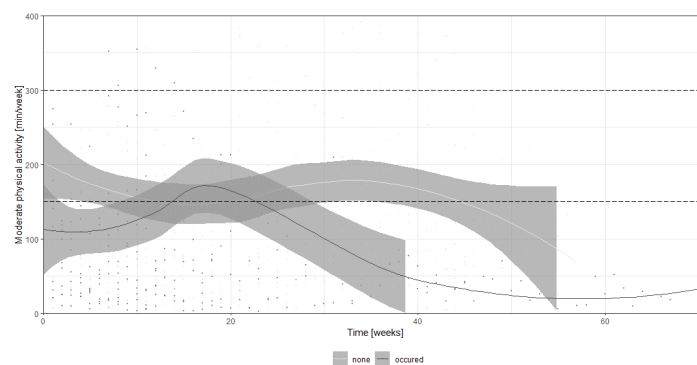

Figure S2 Weekly moderate physical activity stratifying for the occurrence of composite clinical outcome. Analysis was performed using LOESS regression analysis and 95% CI is shown. Bandwidth of per WHO recommended weekly moderate physical activity using dashed lines.

Table S1 Daily median physical activity measured by the FitBit®

Characteristics	Medians (IQR)[†]
Steps	4,661.0 (1,685.0–8,609.0)
Distance travelled (m)	3,255.0 (1,110.0–6,100.0)
Floors climbed	4.0 (0.0–9.0)
Time spent sitting (min)	947.0 (708.0–1,366.8)
Energy expenditure total (kcal)	2,159.0 (1,780.0–2,610.0)
Energy expenditure during activities (kcal)	717.5 (85.2–1,265.8)
Low physical activity (min)	166.0 (22.0–247.0)
Moderate physical activity (min)	0.0 (0.0–18.0)
Vigorous physical activity (min)	0.0 (0.0–11.0)

[†], 7,270 data points in n=35, significances assessed using Mann-Whitney *U*-test.

Table S2 Analysis of weekday effect on physical activity

Variable	Sunday (N=10,371)	Monday (N=10,401)	Tuesday (N=1,0361)	Wednesday (N=10,371)	Thursday (N=10,351)	Friday (N=10,431)	Saturday (N=10,421)	P value
Steps	3,460.0 (1,028.0–7,521.0)	4,818.0 (1,877.0–8,684.5)	4,356.0 (1,672.5–7,932.5)	4,916.0 (1,897.0–8,592.0)	4,806.0 (1,906.5–8,774.5)	5,156.0 (1,939.5–8,642.0)	5,300.5 (1,990.8–9,987.0)	<0.001
Distance travelled (m)	2,370.0 (700.0–5,310.0)	3,350.0 (1,230.0–6,032.5)	3,000.0 (1,120.0–5,585.0)	3,410.0 (1,260.0–6,100.0)	3,360.0 (1,290.0–6,175.0)	3,660.0 (1,290.0–6,065.0)	3,660.0 (1,340.0–7,037.5)	<0.001
Floors climbed	2.0 (0.0–8.0)	4.0 (0.0–9.0)	4.0 (0.0–9.0)	4.0 (0.0–10.0)	4.0 (0.0–9.0)	4.0 (0.0–9.0)	4.0 (0.0–11.0)	<0.001
Time spent sitting (min)	955.0 (702.0–1,400.0)	966.0 (713.5–1,357.0)	967.5 (722.5–1,355.2)	943.0 (709.0–1,378.0)	926.0 (710.5–1,348.0)	964.0 (718.0–1,378.0)	919.0 (674.0–1,347.0)	0.421
Energy expenditure total (kcal)	2,074.0 (1,708.0–2,478.0)	2,168.0 (1,803.8–2,605.5)	2,126.0 (1,758.8–2,567.8)	2,158.0 (1,781.0–2,623.0)	2,171.0 (1,796.5–2,601.0)	2,173.0 (1,824.0–2,658.5)	2,244.5 (1,820.5–2,739.5)	<0.001
Energy expenditure during activities (kcal)	571.0 (30.0–1,162.0)	729.5 (87.2–1,264.2)	684.0 (121.0–1,194.8)	743.0 (104.0–1,271.0)	728.0 (71.5–1,262.0)	756.0 (46.0–1,307.0)	814.5 (132.5–1,351.5)	<0.001
Low physical activity (min)	131.0 (8.0–205.0)	166.0 (26.5–255.0)	172.0 (34.5–250.0)	172.0 (26.0–249.0)	168.0 (22.5–249.0)	178.0 (14.5–264.0)	174.5 (37.0–249.0)	<0.001
Moderate physical activity (min)	0.0 (0.0–20.0)	0.0 (0.0–19.0)	0.0 (0.0–14.0)	0.0 (0.0–18.0)	0.0 (0.0–18.0)	0.0 (0.0–17.0)	0.0 (0.0–22.8)	<0.001
Vigorous physical activity (min)	0.0 (0.0–11.0)	0.0 (0.0–11.0)	0.0 (0.0–8.0)	0.0 (0.0–14.0)	0.0 (0.0–11.5)	0.0 (0.0–10.0)	0.0 (0.0–16.0)	0.006

Values are given in medians (IQR) for continuous variables and significances assessed using Kruskal-Wallis *H* test.