Available online at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Low physical activity level in out-of-hospital cardiac arrest survivors with obesity, mobility problems and cognitive impairment: Results from the TTM2 trial

Katarina Heimburg[a,b,*], *Erik Blennow Nordström*[a,c], *Josef Dankiewicz*[b,d], *Hans Friberg*[e,f], *Anders M. Grejs*[g,h], *Matthias Hänggi*[i,j], *Thomas R. Keeble*[k,l], *Hans Kirkegaard*[g,m], *Niklas Nielsen*[n,o], *Christian Rylander*[p], *Åsa B. Tornberg*[q], *Susann Ullén*[r], *Matthew P. Wise*[s,t], *Tobias Cronberg*[a,u], *Gisela Lilja*[a,u]

Abstract

Aims: To describe the level of physical activity 6 months after an out-of-hospital cardiac arrest (OHCA) and to explore potential risk factors of a low level of physical activity.

Methods: Post-hoc analyses of the international multicentre Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac arrest (TTM2) trial. At 6 months, survivors at 61 sites in Europe, Australia and New Zeeland were invited to a follow-up. The participants answered two questions on self-reported physical activity. Answers were categorized as a low, moderate, or high level of physical activity and further dichotomized into a low versus moderate/high level of physical activity. Potential risk factors for a low level of physical activity were collected and investigated by univariable and multivariable logistic regression.

Results: At 6 months, 807 of 939 (86%) OHCA survivors answered the two questions of physical activity; 34% reported a low, 44% moderate and 22% high level of physical activity. Obesity (OR = 1.75, 95% CI 1.10–2.77, p = 0.018), mobility problems by EuroQol 5 dimensions 5 levels (OR = 1.73, 95% CI 1.06–2.84, p = 0.029), and cognitive impairment by Symbol Digit Modalities Test (OR = 1.78, 95% CI 1.13–2.82, p = 0.013) were significantly associated with a low level of physical activity in the multivariable analysis.

Conclusion: One third of the OHCA survivors reported a low level of physical activity. Obesity, mobility problems, and cognitive impairment were associated with a low level of physical activity.

ClinicalTrials.gov Identifier: NCT02908308.

Keywords: Cardiac arrest, Physical activity, Patient-reported outcome, Physical function, Cognitive function, Cardiovascular risk factors

Introduction

In out-of-hospital cardiac arrest (OHCA) survivors, several potential risk factors may contribute to an individual not attaining the recommended dose of physical activity.[1] Previous studies have shown that women and individuals ≥ 65 years old report more difficulties with physical aspects of their health compared to men and younger OHCA survivors.[2,3] Cognitive impairment, which is common after OHCA,[4] was associated with lower exercise capacity after OHCA.[5] Symptoms of anxiety and depression were factors negatively affecting the self-reported physical function of OHCA survivors.[6].

The World Health Organization (WHO) and the European Society of Cardiology recommend that all adults undertake regular physical activity, at moderate intensity 150–300 min/week or vigorous intensity 75–150 min/week, or a combination of both, to decrease all-cause mortality and morbidity.[1,7,8] More health benefits are achieved with a higher dose.[1] Myocardial infarction (MI) is the most

* Corresponding author at: Skane University Hospital, Center for Cardiac Arrest at Lund University, Remissgatan 4, 221 85 Lund, Sweden.
E-mail address: katarina.heimburg@med.lu.se (K. Heimburg).

https://doi.org/10.1016/j.resuscitation.2024.110407
Received 2 August 2024; Received in Revised form 18 September 2024; Accepted 28 September 2024

common cause of OHCA.[9,10] Following an MI, supervised exercise-based cardiac rehabilitation (CR) is recommended at least 3 days/week at moderate to high intensity for ≥ 20 min per session during the first months, with a goal to increase the physical activity level to reduce the risk of new cardiac events.[11]

The recommendation after the CR programme ends is moderate intensity physical activity at 30 min per day for 5 days a week (i.e., 150 min/week) or vigorous intensity physical activity at 15 min per day for 5 days a week (i.e., 75 min/week), of or a combination of both.[11] After MI, adherence to the physical activity guidelines is associated with fewer hospital readmissions and improved survival.[12] The level of physical activity and factors associated with a lower adherence to physical activity guidelines[1,7,11] amongst OHCA survivors are unknown.

The aims of this study were to describe the level of physical activity 6 months after an OHCA and to explore potential risk factors of a low level of physical activity. Our focus was to identify the OHCA survivors with a low physical activity, potentially with an increased risk of suffering a new cardiac event.[13,14]

Methods

Procedure and study design

This is a cross-sectional *post-hoc* study and an extension of the international multicentre randomised clinical Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac arrest (TTM2) trial (Clinical trials NCT02908308). The TTM2 trial was designed to assess whether targeted temperature management at 33 was superior to normothermia and early treatment of fever (≥37.8),[15,16] and performed at 61 sites in Europe, USA, Australia and New Zeeland. At 6 months, all survivors were invited to a face-to-face follow-up together with a relative or a close friend.[17,18] The TTM2 trial included participants from November 2017 to January 2020 and the final 6-month follow-ups were performed in October 2020. Since there were no differences between the intervention groups in the primary (death), secondary (poor functional outcome)[16] or exploratory (cognition and societal participation)[18] outcome analyses of the TTM2 trial, the two intervention groups were here pooled into one group of OHCA survivors for this study.

The TTM2 trial was undertaken according to the Code of Ethics of the World Medical Association (Declaration of Helsinki)[19] and the trial research protocol[17] was approved by ethical review boards in all countries. We obtained written informed consent from all participants before the 6-month follow-ups.

Participants

The TTM2 trial included comatose adults (18 years or older) who had an OHCA of a presumed cardiac or unknown cause. The main exclusion criteria were an interval from return of spontaneous circulation to screening of more than 180 min, unwitnessed cardiac arrest with asystole as the initial rhythm, and limitations in care.[16]

Outcome assessments and outcome assessors

A protocol for outcome reporting in the TTM2 trial was published.[17] Sociodemographic characteristics and information about the cardiac arrest were collected from the TTM2 trial database. The outcome variables were obtained during the structured 6-month follow-ups performed by study trained local outcome assessors blinded to the intervention. To minimize avoidable missing data, a central coordinator provided support and reviewed the follow-up data at regular intervals.[17,18]

Self-reported physical activity (main outcome)

At the 6-month follow-ups, data on self-reported physical activity were collected by two questions based on physical activity recommendations to promote and maintain health by Haskell *et al.*[20] The first question addressed the frequency of moderate intensity physical activity totaling 30 min or more per day, and the second vigorous intensity physical activity exceeding 20 min per day during the previous week (Table 1). The range of answers is from 0 to 7 days for moderate and vigorous intensity physical activities respectively.[20] The questions were followed by examples of moderate and vigorous intensity physical activities. For example, a brisk walk that leads to a moderate level of effort and noticeably accelerates the heart rate illustrates moderate intensity physical activity. Vigorous intensity physical activity is exemplified by jogging that causes rapid breathing and a substantial increase in heart rate.[20]

Based on the physical activity recommendations,[1,7,11,20] the two questions were further categorized as a low, moderate, or high as explained in Table 2. A low level of physical activity corresponds to a level below that recommended for primary prevention.[1,7,20] A moderate level attain the level of primary prevention. A high level includes both moderate and vigorous intensity physical activity in accordance with secondary prevention during exercise based cardiac rehabilitation.[11] The three categories were then further dichotomized as a low versus a moderate/high level of physical activity. These questions have shown evidence to be a valid assessment of physical activity in both OHCA survivors and patients after MI, based on significant agreement with an objective assessment of physical activity as the gold standard.[21,22]

Potential risk factors of a low level of physical activity

We investigated the following potential risk factors based on a theoretical assumption of being associated with a low level of physical activity and the following variables were included:

Sociodemographic variables (n = 3): higher age (years), female sex (yes), and a low level of education (<12 years).

OHCA-related variables (n = 5): non-shockable rhythm (yes); longer time to return of spontaneous circulation (ROSC) (minutes), other cause than MI to the OHCA (yes), moderately to severely reduced left ventricular ejection fraction (LVEF) of the heart (yes) and longer intensive care unit (ICU) length of stay (days).

6-months variables (n = 15): not provided exercise-based cardiac rehabilitation (yes), cardiovascular risk factors: smoking (yes), diabetes (yes), hypertension (yes), overweight (body mass index (BMI) 25–29.9), obesity (BMI ≥ 30),[23] poor overall functional outcome by modified Rankin Scale[24] (mRS 4–5), any problems reported by the EuroQol health survey 5 dimensions 5 levels response version (EQ-5D-5L)[25,26] (level 2–5) with the domains mobility, self-care, usual activities, pain/discomfort and anxiety/depression, impaired physical function by Timed Stands Test (TST)[27,28] (yes), global cognitive impairment by Montreal Cognitive Assessment (MoCA)[29] (<26) and impaired mental processing speed/attention by the Symbol Digit Modalities Test (SDMT) (age and education level adjusted z-score of < -1.5 SD).[30]

Statistical analysis

We present descriptive statistics as numbers and percentages for binary and categorical variables, and for continuous variables as

Table 1 – Survivors answered two questions on physical activity at the 6 months follows-up in Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial.

	Questions about physical activity	Examples given to the out-of-hospital cardiac arrest survivors
Question 1 Moderate intensity physical activity	In the last week, how many days have you engaged in moderate intensity physical activities for at least 30 min a day? (could be performed in blocks that last for at least 10 min adding up to a total of 30 min or more)	Moderate intensity physical activities denote activities performed for at least 10 min that leads to a moderate level of effort and a noticeably accelerate of heart rate. Examples of activities on this level include a brisk walk, heavy cleaning, washing windows, cleaning the car, carpentry, bicycling with light effort, golf, swimming leisurely or similar. For more examples, see Haskell.[20]
Question 2 Vigorous intensity physical activity	In the last week, how many days have you engaged in vigorous intensity physical activities for at least 20 min (in one block)?	Vigorous intensity physical activities are an activity that leads to a substantial increase in heart rate and e.g. causes rapid breathing. Examples of activities at this level includes jogging, running, walking very very brisk, shoveling/digging, bicycling with a moderate effort/fast, swimming moderate/hard, tennis or similar. For more examples, see Haskell.[20]

Table 2 – Categorization in three ordered groups based on number of days of self-reported 30 min in total of moderate and 20 min of vigorous intensity physical activity a day during the last week[47] in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial.

Group of physical activity level	Self-reported moderate intensity and vigorous intensity physical activity in days
Low level of physical activity	<5 days of moderate intensity physical activity at least 30 min in total per day/ <3 days of vigorous intensity physical activity at least 20 min per day
Moderate level of physical activity	≥ 5 days of moderate intensity physical activity at least 30 min in total per day/ ≥3 days vigorous intensity physical activity at least 20 min per day
High level of physical activity	≥2 days of moderate intensity physical activity at least 30 min in total per day and ≥ 3 days vigorous intensity physical activity at least 20 min per day

mean and standard deviation (SD) when normally distributed, or median and quartiles [q25:q75] when non-normally distributed.

Logistic regression was used to identify risk factors of a low level of physical activity, with the dichotomized value of the two questions (a low level versus a moderate/high level of physical activity) as the dependent outcome variable. First, univariable binary logistic regressions were performed for all the selected pre-defined variables of potential risk factors. We then continued with multivariable logistic regression modelling including variables with a p-value < 0.25 in the univariable logistic regressions.[31] Subsequently, we performed three separate multivariable models. Model A included the remaining sociodemographic and OHCA variables and Model B the 6 months' variables. Model C included all variables included in Model A and B. The Variance Inflation Factor was low, indicating no problems with multicollinearity (Model A: 1.01–1.05, Model B: 1.04–1.71, Model C: 1.05–1.73). The Hosmer-Lemeshow goodness-of-fit test for the models were not significant for the three models indicating that the valid models fitted (Model A: p = 0.10, Model B: p = 0.94, Model C: p = 0.94).

Results from the logistic regression models are reported as odds ratios (OR) with 95% confidence intervals (CIs) and p-values. Due to the explorative design of this study, p-values < 0.05 were used to indicate potentially statistically significant differences in the final model. Data were analyzed using the IBM® Statistical Package for Social Sciences (SPSS) 29.

Results

At 6 months, 939 of 1861 (50%) OHCA survivors were alive and invited to a follow-up. Of those, 103 of 939 (11%) declined or were missing. Finally, 836 OHCA survivors participated in the follow-up and 807 of 836 (97%) answered the two questions on physical activity. A flow-chart of the inclusion is presented in Fig. 1. There were no differences between all OHCA survivors included in the TTM2 trial (n = 939) compared to those who answered to the two questions about physical activity at the 6-month follow-ups (n = 807) regarding age, sex, Clinical Frailty Scale,[32] Charlson Comorbidity Index[33] or neurological outcome assessed by modified Rankin Scale[24] in the 6-month follow-ups (Supplementary Table A).

The participants' median age was 61 years [Q1:51, Q3:70] and 84% (676 of 807) were male. 34% (275 of 807) of OHCA survivors reported a low, 44% (355 of 807) a moderate and 22% (177 of 807) reported a high level of physical activity.

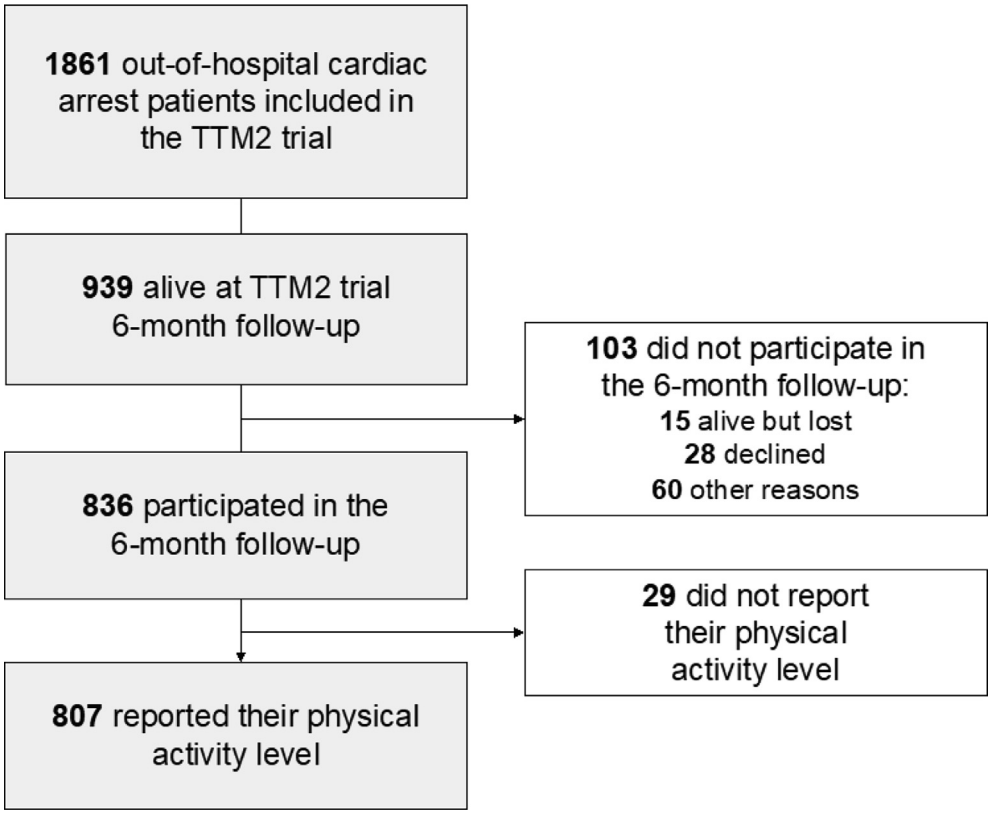

Fig. 1 – Flow chart of included out-of-hospital cardiac arrest (OHCA) survivors in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial who had answered the two questions on physical activity.

In Table 3, we present characteristics for all participants (n = 807) and additionally stratified for those with a low (n = 275) or moderate/high (n = 532) level of physical activity separately. Those with a low level of physical activity, compared to the more physically active, were more often females (21% versus 14%), had a higher prevalence of an initial non-shockable rhythm (93% versus 85%) and a longer stay in both the ICU (6 days versus 4 days) and hospital (18 days versus 14 days). At 6-month follow-ups, more survivors with a low level of physical activity were obese (26% versus 18%), had a poor functional outcome by the mRS (14% versus 1%) and reported more problems in all five domains of the EQ-5D-5L. Those with a low level of physical activity also had more physical impairment by TST (75% versus 69%) and global cognitive impairment (49% versus 36% by MoCA) as well as impaired processing speed (47% versus 26% by SDMT). The OHCA survivors with a low level of physical activity were also less often working at the time of the OHCA (46% versus 57%), and of those working prior to the OHCA, less had returned to work at 6 months (24% versus 40%) (Table 3).

The univariable analyses (Table 4) demonstrated significant associations between a low level of physical activity and female sex, non-shockable rhythm, longer length of stay in the ICU and causes of CA other than MI. For the 6 months variables, there were significant associations between a low level of physical activity and smoking, obesity, poor functional outcome by mRS, any problems reported by the EQ-5D-5L domains, physical impairment by TST and cognitive impairment by MoCA and SDMT.

The multivariable logistic regression Model A, including remaining sociodemographic and OHCA variables from the univariable analyses (Table 4), showed that female sex, non-shockable rhythm and longer stay in an ICU were significantly associated with a low level of physical activity at 6 months.

In the multivariable logistic regression Model B, including 6-months' variables from the univariable analyses, obesity, mobility problems by EQ-5D-5L and cognitive impairment by SDMT were significantly associated with a low level of physical activity at 6 months.

In the logistic regression Model C, we combined the variables included in the first and second models. Obesity (OR = 1.75, 95% CI 1.10–2.77, p = 0.018), mobility problems by EQ-5D-5L (OR = 1.73, 95% CI 1.06–2.84, p = 0.29), and cognitive impairment by SDMT (OR = 1.78, 95% CI 1.13–2.82, p = 0.013) remained statistically significantly associated to the level of physical activity (Table 4).

Discussion

One third of the OHCA survivors in this large, international cohort reported a low level of physical activity, which is insufficient to attain current recommendations of physical activity. Obesity, mobility problems, and cognitive impairment were associated with a low level of physical activity. This is important as those with a low level of physical activity may run an increased risk of suffering a new cardiac event.[13,14] The findings strengthen the conclusion of promoting physical activity[34] amongst OHCA survivors.

Obesity was negatively associated with the level of physical activity, which was expected. The results are in line with a systematic

Table 3 – Sociodemographic variables, OHCA variables, in-hospital variables, and cardiovascular risk factors and 6 months outcome variables among all OHCA survivors who had reported their physical activity level in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial. The OHCA survivors have then been categorized into a low versus a moderate/high level of physical activity.

	All OHCA survivors	OHCA survivors with a low level of physical activity	OHCA survivors with a moderate/high level of physical activity
OHCA survivors n (%)	807 (100)	275/807 (34)	532/807 (66)
Sociodemographic variables			
Age years median [Q1:Q3]	61 [52:70]	62 [52:71]	61 [52:69]
Male sex n (%)	676 (84)	216 (79)	460 (86)
Education university level n (%)	266 (33)	80 (29)	186 (35)
Working before OHCA n (%)	430 (53)	127 (46)	303 (57)
OHCA variables			
Location of OHCA at home n (%)	345 (43)	129 (47)	216 (41)
Bystander witness yes n (%)	744 (92)	252 (92)	492 (93)
Bystander performed CPR yes n (%)	687 (85)	223 (81)	464 (87)
Shockable rhythms yes n (%)	725 (90)	233 (85)	492 (93)
CA to ROSC minutes median [Q1:Q3]	20 [14:30]	20 [13:30]	20 [14:30]
In-hospital variabels			
LOS ICU days median [Q1:Q3]	5 [3:9]	6 [4:10]	4 [3:8]
LOS hospital days median [Q1:Q3]	15 [10:25]	18 [11:31]	14 [10:22]
MI cause to CA n (%)	445 (55)	137 (50)	308 (58)
LVEF $\leq$ 44% n (%)	314 (39)	105 (38)	209 (39)
Cardiovascular risk factors at 6 months			
Smoking yes n (%)	106 (13)	45 (16)	61 (11)
Diabetes yes n (%)	107 (13)	44 (16)	63 (12)
Hypertension n (%)	577 (71)	199 (72)	378 (71)
Obesity BMI $\geq$ 30 n (%)	163 (21)	69 (26)	94 (18)
6 months outcomes			
Cardiac rehab n (%)	228 (28)	65 (24)	163 (31)
Exercise-based cardiac rehab n (%)	166 (21)	47 (17)	119 (22)
Neurological/cognitive rehab n (%)	143 (18)	52 (19)	91 (17)
Other rehab n (%)	42 (5)	15 (6)	27 (5)
Working n (%)	277 (34)	65 (24)	212 (40)
Poor **mRS** 4–5n (%)	46 (6)	39 (14)	7 (1)
EQ-5D-5L:			
Mobility any problems n (%)	229 (29)	126 (46)	103 (20)
Self-care any problems n (%)	106 (13)	71 (26)	36 (7)
Usual activities any problems n (%)	270 (34)	144 (52)	126 (24)
Pain/discomfort yes n (%)	350 (44)	146 (53)	204 (39)
Anxiety/depression yes n (%)	319 (40)	135(49)	184 (35)
Impaired physical function by **TST*** n (%)	378/594 (64)	136 (75)	242 (59)
Cognitive impairment by **MoCA** n (%)	308 (41)	124 (49)	184 (36)
Cognitive impairment by **SDMT*** n (%)	195/593 (33)	87/187 (47)	106/404 (26)

Abbreviations denote CPR = Cardiopulmonary Resuscitation, ROSC = Return of Spontaneous Circulation, LOS = Length of Stay, ICU = Intensive Care Unit, MI = Myocardial Infarction, LVEF = Left Ventricular Ejection Fraction moderately reduced 30–44%, severely reduced < 30%, BMI = Body Mass Index, mRS = Modified Rankin Scale, EQ-5D-5L = EuroQol 5 dimensions 5 levels, TST = Timed Stands Test, MoCA = Montreal Cognitive Assessment, SDMT = Symbol Digit Modalities Test. *= face-to-face follow-up needed, TST: 26% missing, SDMT: 27% missing.

review showing that lower levels of physical activity were associated with obesity.[34] A previous study from the Netherlands found that patients with acute coronary syndrome (ACS) and obesity were less physically active than those with ACS and normal weight.[35] More individuals in The Dutch study were obese compared to our study (27% versus 21%). After a cardiac event, obese individuals may require additional support to increase their physical activity level[35] and reduce weight. A nationwide cohort study of more than 1 million men reported that the BMI in late adolescence was the most important factor associated with cardiovascular diseases (CVD) in adulthood. These findings suggested that obesity should be prioritized for effective CVD prevention.[36]

Mobility problems reported by the EQ-5D-5L had a significant association with a low level of physical activity and this was expected. In this study, 29% of the OHCA survivors had mobility problems, a similar fraction to that reported by Djärv *et al.*[37] In the group with a low physical activity, 46% responded that they had mobility problems compared to 20% in the group with a moderate/high physical activity level. Early mobilisation and rehabilitation could start when the OHCA survivor is still in the ICU[38], and follow-up and screening of mobility problems within the first 3 months is recommended.[39] The EQ-5D-5L a simple and easily administered questionnaire to detect both mobility problems and a low level of physical activity in OHCA survivors.

Table 4 – Associations by univariable and multivariable logistic regression between the level of physical activity and sociodemographic variables, OHCA variables, in-hospital variables, rehabilitation, cardiovascular risk factors and 6 months outcome variables predefined as potential risk factors of a low level of physical activity among survivors in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial (n = 807).

Variables	Univariable Model OR (95% CI)	*p*-value	Multivariable Model AOR (95% CI)	*p*-value	Multivariable Model B OR (95% CI)	*p*-value	Multivariable Model C OR (95% CI)	*p*-value
Sociodemographic								
Older age years	1.00 (0.99, 1.01)	0.564						
Female sex	1.75 (1.20, 2.57)	**0.004**	1.68 (1.13, 2.49)	**0.010**			1.27 (0.76, 2.14)	0.362
Education no university	1.31 (0.95, 1.79)	**0.096**	1.20 (0.87, 1.67)	0.270			0.79 (0.50, 1.17)	0.213
OHCA								
Non-shockable rhythms	2.23 (1.41, 3.53)	**<0.001**	1.85 (1.14, 3.01)	**0.012**			1.41 (0.72, 2.79)	0.319
CA to ROSC minutes	1.00 (0.99, 1.01)	0.871						
ICU LOS days	1.04 (1.02, 1.06)	**<0.001**	1.04 (1.01, 1.06)	**<0.001**			0.99 (0.97, 1.02)	0.617
Other cause than MI to CA	1.40 (1.04, 1.87)	**0.026**	1.29 (0.95, 1.75)	0.100			1.03 (0.69, 1.54)	0.886
Moderate/severely reduced **LVEF**	1.02 (0.75, 1.38)	0.923						
6 months outcomes								
No exercise-based cardiac rehab	1.39 (0.96, 2.02)	**0.084**			1.30 (0.80, 2.13)	0.288	1.30 (0.79, 2.13)	0.310
Smoking	1.55 (1.02, 2.34)	**0.041**			0.98 (0.56, 1.73)	0.947	0.98 (0.55, 1.74)	0.949
Diabetes	1.45 (0.96, 2.20)	**0.081**			1.14 (0.65, 2.01)	0.651	1.13 (0.64, 2.01)	0.675
Hypertension	1.09 (0.78, 1.52)	0.63						
Overweight	1.04 (0.74, 1.46)	0.83						
Obesity	1.66 (1.12, 2.47)	**0.012**			1.71 (1.08, 2.71)	**0.022**	1.75 (1.10, 2.77)	**0.018**
Poor functional outcome by **mRS**	12.08 (5.32, 27.44)	**<0.001**			2.66 (0.90, 7.81)	0.076	2.38 (0.79, 7.21)	0.069
EQ-5D-5L: mobility problems	3.51 (2.55, 4.84)	**<0.001**			1.71 (1.05, 2.78)	**0.031**	1.73 (1.06, 2.84)	**0.029**
EQ-5D-5L: self-care problems	4.72 (3.06, 7.29)	**<0.001**			1.07 (0.53, 2.17)	0.843	1.09 (0.53, 2.22)	0.623
EQ-5D-5L: problems with usual activities	3.25 (2.58, 4.80)	**<0.001**			1.43 (0.88, 2.33)	0.147	1.42 (0.87, 2.31)	0.160

Table 4 (continued)

Variables	Univariable Model OR (95% CI)	*p*-value	Multivariable Model AOR (95% CI)	*p*-value	Multivariable Model B OR (95% CI)	*p*-value	Multivariable Model C OR (95% CI)	*p*-value
EQ-5D-5L: pain/ discomfort	1.80 (1.34, 2.42)	**<0.001**			1.11 (0.72, 1.71)	0.642	1.12 (0.72, 1.73)	0.622
EQ-5D-5L: anxiety/ depression	1.81 (1.34, 2.43)	**<0.001**			1.13 (0.74, 1.72)	0.579	1.09 (0.71, 1.68)	0.686
Impaired physical function by **TST**	2.05 (1.39, 3.03)	**<0.001**			1.34 (0.88, 2.07)	0.183	1.36 (0.89, 2.10)	0.164
Cognitive impairment by **MoCA**	1.69 (1.24, 2.30)	**<0.001**			1.10 (0.71, 1.69)	0.675	1.11 (0.72, 1.73)	0.636
Cognitive impairment by **SDMT**	2.45 (1.70, 3.52)	**<0.001**			1.80 (1.14, 2.83)	**0.012**	1.78 (1.13, 2.82)	**0.013**

Abbreviations denote OR = Odds Ratio, CI = Confidence Interval, OHCA = Out-of-hospital Cardiac Arrest, ROSC = Return of Spontaneous Circulation, LOS = Length of Stay, MI = Myocardial Infarction, LVEF = Left Ventricular Ejection Fraction, BMI = Body Mass Index, mRS = modified Rankin Scale, EQ-5D-5L = EuroQol 5 dimensions 5 levels, TST = Timed Stands Test, MoCA = Montreal Cognitive Assessment, SDMT = Symbol Digit Modalities Test.

The MoCA is a global screening tool whereas the SDMT focuses on processing speed and working memory, but also requiring adequate visual scanning and oculomotor functioning.[40] More survivors in the group with a low level of physical activity had cognitive impairment than in the physical active group. Decreased processing speed by SDMT also had a significant association with the survivors' physical activity level at 6 months. The relationship between physical activity and cognition is currently not well known following OHCA. Studies based on major neurocognitive disorder and minor cognitive impairment progressing to Alzheimer's disease respectively seem to suggest a relationship between cognition and physical activity.[41, 42] Cognitive impairment predicts poorer outcomes within cardiac rehabilitation, including lower cardiac rehabilitation attendance.[43] A review reported a moderate to strong support that physical activity benefits cognitive functioning.[44] This study provides initial evidence of a relationship between OHCA survivors' cognitive function and physical activity.

Not all OHCA survivors are eligible for or have access to cardiac or neurological rehabilitation. This may be explained in part by the aetiology of the OHCA or regional or national variation in delivery of healthcare services, or insurance policies.[45] Participation in exercised-based cardiac rehabilitation reduces cardiovascular mortality, recurrent cardiac events and hospitalization,[13,14] and is aimed to increase physical activity. We report that only 20% of the OHCA survivors in this study were provided with exercise-based cardiac rehabilitation. Somewhat surprisingly, the group of OHCA survivors who received exercise-based cardiac rehabilitation were not more physical active at the 6-month follow-ups. This could, however, be due to confounding on the cause of arrest. Nevertheless, we did not collect any details about the content of the exercise-based cardiac rehabilitation as for example frequency, intensity, and duration of the activity or type of activities. Since we lack detailed information on provided rehabilitation, we do not know if and how this has influenced our results. More detailed studies on effects of rehabilitation interventions regarding physical activity and physical exercise training are needed in OHCA survivors, especially for those in risk of a low level of physical activity as those with obesity, mobility problems and cognitive impairment.

A strength of this study was that it was performed in conjunction with a large randomized clinical trial according to specified protocols,[17] where a majority of the survivors answered the two questions on physical activity. In addition, we used the two questions, which have previously been shown to be valid to screen for a low level of physical activity in both OHCA survivors and MI patients.[21,22]

A limitation is that we lack information about how physically active the survivors were before the OHCA. Their physical function and mobility at baseline could likely have effects on the results. Another limitation is that the results may not be generalizable to all OHCA populations, since we only included survivors from OHCA of cardiac or unknown cause who were unconscious at time of randomization. Furthermore, we have no information regarding the physical activity level of the OHCA survivors who did not respond to the physical activity questions at the 6-month follow-ups. The proportion of missing information may likely have overestimated the activity level. Finally, self-reports create varying amounts of assessments error. One example is recall bias whereby individuals have difficulty in recalling past activities.[46] Previous studies confirm that there were acceptable agreements between self-reported and objectively assessed physical activity.[21,22]

International guidelines recommend follow-up after OHCA that includes screening for cognitive impairment, emotional difficulties, and fatigue[45], but not for physical activity levels. Those with a low

level of physical activity may need extra counselling and additional support to increase their physical activity level. The two questions of physical activity could be useful in clinical practice and research settings to screen for a low level of physical activity.

Conclusion

One third of the OHCA survivors reported a low level of physical activity. Obesity, mobility problems, and cognitive impairment were associated with a low level of physical activity. Those OHCA survivors may benefit from targeted interventions to attain the recommended level of physical activity.

Sources of funding

This work is supported by grants from The Skane University Hospital Foundations 2019-o000032, 2019; Academy of Health Care Sciences Skane University Hospital 2021; Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research 2019 and The Swedish Heart and Lung Association 2020 FA 2020:16. The study sponsors were not involved in the study design, in the collection of data, or in the forthcoming analyses and interpretation of data, writings of manuscript of manuscripts or in the decisions to submit manuscripts for publication.

CRediT authorship contribution statement

Katarina Heimburg: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Erik Blennow Nordström:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Josef Dankiewicz:** Writing – review & editing, Conceptualization. **Hans Friberg:** Writing – original draft, Resources, Project administration, Methodology. **Anders M. Grejs:** Writing – review & editing, Resources, Project administration. **Matthias Hänggi:** Writing – review & editing, Resources, Project administration. **Thomas R. Keeble:** Writing – review & editing, Resources, Project administration, Methodology. **Hans Kirkegaard:** Writing – original draft, Resources, Project administration, Methodology. **Niklas Nielsen:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Christian Rylander:** Writing – review & editing, Resources, Project administration, Methodology. **Åsa B. Tornberg:** Writing – review & editing, Conceptualization. **Susann Ullén:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Matthew P. Wise:** Writing – review & editing, Resources, Project administration, Methodology. **Tobias Cronberg:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Gisela Lilja:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tobias Cronberg is a member of the editorial board of Resuscitation. None of the authors report any disclosures relevant to this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2024.110407.

Author details

[a]*Neurology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden*[b]*Department of Cardiology, Skane University Hospital, Lund, Sweden* [c]*Department of Rehabilitation Medicine, Skane University Hospital, Lund, Sweden* [d]*Cardiology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden*[e]*Anesthesiology and Intensive Care, Department of Clinical Sciences Lund, Lund University, Sweden*[f]*Department of Intensive and Perioperative Care, Skane University Hospital, Malmö, Sweden* [g]*Department of Clinical Medicine, Aarhus University, Aarhus, Denmark* [h]*Department of Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark*[i]*Department of Intensive Care Medicine, University of Bern, Bern, Switzerland* [j]*Department of Intensive Care Medicine, Bern University Hospital, Bern, Switzerland*[k]*MYRC, Anglia Ruskin School of Medicine, Chelmsford, Essex, United Kingdom*[l]*Essex Cardiothoracic Centre, MSE NHSFT, Essex, United Kingdom* [m]*Research Center for Emergency Medicine, Aarhus University Hospital, Aarhus, Denmark*[n]*Anesthesiology and Intensive Care, Department of Clinical Sciences Lund, Lund University, Lund, Sweden* [o]*Department of Anesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden* [p]*Anesthesiology and Intensive Care, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden* [q]*Department of Health Sciences, Lund University, Lund, Sweden* [r]*Clinical Studies Sweden – Forum South, Skane University Hospital Lund, Sweden* [s]*Cardiff University School of Medicine, Cardiff, United Kingdom* [t]*Adult Critical Care, University Hospital of Wales, Heath Park, Cardiff, United Kingdom*[u]*Department of Neurology, Skane University Hospital, Lund, Sweden*

REFERENCES

[1] Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451–62.
[2] Bohm M, Lilja G, Finnbogadottir H, et al. Detailed analysis of health-related quality of life after out-of-hospital cardiac arrest. Resuscitation 2019;135:197–204.
[3] Pek PP, Fan KC, Ong MEH, et al. Determinants of health-related quality of life after out-of-hospital cardiac arrest (OHCA): A systematic review. Resuscitation 2023;188:109794.
[4] Zook N, Voss S, Blennow Nordstrom E, et al. Neurocognitive function following out-of-hospital cardiac arrest: A systematic review. Resuscitation 2022;170:238–46.
[5] Boyce LW, Reinders CC, Volker G, et al. Out-of-hospital cardiac arrest survivors with cognitive impairments have lower exercise capacity. Resuscitation 2017;115:90–5.

[6] Heimburg K, Cronberg T, Tornberg AB, et al. Self-reported limitations in physical function are common 6 months after out-of-hospital cardiac arrest. Resusc Plus 2022;11:100275.
[7] Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021.
[8] Chastin SF, Palarea-Albaladejo J, Dontje ML, Skelton DA. Combined effects of time spent in physical activity, sedentary behaviors and sleep on obesity and cardio-metabolic health markers: a novel compositional data analysis approach. PLoS One 2015;10:e0139984.
[9] Nolan JP. Cardiac arrest and cardiopulmonary resuscitation. Semin Neurol 2017;37:5–12.
[10] Larsen JM, Ravkilde J. Acute coronary angiography in patients resuscitated from out-of-hospital cardiac arrest–a systematic review and meta-analysis. Resuscitation 2012;83:1427–33.
[11] Ambrosetti M, Abreu A, Corra U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol 20202047487320913379.
[12] Ek A, Ekblom O, Hambraeus K, Cider A, Kallings LV, Borjesson M. Physical inactivity and smoking after myocardial infarction as predictors for readmission and survival: results from the SWEDEHEART-registry. Clin Res Cardiol 2019;108:324–32.
[13] Dibben G, Faulkner J, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev 2021;11:CD001800.
[14] Dibben GO, Faulkner J, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis. Eur Heart J 2023;44:452–69.
[15] Dankiewicz J, Cronberg T, Lilja G, et al. Targeted hypothermia versus targeted Normothermia after out-of-hospital cardiac arrest (TTM2): A randomized clinical trial-Rationale and design. Am Heart J 2019;217:23–31.
[16] Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med 2021;384:2283–94.
[17] Lilja G, Nielsen N, Ullen S, et al. Protocol for outcome reporting and follow-up in the targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial (TTM2). Resuscitation 2020;150:104–12.
[18] Lilja G, Ullen S, Dankiewicz J, et al. Effects of hypothermia vs normothermia on societal participation and cognitive function at 6 months in survivors after out-of-hospital cardiac arrest: a predefined analysis of the TTM2 randomized clinical trial. JAMA Neurol 2023.
[19] World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–4.
[20] Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc 2007;39:1423–34.
[21] Heimburg K, Lilja G, Nordstrom EB, et al. Agreement between self-reported and objectively assessed physical activity among out-of-hospital cardiac arrest survivors. Clin Physiol Funct Imaging 2023.
[22] Bargholtz M, Brosved M, Heimburg K, et al. Test-retest reliability, agreement and criterion validity of three questionnaires for the assessment of physical activity and sedentary time in patients with myocardial infarction. Int J Environ Res Public Health 2023;20.
[23] WHO. Obesity and overweight. Geneva: World Health Organization; 2022.
[24] Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: An advisory statement from the international liaison committee on resuscitation. Circulation 2018;137:e783–801.
[25] EuroQoL. EQ-5D-5L User Guide; Basic Information on how to use the EQ-5D-5L instrument. 2021.
[26] Feng YS, Kohlmann T, Janssen MF, Buchholz I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. Qual Life Res 2021;30:647–73.
[27] Csuka M, McCarty DJ. Simple method for measurement of lower extremity muscle strength. Am J Med 1985;78:77–81.
[28] Newcomer KL, Krug HE, Mahowald ML. Validity and reliability of the timed-stands test for patients with rheumatoid arthritis and other chronic diseases. J Rheumatol 1993;20:21–7.
[29] Nasreddine ZS, Phillips NA, Bedirian V, et al. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9.
[30] Smith A. Symbol digit modalities test; manual. Los Angeles: Western Psychological Services; 1982.
[31] Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008;3:17.
[32] Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–95.
[33] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[34] Cleven L, Krell-Roesch J, Nigg CR, Woll A. The association between physical activity with incident obesity, coronary heart disease, diabetes and hypertension in adults: a systematic review of longitudinal studies published after 2012. BMC Public Health 2020;20:726.
[35] den Uijl I, Ter Hoeve N, Sunamura M, et al. Physical activity and sedentary behavior in cardiac rehabilitation: does body mass index matter? Phys Ther 2021;101.
[36] Ballin M, Neovius M, Ortega FB, et al. Genetic and environmental factors and cardiovascular disease risk in adolescents. JAMA Netw Open 2023;6:e2343947.
[37] Djarv T, Bremer A, Herlitz J, et al. Health-related quality of life after surviving an out-of-hospital compared to an in-hospital cardiac arrest: A Swedish population-based registry study. Resuscitation 2020;151:77–84.
[38] Sawyer KN, Camp-Rogers TR, Kotini-Shah P, et al. Sudden cardiac arrest survivorship: a scientific statement from the american heart association. Circulation 2020;141:e654–85.
[39] Cronberg T, Greer DM, Lilja G, Moulaert V, Swindell P, Rossetti AO. Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. Lancet Neurol 2020;19:611–22.
[40] Strober LB, Bruce JM, Arnett PA, et al. A new look at an old test: Normative data of the symbol digit modalities test -Oral version. Mult Scler Relat Disord 2020;43:102154.
[41] Mielke MM, Roberts RO, Savica R, et al. Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. J Gerontol A Biol Sci Med Sci 2013;68:929–37.
[42] Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. Arch Neurol 2006;63:1763–9.
[43] Andrell C, Dankiewicz J, Hassager C, et al. Out-of-hospital cardiac arrest at place of residence is associated with worse outcomes in patients admitted to intensive care. A post-hoc analysis of the targeted temperature management trial. Minerva Anestesiol 2019;85:738–45.

[44] Erickson KI, Hillman C, Stillman CM, et al. Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. Med Sci Sports Exerc 2019;51:1242–51.
[45] Nolan JP, Sandroni C, Bottiger BW, et al. European resuscitation council and european society of intensive care medicine guidelines 2021: post-resuscitation care. Resuscitation 2021;161:220–69.
[46] Innerd P. Physical activity assessment: a lifecourse approach. Routledge; 2020.
[47] Heimburg K, Lilja G, Tornberg AB, et al. Physical activity after cardiac arrest; protocol of a sub-study in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2). Resusc Plus 2021;5:100076.