PhD thesis

REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care,
Faculty of Health Sciences, University of Southern Denmark and Odense University Hospital

Physical and psychological problems reported by cardiac arrest survivors and interventions to treat these problems

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September 2022

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Financial disclosures

This PhD project was partially funded by a PhD Faculty scholarship from the University of Southern Denmark and a stipendium from the Region of Southern Denmark (19/15041). REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care, University of Southern Denmark, funded the remaining PhD candidate's salary costs.

Further, REHPA provided operational costs for the DANCAS survey, the clinical intervention part of the SCARF study and Open access charge for Paper 1.

Preface

My interest in cardiac arrest survivorship began in 2015 when I met a survivor referred to our community neurorehabilitation service in the UK. I had been a specialist neurological physiotherapist for many years and at that time cardiac arrest survivors were not considered as 'neurological' patients in our service. Hence, I began exploring the evidence to understand the secondary problems after cardiac arrest and the rehabilitation survivors should receive. Shortly after this, I moved to Denmark and was fortunate to meet Professor Ann-Dorthe Zwisler who also shared my interest in cardiac arrest survivors and invited me to work at REHPA.

From our initial meetings was born the idea of the DANCAS (DANish Cardiac Arrest Survivorship) network. The network brings together researchers, clinicians, survivors, relatives and other stakeholders with an interest in post-cardiac arrest survivorship. The first activities of the network were to establish clinical and research priorities through user-involvement workshops. The stories and experiences generously shared by survivors and relatives in those early meetings were a huge motivation for making this research project happen.

At that time, REHPA primarily delivered rehabilitation programmes to cancer survivors but wished to expand into other patient groups with life threatening diseases. Hence, together with my other supervisors Lars Tang and Jørgen Feldbæk Nielsen, the research clinic team at REHPA, and the Center for Brain Injury in Copenhagen, we designed the first multidisciplinary rehabilitation programme for cardiac arrest survivors at REHPA (the SCARF intervention).

During my PhD, I have been employed by REHPA as a physiotherapist to deliver group-based exercise sessions and help to design the neurological rehabilitation aspects of the patient programmes including fatigue management and problems-solving therapy. I have coordinated the activities of the DANCAS network including the annual conference and undertaken many presentations, workshops and webcasts to raise awareness of the secondary consequences of cardiac arrest and the current research and knowledge gaps in this area. This included the Resuscitation Users Network, the Danish Heart Foundation and Citizen Science network at the University of Southern Denmark. Internationally, I have presented at the European Resuscitation Council conferences in 2020 and 2022, and at the Post-cardiac arrest care Symposium in Lund, Sweden in 2019. For this years' Symposium in Lund, I have been invited to speak on long-term rehabilitation after cardiac arrest. I feel that this a sign of how far the field has come since I started and is a huge credit to the whole DANCAS project group and the hard work of the research clinic at REHPA, that continues to deliver

one of the world's first rehabilitation interventions for cardiac arrest survivors. As part of my PhD, I have also taken part in undergraduate teaching activities as a lecturer and assessor on the module "Patient involvement in research" for the Bachelor of Medicine degree.

During my PhD, I have been lucky enough to be welcomed into the small but very passionate world of international researchers involved in cardiac arrest survivorship. This includes being a member of the newly proposed ILCOR (International Liaison Committee on Resuscitation) working group "Cardiac Arrest Recovery and Survivorship" and part of the expert group supporting the development of a new post-cardiac arrest outcome measure anchored at Warwick University (CASHQoL). I also co-authored a paper with Young Kim based on data from a study to design and test a fatigue intervention for cardiac arrest survivors, which he later kindly helped us adapt for the SCARF feasibility study. The last five months of my PhD have been spent at the School of Health and Wellbeing at University of Glasgow with Professor Rod Taylor. This has been a fantastic opportunity to spend time in a different research environment learning about complex intervention research and clinical trial design.

The PhD programme was completed from 1 October 2019 to 30 September 2022.

Vicky Joshi
Copenhagen, September 2022

Acknowledgements

This PhD would not have been possible without the help and support of many people.

First and most importantly, thank you to all the survivors and relatives who took part in the user-involvement activities, national DANCAS survey, and SCARF feasibility study.

A huge thank you to my three supervisors, Ann-Dorthe Zwisler, Lars Tang and Jørgen Feldbeck Nielsen for sharing their knowledge, expertise, and passion for research for me. Thank you for your patience, encouragement and wise words. The PhD journey can be long and hilly, but I have never felt that I was travelling it alone.

Thank you so much to all my colleagues at REHPA. I have been very fortunate to work with experienced clinicians and researchers who were so generous with their time and knowledge. Thank you to Rikke Tornfeldt Martens for leading the SCARF programme and to Dorthe Søsted Jørgensen, Jan Børge Toft, Susan Johansson, Nina Rottmann, Annette Rasmussen, Sayed Alam and Nikolaj Nielsen for planning and delivering the content. Thank you to Birthe for her support with administration and recruitment and also thank you to Heidi Lenox. Thank you to Morten, Frank and Lone from the Center for Brain Injury for their help with the SCARF programme. Thank you to Christina Strandsberg and Christina Wendelboe for their support with communication and coordinating the DANCAS network meetings. Thank you to everyone in the DANCAS network and the clinicians who helped with publicizing and recruiting for the SCARF study. Thank you to Jan Christensen for his guidance on the systematic review.

Thank you to Tina Broby Mikkelsen who worked tirelessly on the SCARF study data collection and the DANCAS survey and also to Britt Borregaard and Sofie Christiansen. Thank you to Helle Collatz Christensen and the Danish Cardiac Registry who made the DANCAS survey possible. Thank you to Annette Kjær Ersbøll for statistical support and to Line Zinckernagel for her insight into cardiac disease populations and national surveys.

I am very grateful to my fellow PhD students, for so many interesting discussions, new ideas and help with tricky problems, Mette Wagner, Jahan Shabnam, Jens-Jakob Kjer Møller, Henriette Søby Gartner, Anders Wieghorst, Marianne Boll Kristensen, Graziella Zangger, Tobias Anker Stripp, and a special thank you to Henriette Knold Rossau.

Thank you to my international network for their guidance and enthusiasm, Sachin Agarwal, Kirstie Haywood, Tom Keeble, Gisela Lilja and Kelly Sawyer. Thank you very much to Johan Israelsson for

an inspiring visit to his research group in Sweden. A special thank you to Young Kim for his help in adapting his Energy conservation and problem-solving therapy for the SCARF study.

I owe a great deal to Professor Rod Taylor for his advice and support from the start of this project and for welcoming me as a visiting researcher at the University of Glasgow for the last five months of my PhD.

Thank you to the University of Southern Denmark, the Region of Southern Denmark and REHPA for funding this project.

Finally, thank you to my friends and family for their support, to Deborah Fox for always listening when I need advice and to Colin Rich for teaching me about resilience. Thank you to my husband Fran without whose help and love I could not never have undertaken this PhD and to Eve and Callum, who always ask the best, most difficult questions of anyone I know.

Publications and manuscripts in this thesis

Papers 1-4 can be found in Appendices 1-4. An overview of related publications and scientific conference contributions during the PhD programme is provided in Appendix 5.

STUDY 1	
Paper 1	Joshi VL, Tang LH, Borregaard B, Zinckernagel L, Mikkelsen TB, Taylor RS, Christiansen SR, Nielsen JF and Zwisler AD. **Long-term physical and psychological outcomes after out-of-hospital cardiac arrest-protocol for a national cross-sectional survey of survivors and their relatives (the DANCAS survey).** BMJ Open 2021; 11(4): e045668.
Paper 2	Joshi VL, Tang LH, Mikkelsen TB, Nielsen JF, Zinckernagel L, Borregaard B, Agarwal S, Ersbøll AK, Kragholm K, Yonis H, Hassager C, Zwisler AD **Does time heal fatigue, psychological, cognitive and disability problems in people who experience an out-of-hospital cardiac arrest? Results from the DANCAS survey study** *Status: Submitted to Resuscitation September 2022*
STUDY 2	
Paper 3	Joshi, VL, Christensen J, Lejsgaard E, Taylor RS, Zwisler AD and Tang LH. **Effectiveness of rehabilitation interventions on the secondary consequences of surviving a cardiac arrest: a systematic review and meta-analysis** BMJ Open 2021; 11(9): e047251.
STUDY 3	
Paper 4	Joshi VL, Tang LH, Kim YJ, Wagner MK, Nielsen JF, Tjoernlund M, Zwisler AD. **Promising results from a residential rehabilitation intervention focused on fatigue and the secondary psychological and physical consequences of cardiac arrest: The SCARF feasibility study** Resuscitation. 2022; Apr; 173:12-22.

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List of abbreviations

CA	Cardiac arrest
CPR	Cardiopulmonary resuscitation
CR	Cardiac rehabilitation
DANCAS	Danish cardiac arrest survivorship
DHF	Danish Heart Foundation
DRC	Danish Resuscitation Council
ERC	European Resuscitation Council
GRADE	Grades of Recommendation, Assessment, Development and Evaluation system
HADS	Hospital anxiety and depression scale
HRQoL	Health related quality of life
ICD	Implantable cardioverter defibrillator
IHCA	In-hospital cardiac arrest
IPAQ-SF	International Physical Activity Questionnaire Short Form
MD	Mean difference
MET	Metabolic equivalent
MFI-20	Multidimensional fatigue inventory
MFIS	Modified Fatigue Impact Scale
MoCA	Montreal Cognitive Assessment
OHCA	Out-of-hospital cardiac arrest
RCT	Randomised controlled trial
REHPA	Danish national knowledge center for rehabilitation and palliative care
SCARF	Survivors of Cardiac ARest focused on Fatigue
SMD	Standardized mean difference
TSQ	Two simple questions: everyday activities and mental recovery
WHODAS 2.0	World Health Organisation disability assessment schedule 2.0.

Introduction

The number of CA (cardiac arrest) survivors is increasing and multiple studies have described the short-term secondary physical and psychological problems experienced by CA survivors. However, less is known about whether these problems resolve with time. Interventions to meet the needs of CA survivors are recommended in international guidelines but these guidelines are based on a very small number of studies and the evidence for efficacy of interventions for CA survivors has not been previously systematically reviewed. If CA survivors continue to have problems in the long-term this suggests interventions are required to meet their needs. Further, if effective interventions do not already exist then new interventions need to be developed and tested.

Aims and objectives

The overall aim of this thesis was to investigate physical and psychological problems reported by CA survivors and interventions to treat these problems. Specific objectives were as follows:

1. To investigate self-reported fatigue, anxiety, depression, mental recovery and disability in survivors 1-5 years after out-of-hospital cardiac arrest (OHCA). Further, whether the results are different at different time points post-event.
2. To assess and summarize the existing evidence for the effectiveness of rehabilitation interventions for CA survivors.
3. To develop and test the feasibility of a rehabilitation intervention for CA survivors.

Background

Out-of-hospital cardiac arrest

OHCA is a leading cause of death globally.[1] It is defined as "the loss of functional cardiac mechanical activity in association with an absence of systematic circulation".[2] Around 84 per 100,000 people have an OHCA in Europe every year[3] with an estimated 49 patients out of 100,000 treated with cardiopulmonary resuscitation (CPR) started by either the emergency medical services or a bystander.[3]

Up to 80% of OHCAs have a cardiac cause.[2] Most commonly this is ischemic heart disease followed by lethal arrhythmia and cardiomyopathy.[2] Those reported as having an 'unknown cause' (13%) are also likely to be cardiac in origin. Non-cardiac causes include trauma, asphyxia (for example, drowning or hanging) and hypoxia (for example, pneumonia or pulmonary embolism).[2]

Successful survival after CA depends on a series of interdependent, time sensitive therapies termed 'the chain of survival' (Figure 1).[2 4] In recent years, bystander resuscitation has increased[5] through efforts to promote training of the general public in CPR, improved dispatcher telephone guided CPR, increased access to automated external defibrillators in the community[6] and development of phone applications to inform community responders.[2]

Figure 1. European Resuscitation Council Chain of Survival (first published in 2006,[4] reproduced with permission)

On arrival at hospital, acute medical strategies aim to stabilize the heart and protect the brain. If the OHCA is of a likely cardiac cause, treatment will include acute coronary angiography followed by, if necessary, percutaneous coronary intervention.[7] Intensive care management involves optimizing respiratory, haemodynamic, and metabolic variables, together with targeted temperature management and protective ventilation.[8] However, several recent large well-designed trials[9-11] have found that some these interventions are not as successful as initially hypothesized and research in this area continues.

After the acute management stage, survivors of a CA due to cardiac disease may be prescribed medication or be advised to make lifestyle changes, for example, stopping smoking, changing their diet or increasing physical activity.[12] Secondary prevention of CA due to an arrhythmia may include treatment with an implantable cardioverter defibrillator (ICD).[8]

On a population level, mortality rate for CA survivors is higher than for the general population.[13] On an individual level, if the underlying cardiac condition is treated, the risk of another CA may be very low.[14]

In-hospital CA

In-hospital CA (IHCA) sufferers have historically been considered as a separate population to OHCA sufferers.[15] [16] Around 50-60% of IHCAs are due a cardiac cause (a smaller proportion than OHCAs) with 15-40% due to respiratory insufficiency.[17] Research in the field of CA primarily involves OHCA sufferers, however, not all existing literature or research studies differentiate between IHCA and OHCA survivors,[18-20] and the question on whether they should be considered as a separate population or not has yet to be definitively answered. Therefore, we chose, where possible, to include both IHCA and OHCA populations in this research project. Throughout the thesis, we state, when known, where research refers to just OHCA survivors or CA survivors (potentially a mixed IHCA/OHCA survivor population).

Survival post-CA

Due to the advances in pre-and post-resuscitation care described above, survival rates after CA are almost universally improving particularly in Western countries;[21] rates differ between countries but are generally in the range 8-10%.[21] In Denmark, survival to one year is now 13%, a fourfold increase from 2001.[22] IHCA survival in Denmark is higher still, with 20% alive one year post event in 2018.[23]

Improvements in CA survival have led to a growth in research investigating the secondary problems after CA. While most survivors return home and live independently,[24] CA survivors can also suffer a wide range of physical, psychological and cognitive problems affecting their long-term quality of life.[25-29] Hypoxic brain injury is the main cause of cognitive problems.[30] Severe brain injury is uncommon, occurring in less than 10% of cases.[31] However, up to 50% of survivors have been found to have cognitive impairments including deficits in memory, attention and executive function.[31-33] Psychological problems are also reported after CA including fear, anxiety,[34] depression,[35] and post-traumatic stress disorder.[26] These can be due to multiple reasons, such as surviving a near death experience, fear of re-occurrence,[12] implantation of an ICD,[34] or secondary to changes in their physical, social, work or home situation.[36 37]

The most common problem described by CA survivors is fatigue, reported by up to 60% of survivors.[38-40] The exact cause of post-CA fatigue is unknown but is probably related to several interconnected problems such as increased cognitive processing[31 41] depression,[42] sleep disturbances,[41] cardiac disease[43] and reduced exercise levels.[44] Studies show fatigue after CA is association with long-term effects for survivors including decreased physical activity,[45] return to work rates[40] and social participation.[45]

Most studies examining problems post-CA involve survivors less than 12 months after their event. Where longer term studies do exist (see Table 1 in this thesis, and Table 1, Appendix 2b) they are generally small,[27 32 46-51] include a select group of survivors, for example, as part of target temperature management studies[47 49 50] or only use global measures of neurological status and/or health related quality of life (HRQoL).[24 28 51 52] These global measures are important for assessing the effect of pre- or post-resuscitation interventions and delivering information on general CA survivor status. However, to understand the post-CA needs of survivors, domain specific information is needed, for example, the proportion of survivors with fatigue or anxiety. Also, considering the long-life expectancy of survivors[48] it is essential to understand whether the short-term problems described above resolve over time without the need for specific health interventions.

Table 1. Summary of studies investigating long term (≥12 months) self-reported outcomes in cardiac arrest survivors (a more detailed table and the search strategy used for identifying studies can be found in Table 1, Appendix 2b)

					SELF-REPORTED STUDY OUTCOMES						
					Global		**Domain specific**				
Author	**Year**	**N**	**Time (years)**	**Survivor population**	*HRQoL*	*Neurological status*	*Physical*	*Psychological*	*ADL*	*Cognitive*	*Disability*
Nehme[53]	2015	928	1	OHCA	x	x					
Moulaert[46]	2017	141	1	CA	x		x	x	x	x	
Tiainen[54]	2018	206	1	OHCA treated in ICU	x	x			x		
Viktorisson[27]	2019	74	1	OHCA CPC>2	x	x		x			
Kowalik[49]	2014	31	2.3	OHCA, TTM	x				x		x
Caro-codon[47]	2018	79	3.1	OHCA, TTM	x	x				x	
Geri[55]	2017	255	3.2	OHCA treated in ICU	x				x		
Deasy[24]	2013	56	5	OHCA, 18-40 years	x	x					
Saarinen[50]	2012	10	7	OHCA with initial PEA	x	x			x		
Andersson[48]	2015	8	17	OHCA				x	x	x	

ADL: Activities of daily living; CA: Cardiac arrest (in and out of hospital); CPC: Cerebral performance category; HRQoL: Health related quality of life; OHCA: Out-of-hospital Cardiac Arrest; PEA: Pulseless electric activity; TTM: Therapeutic temperature management (survivors recruited as part of a TTM study).

Post-cardiac arrest interventions

The importance of post-CA interventions for CA survivors has been recognized in international guidelines[56 57] including the European Resuscitation Council (ERC) who added a section on rehabilitation after CA to their post-resuscitation guidelines in 2015.[8] The ERC guidelines recommend there should be a systematic organisation of follow up care for CA survivors including provision of information on the consequences of CA and early screening for cognitive and emotional problems.[8] Those found to have these problems should then be referred to tailored specialist rehabilitation.

Definitions of post-cardiac arrest interventions

As with many emerging research fields, post-CA survivorship does not yet have established frameworks or terminology.

Different terms are employed in the literature to describe interventions received by CA survivors in the phase after acute medical management. They include 'follow-up', 'support', 'therapy', 'care path', 'recovery' and 'rehabilitation' and the terms are used interchangeably to refer to components of an intervention or the overarching area. We considered using the term 'rehabilitation' rather than 'post-CA interventions' in this project. However, the definition of 'rehabilitation' differs depending on country, culture or health system, for example, some definitions focus on 'persons with disability'[58] and others extend this to 'persons likely to experience disability'.[59 60] The first, narrower definition, could exclude activities such as early information provision before any 'disability' has been established. As the aim and objectives of this project were exploratory in nature we elected to be as inclusive as possible and chose the broad umbrella term of 'post-CA interventions'. This includes rehabilitation and all the terms stated above but excludes interventions that are primarily pharmacological, surgical or technological.[61]

There are existing frameworks and terminology that could be used to structure outcomes and interventions for CA survivors for example the International Classification of Functioning, Disability and Health.[59] However, choosing one framework on rehabilitation could narrow the field of view which we were not ready to do at this early exploratory stage.

Research involving post-cardiac arrest interventions

The recommendations found in international guidelines on post-CA care are based, in part, on a very small number of research studies. The most prominent is a RCT by Moulaert et al. (2015)[62]. CA survivors received early screening for cognitive and emotional problems and were provided with information and support by specialist nurses leading to improved emotional well-being and HRQoL.[62 63] Two other studies have also shown some possible benefits from a psychosocial intervention using self-management, relaxation and health education.[64 65]

Fatigue is the problem most commonly reported by CA survivors, however, there are no evidence-based treatments recommended for fatigue after brain injury.[66-68] Still, potential benefits have been shown in the treatment of individual modifiable psychological or lifestyle factors through education[69] and behavior change strategies.[41 70] These include cognitive behavioral therapy, mindfulness-based stress reduction, physical activity[71 72] and sleep hygiene.[41 68 70] One small observational study involving a sub-group of CA-survivors with chronic fatigue found a significant decrease in self-reported fatigue impact with a telephone based energy conservation and problem solving therapy intervention (EC+PST).[73]

Cardiac rehabilitation (CR) is recommended for CA survivors as an important part of secondary prevention of further cardiac events.[74] CR is a comprehensive programme traditionally delivered in a group setting with elements of education, psychosocial interventions and physical training.[75] CR has been shown to reduce cardiovascular mortality[76] and improve HRQoL in patients with ischemic heart disease.[77]

However, those with cognitive problems or fatigue, as outlined above, may have challenges participating[12] and CR clinical staff may not have experience in managing the specific problems of CA survivors. A group in the Netherlands have tested a possible solution to this problem by using an integrated cognitive/cardiac care path.[12] Survivors were initially screened for cognitive problems and then referred to one of three pathways: for survivors with no cognitive problems they were offered standard CR, for mild-moderate cognitive impairments survivors were offered combined cognitive/cardiac rehabilitation and finally if survivors had severe cognitive problems they were offered individual cognitive rehabilitation.[12] The combined cognitive/cardiac rehabilitation was provided in smaller groups with a therapist trained in managing post-CA problems.[12] Follow-up focus groups showed survivors were satisfied with the care path but the effect of the intervention has not yet been tested.[12]

There may be other studies investigating interventions for CA survivors then those described above, however, to date, there has never been a systematic review or meta-analysis examining the efficacy of post-CA interventions for survivors.[78]

CA in Denmark

CA survivor population

In the period 2001-2018 the median age of OHCA sufferers in Denmark was 71 years of age (inter-quartile range 59-80) and 64% were men.[22] Three-quarters of OHCAs occurred in private homes.[22] There was a marked increase in bystander resuscitation from 18% in 2001 to 77% in 2018 and use of automated external defibrillators increased from 1 to 9%.[22]

In 2019, IHCA suffers were found to be slightly older than OHCA sufferers, median age 74 years (IQR 65-81) and 61% were men.[23]

Post-acute CA management in Denmark

Denmark is a high income country with a population of 5.8 million people. It is made up of five regions each with a tertiary cardiac center receiving CA survivors. In-patient post-CA medical care is the responsibility of the regions.[79] Primary responsibility for health interventions at home, including rehabilitation, lies with one of the 98 Danish municipalities.[79] Denmark currently has no specialist patient pathway for detecting problems post-CA or specialist interventions to treat any problems discovered.[80] CA survivors may be offered a follow-up appointment with a cardiologist or specialist nurse particularly if they have ongoing treatment for their cardiac condition, for example, implantation of an ICD. Some Danish CA survivors will be offered CR but only if their CA is due to ischemic cardiac disease.[81] A survey of Danish CR provision in 2018[82] found all hospitals and municipalities provide some elements of CR to CA survivors but provision was not as high as for post-acute myocardial infarction patients.

REHPA, the National Knowledge Centre for Rehabilitation and Palliative Care

REHPA, the National Knowledge Centre for Rehabilitation and Palliative Care was established in 2015. It is centrally funded by a grant from the Danish Government and is anchored from an organizational perspective at Odense University Hospital and the Department of Clinical research at the University of Southern Denmark. REHPA produces national research and experience-based knowledge about rehabilitation and palliation care to achieve the best quality of life for people with

life-threatening illnesses and their relatives.[83] Among various research activities, REHPA maps current healthcare service provision, conducts national patient surveys and delivers multidisciplinary residential rehabilitation courses to cancer survivors. These courses are based on current best evidence and clinical experience and provide both an intervention while at the same time having a research purpose.[83] In 2018, REHPA began adapting their cancer rehabilitation course for other groups with life-threatening diseases. The first of these groups was CA survivors and the first preliminary course ran for four days in October 2018.[80] At the end of the four days, CA survivors and their relatives participating in the course, along with members of the DANCAS network, (DANish Cardiac Arrest Survivorship) took part in a user-involvement workshop hosted by REHPA (see User-involvement section in the Methods for further detail).

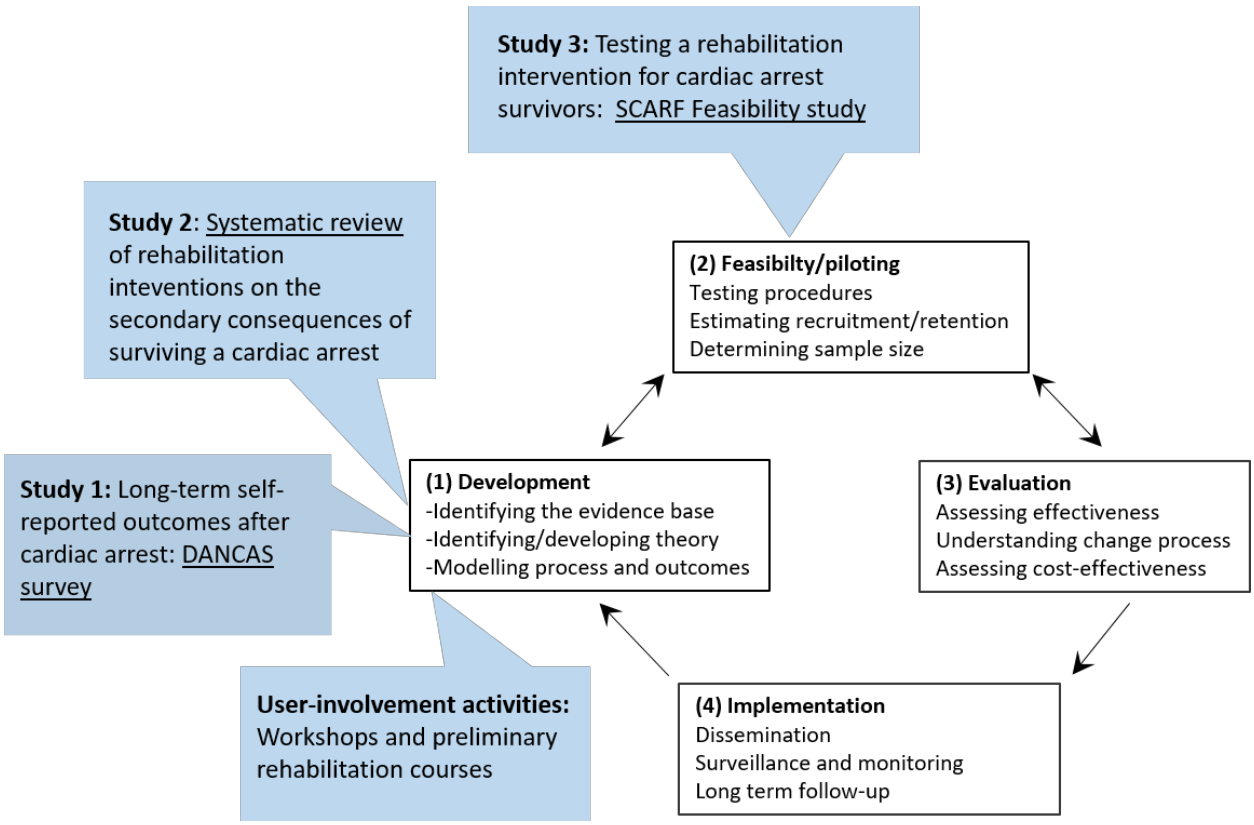
Methods

Framework for developing complex interventions

The Medical Research Council (MRC) state that in clinical research there is a tendency to prioritize the main evaluation of an intervention with inadequate development and piloting work.[84] This can lead to weaker interventions that are less likely to be implemented.[84] They define complex interventions as interventions that have several interacting components, need various behaviors to be delivered (or received), have various outcomes and where tailoring of the intervention is expected.[84] Post-CA interventions for survivors fulfill these criteria.

The MRC recommends four stages are followed when developing and evaluating complex interventions; 1) development stage; 2) feasibility stage; 3) evaluation stage and; 4) implementation stage. Figure 2 illustrates these stages and how the studies and methods chosen for this project meet the recommended activities for stages 1 and 2.

Figure 2. The four key stages of developing complex interventions (Adapted from Craig et al., 2019[84]) and how the studies in this thesis match the first two stages.



Domains and outcome measures used in studies with CA survivors

The term 'domain' in clinical trials usually refers to 'what' is being assessed and 'outcome measure' to how it is being assessed.[85] Health related outcome measures can be clinical (such as cardiac function), performance based (such as step counters), observer-reported (such as cognitive function) or self-reported.[86] Self-reported (or patient-reported) outcome measures are generally in the form of questionnaires that ask patients to assess their own health. They are essential for quantifying health status or assessing the effect of health interventions[87] and may measure global status (for example, HRQoL) or be domain specific (for example, fatigue or anxiety).[52]

Numerous different outcome measures have been used in CA studies.[85 88] However, there are currently no outcome measures specific to the unique situation of CA survivors.[89] Recently, work has been undertaken to identify a core-outcome set for CA studies and recommends the inclusion of measures to assess: survival, neurological function and HRQoL.[89] Yet, these core outcomes do not encompass all the potential secondary problems after CA outlined above and selecting outcome measures that encompass the full range of problems potentially suffered by CA survivors remains challenging. Currently, studies involving CA survivors tend to use self-reported outcome measures that are either generic health outcomes or have been developed for patient populations that have potentially similar characteristics to CA survivors, for example, cardiac disease, brain injury or neurological disorders (see Table 1, Appendix 2b).

In all three studies in this project, we have chosen to assess domains that reflect common problems described by CA survivors in existing literature. Choice of outcome measures to assess these domains or problems in Studies 1 and 3 were a balance between validity and reliability in CA survivors (or similar patient populations), cost, availability in Danish and length/complexity of measure to complete.

Individual study methods

Summary

Table 2 presents a summary of recruitment, population, data collected and data analysis for the three studies. For studies 1 and 3 participants were recruited nationally in Denmark. Study 1 included only OHCA survivors while participants in Study 2 and 3 could be IHCA or OHCA survivors.

Timeframe

Study 1 was conducted from October 2020 to March 2021. For Study 2, initial literature searches were conducted during 2019, with searches updated in April 2021. Study 3, the SCARF feasibility study, was conducted from October 2019 to June 2021.

Table 2. Summary of study methods

	STUDY 1 **DANCAS national survey**	**STUDY 2** **Systematic review**	**STUDY 3** **Feasibility study**
Recruitment	Identified via the Danish Cardiac Arrest Registry	Not applicable	▪ Study was publicised via REHPA, DHF and DRC websites and at the 5 Danish tertiary cardiac centers ▪ Referral from a cardiologist or their general practioner
Population	▪ ≥18 years old ▪ 1-5 years post-OHCA ▪ Resident in Denmark ▪ Alive 30-days after OHCA	▪ ≥ 18 years old ▪ CA survivors Studies were eligible if they were: ▪ RCTs or observational studies ▪ Tested a rehabilitation intervention ▪ Any comparator or none	▪ ≥ 18 years old ▪ ≥ 3 months post their CA ▪ Able to understand Danish ▪ Independent with self-care ▪ Self-identified rehabilitation needs (score of ≥3 on the REHPA scale) confirmed by a doctor
Data collected	▪ MFIS ▪ HADS ▪ TSQ ▪ WHODAS 2.0 Short (12-item) ▪ Sociodemographic data from Danish national registries ▪ Circumstances of CA from the Danish Cardiac Arrest Registry	▪ Study characteristics ▪ Primary outcome: HRQoL ▪ Main secondary outcome: neurological function ▪ Secondary outcomes: Survival, safety (serious and non-serious), psychological well-being, fatigue, exercise capacity, and physical capacity	▪ Progression criteria (Table 4) ▪ Participant/clinician satisfaction ▪ MFIS[90-92] ▪ MFI-20[93 94] ▪ EuroQol 5D 5L[95 96] ▪ HADS[97-99] ▪ WHODAS 2.0 (36-item)[100 101] ▪ IPAQ-SF (MET per week)[102 103] ▪ 30-second chair-stand test[104] ▪ 6-minute walk test[105] ▪ Hand grip strength[106]
Data analysis	Summary of survey outcomes: ▪ Mean scores ▪ Proportion with symptoms using outcome cut-offs (%) ▪ 95% confidence intervals ▪ Venn diagram with three of the dichotomized domain scores Change with time: ▪ Kruskall-Wallis test (mean scores) ▪ Chi square test (proportions) ▪ Regression analysis to adjust for any identified confounders	▪ Risk of bias: RoB 2[107] (RCTs) and National Institute of Health Quality Assessment Tool for Before-After (Pre-Post) studies with No Control Group.[108] ▪ Clinical heterogeneity of studies ▪ Effectiveness of rehabilitation interventions summarized as MD or SMD ▪ Data pooled using random effects meta-analyses ▪ Quality of evidence: GRADE[109]	▪ Progression criteria calculated as proportions (n/%) ▪ Satisfaction: mean scores overall and for sub-sections/statements ▪ Change in outcomes (mean difference) baseline to follow-up time points: -Two-sided paired t-test (effect size Cohen's *d*) -Wilcoxon matched-pairs signed rank test (effect size *r*)

CA: cardiac arrest DANCAS; Danish cardiac arrest survivorship; DHF: Danish Heart Foundation; DRC: Danish Resuscitation Council; GRADE: Grades of Recommendation, Assessment, Development and Evaluation system; HADS: Hospital anxiety and depression scale; HRQoL: Health related quality of life; IPAQ-SF: International Physical Activity Questionnaire Short Form; MD: Mean difference; MET: Metabolic equivalent; MFIS: Modified Fatigue Impact Scale; MFI-20: Multidimensional fatigue inventory; RCT: Randomised controlled trial; REHPA: Danish national knowledge center for rehabilitation and palliative care; SMD: Standardized mean difference; TSQ: Two simple questions: everyday activities and mental recovery; WHODAS- 2.0: World Health Organisation disability assessment schedule 2.0.

Study 1: DANCAS National survey (Papers 1+2)

This study uses a sub-set of data from the cross-sectional DANCAS survey that asked OHCA survivors and their relatives about long-term physical and psychological problems and experiences of post-CA care. Paper 1 (Appendix 1a) describes the rationale and methods for the full DANCAS survey. Paper 2 (Appendix 2a) details Study 1 which is based on a portion of the survivor survey results only and fulfills Objective 1 of this thesis.

Survivors, 1-5 years after OHCA, were identified through the Danish Cardiac Arrest Registry which collects pre-hospital data on all OHCAs in Denmark.[22] The size and time frame of the registry provides information at a national level on OHCA sufferers and can be combined with other Danish national registries of sociodemographic and clinical data to answer key research questions. Similar registries existing in other countries have been used to contact and survey CA survivors[28 110] but the Danish Cardiac Arrest Registry has not yet been used for this purpose.

If survivors met the inclusion criteria (Table 2) they were sent an electronic survey or if they did not have electronic mail they received a postal survey. The information letter sent with the survivor survey asked survivors to identify their closest relative and request them to complete a relative's survey. Table 3 lists the outcome measures (questionnaires) in the DANCAS survey with further detail on the scoring and Danish translations to be found in Table 1, Appendix 1b. Only a sub-set of results from the DANCAS survivor survey were included in Study 1 (blue section Table 3). Results from all other outcomes in the survivor survey and the relative survey are not in this thesis but will be presented in subsequent publications.

Survey data was enriched with sociodemographic and health data from Danish national registries with data on circumstances of OHCA provided by the Danish Cardiac Arrest Registry.

Table. 3. Content of survivor and relative surveys

	SURVIVOR SURVEY	RELATIVE SURVEY*
Domain	**Outcome measure/questionnaire**	
Generic health	EuroQol 5D-5L[96]*	
Psychological well-being	Hospital anxiety and depression scale[98 111]	Hospital anxiety and depression scale World Health Organisation-5[112]
Neurological function	Two simple questions: everyday activity and mental recovery[113 114]	Informant questionnaire on cognitive decline in the elderly, Cardiac arrest version[115]
Fatigue	Modified fatigue impact scale[90 116]	
Disability	12-item World Health Organisation disability assessment schedule 2.0[100 101 117]	
Life satisfaction/ rehabilitation need	REHPA scale*	
Experience of post-out-of-hospital cardiac arrest interventions	6-items asking if rehabilitation needs were met* 7-items asking if information needs were met*	4-items on the level and type of support they received
Caregiver strain		Modified caregiver strain index[118]
Labour market		7-items on labour market status and sick leave
Social isolation		One item on loneliness

The blue section designates the outcome measures included in Study 1 (Paper 2). Results from all other outcomes, including the relative survey, are not in this thesis but will be presented in subsequent publications.

Study 2: Systematic review (Paper 3)

This study was a systematic review and meta-analysis to assess the effectiveness of rehabilitation interventions on the secondary problems post-CA for adult survivors. The protocol (see Appendix 3b) was registered pre-study with PROSPERO (CRD42018110129).[119]

A literature search of electronic databases was performed (MEDLINE, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Psychological Information Database, Excerpta Medica database ,Web of Science and Cochrane Central Register of Controlled trials) up to 18 April 2021. Study inclusion criteria, primary and secondary outcomes and data collected are described in Table 2 and a detailed search matrix can be found in Table 1, Appendix 3b. Two researchers independently extracted data from included studies and made the risk of bias assessment.

Study 3: Feasibility study (Paper 4)

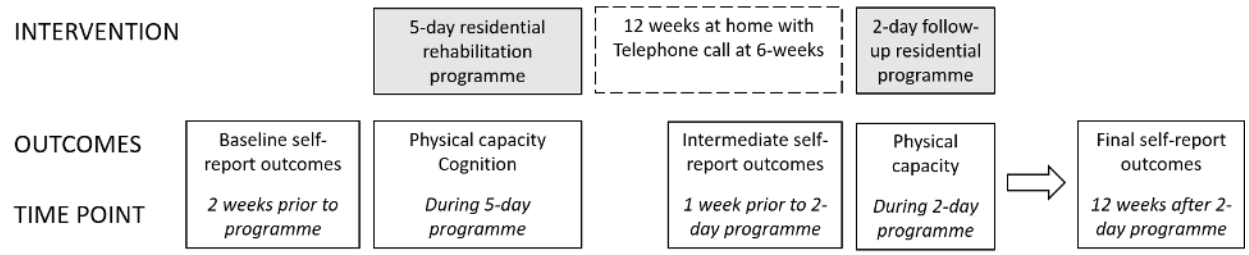
Study 3 was a prospective one-armed observational study investigating the feasibility and potential effect of SCARF (Survivors of Cardiac ARest focused on Fatigue) a multidisciplinary rehabilitation intervention focused on fatigue, and physical and psychological problems post-CA.

Feasibility studies are used to answer key uncertainties about a study design or new intervention including recruitment, variance in outcome measures and acceptability of the study increasing the likely success of any subsequent effect study.[84] Given the breadth and complexity of potential problems for CA survivors, the organisation, content and timing of any intervention requires careful feasibility testing before the effect can be evaluated.[84]

To be eligible for SCARF, participants needed to have self-identified rehabilitation needs (i.e. they themselves felt they needed help with problems after their CA) and this need for rehabilitation was confirmed by their doctor (either their cardiologist or general practitioner) who then sent the referral for the rehabilitation course to REHPA.

SCARF consisted of a five-day initial stay, followed by a two-day follow-up stay 12-weeks later with a telephone call during the 12-weeks at home. Figure 3 illustrates the structure of Study 3. The SCARF programme was delivered four times at REHPA between October 2019 and March 2021.

Figure 3. Structure of Study 3: SCARF feasibility study



The delivery structure of SCARF was adapted from a current REHPA rehabilitation course for cancer survivors.[83 120 121] The intervention included group education and individual activity sessions. Survivors could attend with a relative for support though the course was not designed to meet the specific needs of relatives. Several components were adapted directly from the course for cancer survivors where problems overlap with CA survivors, for example, fatigue,[122] fear,[123] anxiety and depression, others were designed specifically for SCARF.

SCARF was developed based on current research with CA survivors[61 73] and other patient groups with comparable problems and refined by activities with our user-involvement groups (see Table 4, Appendix 4b for full details on intervention development). As part of the development process a Theory of change model was devised illustrating how SCARF may effect changes (Figure 2, Appendix 4a) and a Logic model pinpointed required resources/inputs and activities, expected outputs, outcomes and long term impact[124] (Table 5, Appendix 4b).

Feasibility was established using six progression criteria chosen by the research group as key uncertainties that could impact the success of a future effect study (RCT).[125] The six criteria and rationale for the category levels are presented in Table 4.

Participant satisfaction was collected from paper surveys at the end of the 2-and 5-day programmes. Each session was rated for 'relevance' and 'benefit' on a 5-point Likert scale (0=no relevance to 5=very relevant). Clinician satisfaction was collected by email using five statements covering purpose, content, duration (time), location and adequacy of training, scored on a 5-point Likert scale (1= strongly disagree to 5=strongly agree) (Table 6, Appendix 4b).

We also collected self-reported outcomes (at baseline, 12-weeks and 6 months) and physical outcomes (at baseline and 12-weeks) (listed in Table 2).

Table 4. Progression criteria and rationale for category levels

Progression criteria	Categories			Rationale for category levels
	Green	Amber	Red	
Recruitment and retention:				
1 Initial application recruitment rate (participants per month)	>6.1	4.5-6.1	<4.5	Based on MFIS scores from a previous CA study,[73] a power calculation indicated 124 participants is needed to have sufficient statistical power to identify a treatment effect. Assuming a 3-year recruitment period, 25% loss from application to participation, and a 25% loss to final follow-up, 220 applicants are needed for a future RCT (6.1 per month).
2 Conversion of applicants to study participants (%)	>75	50-75	<50	
3 Participation in mid-intervention telephone call (%)	>80	70-80	<70	Due to uncertainty about whether participants would be engaged in the new SCARF intervention and attend for all the elements.
4 Participation in 2-day follow-up (%)	>80	70-80	<70	
Completion of self-reported outcomes at:				
5 Baseline (%)	>90	80-90	<80	Due to uncertainty if participants would be motivated and able to complete the electronic survey.
6 Final follow-up (26 weeks) (%)	>75	65-75	<65	Testing the assumption of a 25% loss at final follow-up.

MFIS: Modified fatigue impact scale; Categories: Green: progress to effect study; Amber: amend when progressing to effect study; Red: must be resolved before progression to effect study

Data management

Survey and self-reported outcome data were collected online using REDCap (Research Electronic Data Capture). Postal surveys from Study 1 were scanned and entered into an electronic data file.

Data analyses

For all three studies, descriptive statistics were used to summarize sociodemographic and clinical characteristics and quantitative outcomes.

To examine change with time since OHCA, participants in the survey (Study 1) were divided into four groups by months since event (12-24, 25-36, 37-48 and 49-56). Differences between groups were calculated using the Kruskall-Wallis test for the mean scores and Chi square test for the proportion of survivors with symptoms. None of the sociodemographic and clinical variables

available to Study 1 were thought to be potential confounders for the association between survey outcomes and time groups. However, if large differences were identified a further regression analysis would be conducted adjusting for these variables.

In the systematic review (Study 2), where studies were clinically comparable, data were pooled using a random effects meta-analysis with separate analyses conducted for RCTs and observational studies.

In Study 3, mean difference was calculated to assess change in self-reported and physical capacity outcomes. Effect size was then estimated with Cohen's *d* for normally distributed data and for non-normally distributed data, where differences were tested with Wilcoxon matched pairs signed-rank test, effect size (*r*) was estimated by dividing the test statistic z by the square root of the number of observations. STATA V.16 (StataCorp) statistical software was used to conduct all analyses. Values of 0.3, 0.5 and 0.8 were interpreted as small, medium and large effect sizes respectively for Cohen's *d*.[126] while associated values for *r* were 0.15, 0.24 and 0.37.[127]

Ethical considerations

The Region of Southern Denmark confirmed that none of the studies were subject to ethical approval in Denmark (journal numbers 20192000-19; 20192000-66).

Studies were conducted in accordance with the Declaration of Helsinki. Informed written consent was received from all participants in studies 1 and 3. Participants received an information letter providing details of the study, the name of the principal investigator and an explanation that they could withdraw their consent at any time. In Study 1, a telephone number was supplied if participants had any questions about the survey. All personal data was kept confidential and presented in a way that meant no individual participant was identifiable.

Study 1 and 3 were registered with The Danish Data Protection Agency (journal number 19/8559 and 19/15603) and Study 3 in the database Clinical Trials (www.clinicaltrials.gov, NCT04114773) before inclusion of participants.

User-involvement activities

Involving users in research means to undertake research *with* patients and the public so they are not just participants.[128] This is an important part of complex intervention research. In this project, CA survivors were members of the project research group taking part in research meetings throughout the project. In addition, pre-project in November 2018, we ran a workshop with ten CA survivors

with rehabilitation needs and their relatives. In this workshop, participants discussed their post-CA problems, their experiences of post-CA interventions in Denmark and how they felt this could be improved.[80] This material informed the aims and objectives for this project. Data from this first workshop also helped to identify important aims for the systematic review (Study 2) and refine the structure and content of the REHPA rehabilitation course for CA survivors that would be become the SCARF intervention tested in Study 3 (see Figure 1, Appendix 4b for further details).

In April 2019, another workshop was run with a second group of CA survivors to help develop the content of the DANCAS survey (Study 1) by initially testing and discussing the merits of different questionnaires. Subsequently, members of this group then generously provided further feedback on the whole survey during the following year, leading to the questionnaire being shorter, clearer and with additional detail in the information letter.

In addition to the user-involvement activities, we also set up the DANCAS network in 2017 with the purpose of sharing knowledge and collaborating nationally on research with CA survivors and their relatives. The network includes researchers, clinicians and other stakeholders who have an interest in post-CA care along with several CA survivors. The network provided feedback on the design of the research studies in this project and helped with recruitment of participants for Study 3.

Results

The following chapter presents the most important results from the three studies. Table 5 provides a summary of participant characteristics for all three studies, and Table 7 at the end of the chapter presents a comparison of self-reported outcomes in Study 1 and 3.

Table 5. Summary of participant characteristics

	STUDY 1 (n=1258)	**STUDY 2** (n=721)	**STUDY 3** (n=40)
Age (years), mean (range)	62.4 (13.9-92.3)	59.1 (46.8-69.0)	57.4 (33-79, 20.72)
Male (n, %)	1015 (80.7)	535 (74.2)	25 (62.5)
Living alone (n, %)	318 (25.3)	-	13 (32.5)
Children living at home (n, %)	221 (17.6)[a]		13 (32.5)[b]
Time since cardiac arrest (months) median (IQR, range)	34.4 (26.0-46.5)	-	13 (10.5, 3-49)

[a]Children <25 years of age. [b]Children <18 years of age

Study 1

The total survey population that met the eligibility criteria was 2116, of these, 1258 survivors (60%) responded to the survey (Figure 1, Appendix 2a). Survey respondents compared to non-respondents, were significantly older, more were male, they had more years of education, received a higher income; more were Western born, their OHCA was in a public place, more received bystander resuscitation, and they had a shorter length of hospital stay and less co-morbidities (Table 2, Appendix 2b). Further, the response rate for the electronic survey was 66% compared to 25% for the postal survey.

Overall, 1-5 years after OHCA, 29% of survivors reported fatigue, 20% anxiety, 15% depression and 27% disability. When split into four groups based on time since OHCA, no significant differences were found between groups for any outcome (mean scores or proportions) (p=0.28 to 0.88).

No large differences were found between time groups for any survivor characteristics, therefore, no regression analysis was performed.

Study 2

Fourteen studies were included in the systematic review from 6715 studies found in the searches (Figure 1, Appendix 3a). There were three RCTs and eleven observational studies. Risk of bias assessment found two out of the three RCTs and ten out of eleven observational studies had a high risk of bias (Figure 2, Appendix 3a).

Meta-analyses

HRQoL

For the primary outcome HRQoL, pooling the data from two RCTs[62 65] showed low-quality evidence for no effect on physical HRQoL (SMD) 0.19, (95% CI: -0.09 to 0.47) and no effect on mental HRQoL (SMD 0.27 (95% CI: -0.01 to 0.55) (Figure 3, Appendix 3a).

Neurological function

For the main secondary outcome neurological function, very low quality evidence was found for improvement associated with inpatient rehabilitation for CA survivors with acquired brain injury from five observational studies[18 19 129-131] (SMD 0.71, (95%CI: 0.45 to 0.96)) (Figure 5, Appendix 3a).

Exercise capacity and physical capacity

Pooled data from two observational studies[132 133] found an 8-week exercise-based rehabilitation programme significantly increased duration of exercise (mean difference 3.7 minutes, 95% CI: 0.49 to 6.95, p=0.02) but did not increase exercise capacity (SMD 0.41; 95% CI -0.23 – 1.04, p=0.32) (Figure 2 and 3, Appendix 3b).

Studies not included in the meta-analyses

Meta-analyses for all other results were not possible due to high heterogeneity in outcome measures, CA survivor populations, interventions and settings between the studies. Hence, the main results for these are presented narratively, detailed results can be found in Paper 3 (Appendix 3a) and in Table 1 (Appendix 3c).

Psychological well-being

One RCT[62] showed a positive effect on self-reported total anxiety and depression compared with standard care at 1 year follow-up for an education-based intervention.

Safety

Exercise-based rehabilitation interventions were shown to be safe in two small observational studies.[132 133]

Fatigue

One observational study[73] involving an energy conservation and problem solving therapy intervention over the telephone, found between baseline and study end (3-5 weeks) a significant decreased in self-reported fatigue.

Study 3

Progression criteria

Recruitment rate was scored red with a rate of 2.9 survivors per month recruited and therefore half the estimated required rate of 6.1 (Table 6). Completion of self-report outcomes at final follow-up was scored amber being 10% lower than the estimated required proportion of 75%. The other four criteria were green.

Table 6. Progression criteria results

	Progression Criteria	Result	Category Result
Recruitment and retention:			
1	Initial application recruitment rate (participants per month)	2.9	Red
2	Conversion of applicants to study participants	93%	Green
3	Participation in mid-intervention telephone call (%)	100%	Green
4	Participation in 2-day follow-up (%)	87.5%	Green
Completion of self-report outcomes at:			
5	Baseline (%)	97.5%	Green
6	Final follow-up (26 weeks) (%)	65%	Amber

Categories: Green: progress to effect study; Amber: amend when progressing to effect study; Red: must be resolved before progression to effect study

Participant and clinician satisfaction

Satisfaction was scored overall as high for both groups though clinicians scored two of the statements: 'content appropriate for participants' and 'enough time', lower than the other three: 'purpose', 'location' and 'adequacy of training'.

Intervention outcomes

Between baseline and final follow-up small to moderate effect size changes (r = 0.18–0.26) were found for self-reported fatigue, quality of life, anxiety, depression, and disability; and a large effect size change for the WHODAS 2.0 'Life activities domain' (r = 0.46) (Table 3, Appendix 4a).

Between baseline and intermediate follow-up a moderate effect size was found for the 30-second chair-stand test (d = 0.52) and small effect size for the 6-minute walk test (d = 0.46).

Table 7 presents a comparison of self-reported outcomes in Study 1 and baseline scores for self-reported outcomes in Study 3.

Table 7. Comparison of self-reported outcomes in Study 1 and 3

	Outcome measure	Possible range	Study 1	Study 3
Fatigue	MFIS total, mean	0-84	21.1	29.4
	MFIS total ≥ 30, %	-	28.6	43.6
Anxiety	HADS-A, mean	0-14	4.0	7.7
	HADS-A ≥ 8, %	-	19.6	53.9
Depression	HADS-D, mean	0-14	3.6	5.6
	HADS-D ≥ 8, %		14.7	28.2
Neurological	TSQ 1. [a]Everyday activities, %	-	10.8	-
	TSQ 2. [b]Mental recovery %	-	33.6	-
Disability	12-item WHODAS 2.0, mean	0-48	7.7	-
	12-item WHODAS 2.0 Short ≥ 10, %	-	27.3	-
	36-item WHODAS 2.0, mean	0-100	-	22.1

HADS: Hospital Anxiety and Depression Scale; MFIS: Modified Fatigue Impact Scale; TSQ: Two Simple Questions; WHODAS: World Health Organisation Disability Assessment Scale.

[a]Survivor feels they need help with everyday activities since OHCA,

[b]Survivor feels mental recovery is not complete after OHCA.

Discussion

The aim of this thesis was to investigate the physical and psychological problems suffered by CA survivors and interventions to treat these problems. This chapter will discuss the main findings of the three studies in light of this aim and existing evidence. The chapter finishes with a discussion of the methodological considerations for the three studies.

Main findings

Physical and psychological problems after cardiac arrest

The results of Study 1 (the DANCAS survey) are in broad agreement with existing studies on self-reported outcomes after CA (Table 1, Appendix 2b), showing that a sub-group of OHCA survivors have physical or psychological problems after their event that do not necessarily resolve with time. Thus, underpinning existing guidelines that survivors with potential problems should be identified early and provided with post-OHCA interventions tailored to their needs.

However, our studies and others, differ in the proportion of survivors reporting problems. We found 28% of OHCA survivors reported fatigue 1-5 years after OHCA compared to 36% by Wimmer et al.[134] (at mean 5.3 years post OHCA) and 52% by Moulaert et al.[62] (at 12-months). This variation is perhaps not surprising considering the studies have different outcomes measures, data collection methods, time points and survivor populations. Wimmer and Moulaert both employed the Fatigue Severity Scale while we chose the more comprehensive MFIS. Importantly though, mean MFIS scores were still higher than a population in the USA, 21.1 versus 15.3 points.[91] This is despite the better social and employment support offered in Denmark versus the USA reducing societal pressures and therefore leading to lower fatigue.[135]

Study 1 was the first time the 12-item WHODAS 2.0 was used in a survey of CA survivors. The finding that 27% of survivors were categorized as having significant disability is in agreement with one large previous study[53] but in contrast to several other studies which reported minimal or no long-term disability[50 54 136] (Table 1, Appendix 2b). These studies used clinician-reported measures such as the Cerebral Performance Category, Glasgow Outcome Scale Extended (GOSE) or modified Rankin Scale with broad categories that may lack the sensitivity to identify survivors with long-term disability who could benefit from rehabilitation.

We do not have normal population scores for the 12-item WHODAS 2.0 in Denmark, but our mean finding of 7.7 is more than twice that found in an Australian population (3.1).[117] A German study[137] with long-term myocardial infarction survivors (mean 6.5 year post incident), found comparable 12-item WHODAS 2.0 scores (7.9) to our results. This could indicate that long-term disability is due to the cardiac event. However, the reasons for long-term disability in OHCA survivors is likely a combination of physical, cognitive and psychological problems and co-morbidities, hence, needs further examination. The inclusion of a myocardial infarction comparison group in Study 1 would have allowed us to explore the extra elements suffered by OHCA survivors including the hypoxic brain injury but this was not possible in this instance.

Current guidelines[138] advocate OHCA survivors receive screening and referral to specialized rehabilitation at three months post-event. However, given our finding that survivors may continue to have problems for more than a year, repeat follow-up maybe necessary to identify survivors who have developed chronic problems perhaps not detected at the earlier three month time point.

Comparison of survivors and the results in Study 1 and 3

The participants in Study 3 (the SCARF feasibility study) were a specific, highly selected sub-group of survivors with self-identified rehabilitation needs that were confirmed by a doctor. They were younger than the survivors in Study 1 (57 versus 62 years), more were female (38 versus 19%) and more had children living at home (33 versus 18%) (Table 5). They also differed on CA characteristics with participants in Study 3 having less time since their event to being surveyed (median 13 versus 34 months) and 11 out of 39 had an IHCA while all participant in Study 1 were OHCA survivors (Table 5).

Comparing results for the MFIS, we see 43% of participants in Study 3 reported fatigue versus to 29% in Study 1 (Table 7). Though proportions for Study 3 are higher than in Study 1 the difference is not as great as might be expected considering the survey population includes survivors up to five years after event regardless of whether they have rehabilitation needs or not. Further, it is interesting that less than half of survivors in Study 3 would be classed as not being fatigued considering fatigue was the main focus of the SCARF intervention, chosen because it was the most common problem found in previous CA survivor studies. Indeed, the most commonly reported problem at baseline in Study 3 was anxiety, with HADS anxiety score ≥7 reported by 54% of survivors compared to 20 % in Study 1. Depression was also higher at 28% versus 15%. Study 3 had more women and were younger (Table 5) and we know anxiety and depression can be higher in these groups[139] which could

explain the findings but it is unlikely to have influenced the results to this magnitude. We could have conducted a stratified analysis to see if the results differed by age and gender but we chose not to in this instance.

The separate domains of fatigue, anxiety and depression are interconnected and the link between them and the need for rehabilitation post-CA needs further investigation. However, our findings in Study 3 could indicate that anxiety and possibly depression are important outcomes to include in any future post-CA intervention effect study.

Different versions of the WHODAS 2.0 were used for Study 1 and 3 therefore it is not possible to compare these results between study populations.

Interventions to meet the needs of CA survivors

Study 2 was a systematic review of the effectiveness of rehabilitation interventions for CA survivors.[61] Originally this review was titled 'effectiveness of non-pharmacological interventions' to allow the broadest inclusion of interventions but exclude medically-based post-resuscitation interventions. However, we were directed by the peer reviewers of the paper to use "rehabilitation" as this is more widely understood by the mainly clinical readership of the journal. This highlights the tension created by variation in terminology used in post-CA literature. A systematic review requires precisely worded inclusion and exclusion criteria for transparency and repeatability but too narrow a definition may have excluded potentially beneficial interventions.

Overall, Study 2 found quality of the current body of evidence to be low or very low.[61] Only three RCTs were found; the other eleven studies were observational and these can only show the associated change in outcomes between baseline and follow up time-points and cannot inform the cause and effect of an intervention. No significant effect on HRQoL or neurological function was found on analysis of the results from the RCTs though one RCT reported a positive effect on anxiety and depression.[62] Several of the observational studies suggested improvements in some outcomes, but sample sizes were small with inadequate depiction of the interventions severely reducing the quality of the evidence. Hence, the findings from Study 2 should be interpreted with caution and more evidence is needed which will likely change this Study 2's conclusions.

The RCT by Mouleart et al.[62] when included in the meta-analysis with another RCT showed no improvement in HRQoL but taken on its own found a significant effect in three out of eight SF-36 domains (Table 1, Appendix 3c). However, this is not enough to conclude that education-based

rehabilitation interventions are effective for CA survivors. Our findings are in agreement with similar systematic reviews with coronary heart disease patients that found no definitive evidence for improved HRQoL with education-based interventions.[140] The main secondary outcome for Study 2 was neurological function. The only RCT to report this was by Moulaert et al.[62] who found no change in cognitive function, but the authors themselves state that this was not unexpected as cognitive training was not part of their intervention. However, Mouleart et al. did find a decrease in anxiety and depression which is interesting as the intervention did not provide specific psychological treatment. Possibly, the provided education on post-CA problems and insight into their own cognitive or emotional problems may have improved survivors psychological status. Psychological interventions have been found to be beneficial for patients with coronary heart disease[141] but more evidence is needed before this can be stated in regard to CA survivors.

As well as outpatient interventions, Study 2 included five inpatient observational studies (Figure 5, Appendix 3a). Their results indicate inpatient rehabilitation may improve neurological function. However, they were small in size and none had control arms. As this was the first review of its type, we wished to include all potential rehabilitation interventions but it could be argued that the long-term sequelae of CA for survivors requiring inpatient care are closer to traumatic brain injury patients than CA survivors who return straight home and therefore should be considered separately for research and clinical guideline purposes.

Overall, given the low quality of evidence found in the systematic review it is not possible to determine the effectiveness of rehabilitation interventions for CA survivors. Further, high quality studies are needed, hence, the purpose of Study 3 was to design and test a novel rehabilitation intervention for CA survivors.

Study 3 was purposely a feasibility study with no control group and therefore, as stated above, can only describe associations not effect. Still, placing the change in intervention outcomes in the context of existing evidence is important. SCARF showed a decrease in anxiety and depression in agreement with Moulaert et al.'s[62] RCT. However, as the interventions are quite different, further research is required to understand whether the emotional effects of CA can be treated with education alone or a more comprehensive group-based intervention such as SCARF is needed to achieve improvements in the majority of survivors. This is particularly as education only based interventions have not been found to be effective in other cardiac groups.[140]

Regarding fatigue, only a small effect on the MFI-20 was found and no effect on the MFIS (Table 3, Appendix 4a). Our systematic review (Study 2) reported a study testing an Energy conservation and problem solving therapy with CA survivors.[61 73] They found a significant improvement in the MFIS but only included survivors with chronic fatigue so started with a higher baseline level of fatigue, 50.4 versus 29.4 for SCARF. Further, survivors in Study 3 who completed the final follow-up had lower fatigue (24.3) than non-completers (39.6) (Table 11, Appendix 4b), providing another possible explanation for the lack of change in reported fatigue.

The largest effect size from baseline to final follow-up was found for the WHODAS 2.0 'Life activities' domain. As CA has multiple interconnected consequences, SCARF's design included sessions on work, family life, psychological impact, physical activity and active rest. This comprehensive programme may account for the improvement in 'Life activities' suggesting that rather than using a single domain based outcomes such as fatigue or anxiety a global or composite measure might be more appropriate for a future post-CA intervention effect study. However, as this was the first study to use the WHODAS 2.0 this needs further investigation.

Developing and testing new interventions to meet the needs of CA survivors

Study 3 found the SCARF intervention was feasible with a high retention rate (88%), high participant/clinician satisfaction and potential to improve intervention outcomes. However, the study design requires some modifications before SCARF can be tested in a fully powered RCT. Recruitment was half the required rate and only 65% of participants completed the final outcomes.

Recruitment to the SCARF study was via websites and cardiology clinics requiring clinicians, survivors or their relatives to find and respond to the information. Modifications to achieve the required recruitment rate (Table 4) include screening all CA survivors in outpatient follow-up clinics for post-CA problems or using similar residential facilities in other European countries[142 143] to deliver a multi-center trial design. As there are few residential facilities, alternative delivery models should also be considered including center based, telephone-based or digital solutions. However, the residential nature of SCARF allowed national recruitment for this rare patient group with participants only required to travel twice to the center. Telephone interventions have been successfully used with CA survivors in previous studies[20 73] but reduce the ability for in-person interaction. In a recent qualitative study, CA survivors described peer support groups as an important part of helping them cope after their CA with these taking place digitally and in-person.[144] Digital solutions are growing in popularity in part as a response to in-person restrictions during COVID 19[145] but also due to their

potential to be cheaper than in-person methods[146] and their ability to reach isolated patient groups. However, they may not be suitable for older CA survivors[147] or those with fatigue or cognitive problems. Ultimately, the preferences of survivors themselves needs to be sought and the hybrid model currently being tested in CR[148] may provide the best solution for recruiting and retaining survivors in future studies.

Survivor preferences on filling in self-reported outcome measures could also be vital to improving the completion of final study outcomes. Unfortunately, due to resource constraints, we were not able to undertake a qualitative study with SCARF participants. However, we can speculate on the reasons for loss to final outcome follow-up including difficulties with the digital survey, fatigue, cognitive problems, and/or low motivation. Modifications for future studies include providing the survey on paper,[149] using telephone calls to remind and help survivors with the survey,[150] or reducing the number of questions asked.[149 151]

Delivery of comprehensive rehabilitation interventions

Despite Study 3 showing that the SCARF intervention is feasible, it also highlighted several ongoing challenges. Clinician satisfaction with the intervention was broadly high but they felt they needed more time and that the intervention components were not always appropriate for participants. This could be because the SCARF intervention needs further refinement but may point to the understandable lack of experience most clinicians have in treating CA survivors. CA survivors sit between cardiac and neurological areas of health while also requiring an understanding of the traumatic experience they have survived and the impact on their relatives. The SCARF study was delivered at one site but any future studies, particularly if they are to be multi-centered need to consider how they will recruit and train staff to deliver these complex interventions to CA survivors. A further consideration is the cost and logistics of this type of intervention. No economic evaluation was conducted of the SCARF intervention but certain components such as the one-to-one cognitive screening are expensive and the co-ordination of multiple health professionals delivering different components across a 5-day course requires careful logistical planning.

Methodological considerations for the three studies

Study 1 is one of the largest national surveys of long-term OHCA survivors and reached an excellent response rate of nearly 60%. This was achieved through robust survey development that involved feedback from CA on the length, clarity and relevance of the survey. Further, we used electronic and

postal survey formats and sent multiple reminders to participants. Nevertheless, it was interesting to see how low the postal survey response was: 25% versus 67% for electronic. This suggests that even with hybrid survey methods some CA survivors are difficult to reach with surveys alone.

Response from OHCA survivors with fatigue/cognitive problems may also have been lower due to difficulties filling in the survey which would lead to an underestimation of the proportion of survivors with problems. This challenge of attempting to measure problems with survivors who may also be suffering from these problems was also a concern in Study 3 where the survey was only available electronically. To enable participation of survivors with high fatigue/cognitive problems data collection methods other than surveys may be needed, such as, in-person or telephone interviews particularly for those not using electronic communication or living in residential care.

Non-respondents to the survey were generally more socioeconomically disadvantaged with lower incomes and years of education, and potentially more unwell with longer hospital stays and more co-morbidities. The study may therefore have under represented more vulnerable populations[152] and may have underestimated self-reported problems.

Study 2 was the first systematic review and meta-analysis on the effectiveness of rehabilitation interventions for CA survivors. It provided comprehensive literature searches, included both RCTs and observational studies and had broad intervention inclusion criteria. Nonetheless, there are some limitations. HRQoL was chosen as the primary outcome as it is important in the field of rehabilitation research,[153] and is considered a core outcome for cardiac arrest studies[89] but it is a generic measure with the potential for important details to be missed with large sample sizes needed to show an effect; something that is difficult to achieve given the rarity of CA survivors. Rarity was also the reason we chose to include studies with mixed population that included at least 50% CA survivors. This led to the inclusion of two studies that had CA survivors and patients with anoxic brain injury of other causes. The effect of this on the systematic review results was likely small given similar results were seen in the studies with and without mixed populations, but it raises the question of whether results from studies that involve mixed groups that include CA survivors, for example, CR or interventions for ICD recipients should be considered as post-CA interventions and included in future systematic reviews or clinical guidelines.

The wide range of problems suffered by CA survivors made prioritizing outcomes for Study 2 difficult. Chosen outcomes primarily focused on impairment and function with less focus on activity and participation. We could have chosen a more explorative approach, including all the outcomes

presented in studies that met the other review inclusion criteria (population and intervention) but this risks the review becoming very long and complex. Even with the pre-determined outcome approach, we still had eight outcomes within one systematic review.

Future systematic reviews in this area should consider including activity and participation outcomes, in particular, return to work. High rates of return to work have previously been reported in a Danish registry-based study suggesting it was not a significant problem.[154] However, more recent survey[155] and qualitative studies[144 156] suggest the picture is more complicated with many survivors returning part-time, to lower paid work, or not at all.[155]

To reflect activity and participation as an important outcome we included the 36-item version of the WHODAS 2.0 in Study 3 but work status might also have been valuable. However, there is a balance to be found in the length of any research survey. The survey in Study 3 included many more questions than the survey in Study 1 but the longer survey in Study 3 may have contributed to the 35% loss at final follow-up.

Study 3 successfully answered several uncertainties around the design and deliver of a future effect study for CA survivors. The use of progression criteria provided structure and objective markers that helped to identify essential modifications that is not always present in feasibility studies where the potential for data collection can be wide-ranging and unfocused. We could have included a control group with randomization. However, in this first, exploratory study, we were unsure if recruitment would be sufficient. Moreover, a contemporary RCT,[157] undertaken at REHPA, was successful in using a waiting list design for a RCT and this is a possible model for a future SCARF effect study.

Participant and clinician satisfaction results were restricted to the included survey questions and these survey questions were not derived from validated instruments. Qualitative interview studies with both groups would have increased the extent of information and possibly identified new insights and answers related to the intervention and study design not found via the surveys alone.

This project primarily collected data via self-reported outcomes. Self-reported outcomes are used when data would be difficult to collect via observation, for example, psychological symptoms or HRQoL.[158] However, self-reported outcomes are not perfect. Robust development along with evaluation of validity and reliability in the target population is the ideal but is often challenging in rare diseases.[159] The TSQ is one of the only outcome measures in this project that has been tested in a

CA survivor population but it is a relatively crude measure and is open to recall bias[160] as survivors are asked to compare their present situation to before their CA.

Objective physical tests were conducted with participants in the SCARF study (Table 10, Appendix 4b) and these did show an improvement baseline to 12-week follow-up. However, it is not clear if improvements in exercise capacity are a priority outcome for CA survivors[144 161] and it is not known whether better exercise capacity correlates with other important improvements. So it would perhaps not be the primary outcome of choice for a future effect study that tested a comprehensive rehabilitation intervention for CA survivors.

As stated above, investigating the 'brain injury' aspect of CA survival with self-reported outcomes is challenging. We did undertake objective cognitive tests as part of Study 3. These were conducted by a neuropsychologist to assess cognitive status at baseline (described in Tables 2 and 9, Appendix 4b; data are not presented in this thesis). Results from the cognitive tests were used to inform survivors (and their relatives) about individual deficits and provide tailored advice from the neuropsychologist with onward referral to specialist cognitive assessment if necessary. SCARF did not include cognitive rehabilitation so we did not expect cognitive function to improve and therefore did not repeat the cognitive tests. Individual objective cognitive test batteries are resource intensive and it is unlikely that these can be conducted with all CA survivors.[86] We considered using the Montreal Cognitive Assessment (MoCa) in place of the individual objective tests and a recent study has shown it could be a valid, more cost effective alternative for screening for cognitive impairment in CA survivors.[162] However, further research is needed to determine whether using the MoCA would have delivered the level of detail needed to provide Study 3 participants with the tailored feedback they received as part of the SCARF intervention.

In the preliminary stages of the project we had significant user-involvement. We had planned further activities, for example, a workshop to discuss interpreting the results and priorities for further research and implementation in clinical practice. However, this was not possible, partially due to the restrictions on in-person meetings due to COVID 19 but also because we had limited funding for user-involvement activities.

Finally, the three studies in this project would ideally have been ordered differently with the results from the DANCAS survey (Study 1) being used to inform the development of the SCARF intervention (Study 3). This was not possible due to the length of time required to conduct both studies. However, SCARF was designed based on the user-involvement activities, the preliminary

results from Study 2 and best available evidence from similar patient groups.[163] Further, the findings from Study 1 align with the content we chose to include in the SCARF intervention and that there is a clear need for the development and testing of post-CA interventions.

Conclusions

This project adds important knowledge on the proportion of CA survivors that suffer physical and psychological problems in the long term. We found up to a third of survivors 1-5 years after OHCA report fatigue, anxiety, depression, reduced mental function and disability. This proportion is the same irrespective of time since event. Our findings support the current guidelines that advocate provision of information, early screening and tailored post-OHCA interventions to help the sub-set of survivors with needs adapt to their new situation. Further, our findings suggest survivors may need repeat screening for problems at time points later than the current recommendation of three months.

The systematic review identified fourteen studies involving rehabilitation interventions for CA survivors. However, overall quality of evidence was low, therefore, we cannot conclude the effectiveness of rehabilitation interventions for CA survivors on any of the included outcomes. While we await further high-quality research studies, it is important that existing guidelines on screening and referral to rehabilitation should be followed to meet the high burden of self-reported physical and psychological problems experienced by a sub-set of CA survivors.

Given the small number of existing intervention studies for CA survivors, we decided to design and test a new intervention called SCARF. SCARF was found to be feasible with high participant and clinician satisfaction and with the prospect to change important emotional and life activity related self-reported outcomes. However, study recruitment procedures and methods for collecting final outcome measures need to be amended before a full effect study (RCT) can be conducted.

Perspectives on researching and delivering post-CA interventions

Along with the specific study results and conclusions outlined above, this project has also revealed some of the challenges in conducting research and delivering post-CA interventions. These are discussed followed by a summary of current research gaps identified in this thesis. The chapter finishes with three proposals for improving current clinical care for CA survivors.

CA survivors as a patient population

As the majority of CA sufferers do not survive,[21] CA survivors are relatively rare. Furthermore, identifying survivors can be difficult as their patient journeys through hospitals/out-patient clinics depends on the cause of their arrest, post-resuscitation recovery/co-morbidities and structure of their local health services. The first step in any research or clinical intervention is to identify and contact participants. Results from Study 1 suggest that the Danish Cardiac Arrest Registry is a relatively successful method for contacting OHCA survivors. However, the small numbers of participants in the studies described in Study 2 and the low recruitment rate in Study 3 suggests identifying and recruiting sufficient CA survivors is a key consideration for future intervention studies.

Early in this thesis we raised the dilemma of whether to include all CA survivors or only OHCA survivors. Since Study 1 was conducted, a new study has found IHCA and OHCA patients in Denmark are very similar in demographics and co-morbidities suggesting they should not be considered as separate populations and it was reasonable to include both groups in Study 2 and 3.[164] Further, 13 out of 40 participants in Study 3 had an IHCA and were included because they had rehabilitation needs this could indicate that IHCA survivors should be offered the same post-CA interventions as OHCA survivors. Study 1 was conducted with only OHCA survivors because it was not possible to access the IHCA DANARREST register[23] at the time of the study. However, there is a plan to survey this population in the future and this should help determine if IHCA survivors have the same problems and needs for rehabilitation as found in the DANCAS survey.

Post-CA problems and interventions

Over the last three years, recognition of the importance of post-CA interventions has grown further with new publications describing this via varying graphics and terminology. A new link, 'Recovery', has been added to the Six link Chain of survival in the American Heart Association 2020 guidelines,[165] 'Aftercare' has been added to the Chain of survival in the 2021 Scottish strategy (Figure 4),[57] and the 2021 ERC guidelines contain a new figure to illustrate follow-up and rehabilitation after CA (Figure 5).[138]

Figure 4. Augmented chain of survival (reproduced from Scotland's Out-of-Hospital Cardiac Arrest Strategy 2021-2026[57] licensed under the Open Government License v3.0)

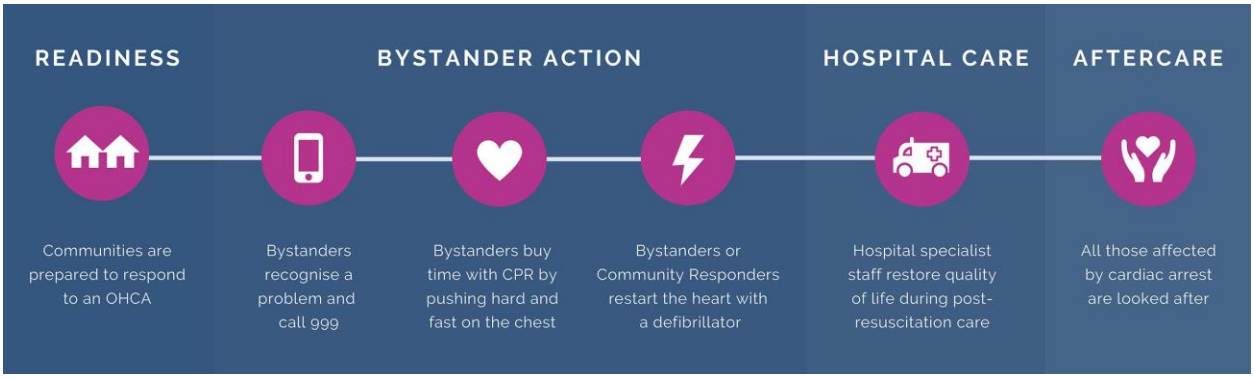
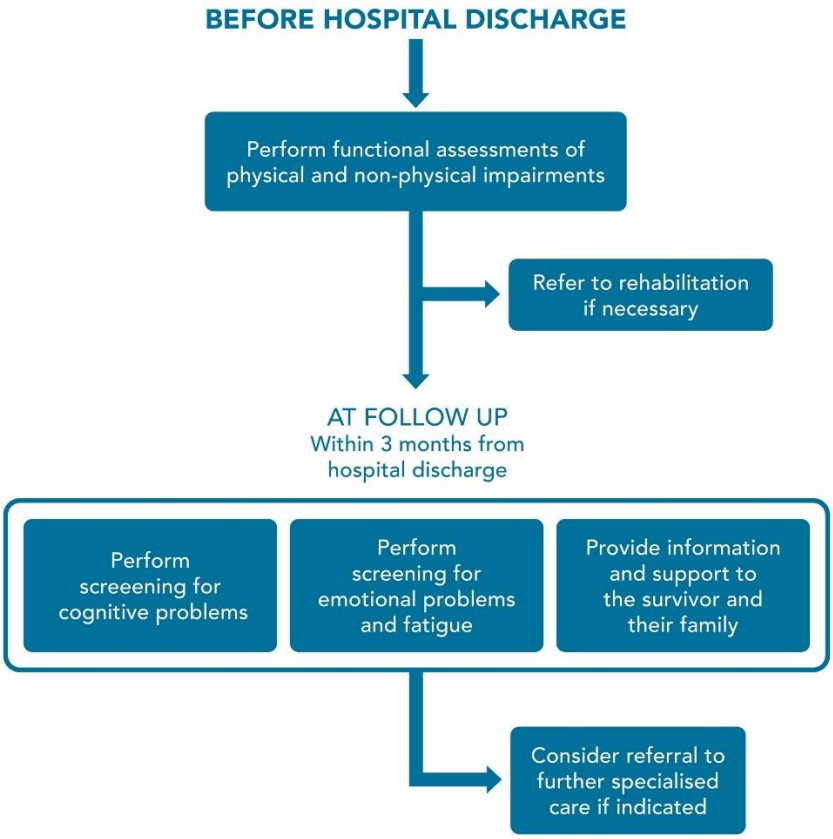


Figure 5. Recommendations for in-hospital functional assessment, follow-up and rehabilitation after CA[138] (reproduced with permission from the 2021 ERC guidelines)



While this new recognition is very positive, the range of possible terms to describe the post-CA phase remains a challenge for researchers. This was evident in Study 2 with our difficulty naming the 'intervention' for the systematic review (rehabilitation versus non-pharmacological interventions) and the long list of search terms needed to cover all possible interventions (Table 1, Appendix 3b). A recent study used the new term 'extra-cardiac symptoms' to describe the problems of CA not related to the cause of the CA.[144] This might help differentiate between post-CA problems that are of cardiac/non-cardiac origin in future studies.

Terminology and heterogeneity

The terminology conundrum may be partly explained by the wide range of neurological, psychological and physical problems potentially suffered by CA survivors as well as the many different cardiac causes of their CA.

This heterogeneity also means compromises much be reached. There is a limit to the number of questions participants in a survey can be asked before the response rate is affected but this means we were unable to ask about all aspects of CA survival, for example, the survey did not contain questions on post-traumatic stress disorder or existential concerns which are also potentially common problems post-CA.[37 166]

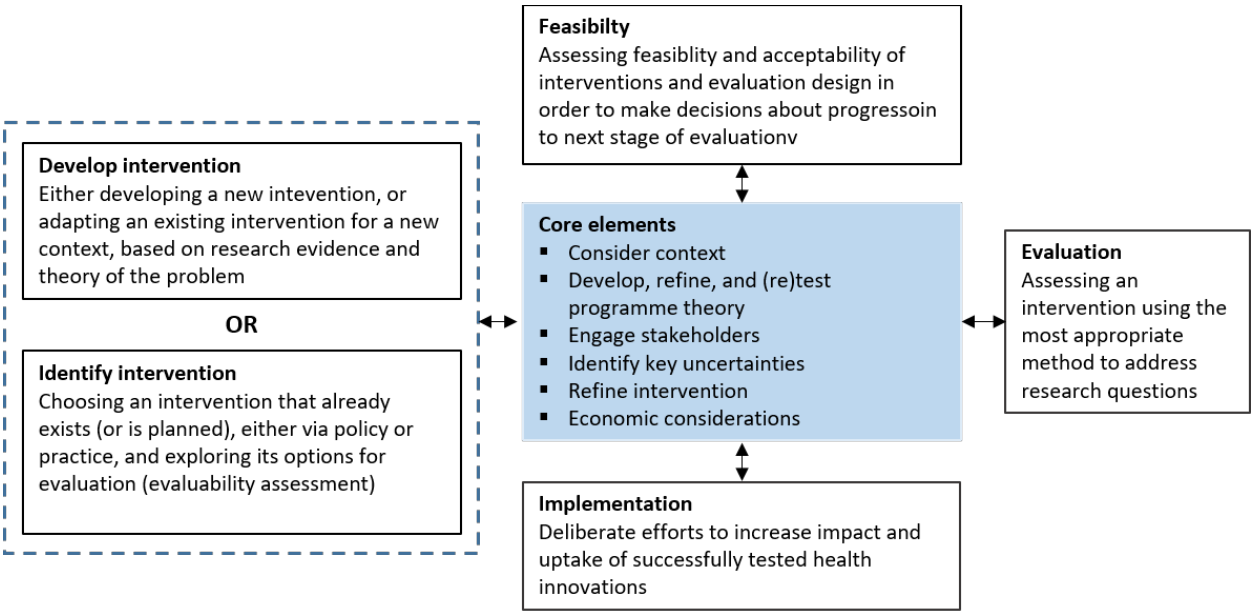
Furthermore, SCARF attempted to provide an intervention that would meet the majority of CA survivors rehabilitation needs, but in meeting so many needs (physical, psychological, cognitive, social) the 'dose' of any one intervention component may be too low to achieve a change. This is particularly the case with components of SCARF that require behavioral changes,[167 168] such as increasing physical activity or employing energy conservation strategies.

Finally, heterogeneity between survivors also makes it difficult to choose a primary outcome for intervention studies. Measuring HRQoL alone may be too crude while domain specific outcomes may show minimal change if participants start the intervention with different rehabilitation needs. Any future CA survivor specific outcome measure will need to balance usability, for instance, time to complete, with covering common post-CA problems. In the meantime, results from this project potentially suggest the WHODAS 2.0 could be sensitive to change and be a surrogate measure for some of the domain specific outcomes, but this needs further investigation.

Developing and evaluating complex interventions: Considerations for CA survivor research

The three studies and user-involvement activities in this project were designed to meet the needs of the four key stages of developing complex interventions (Figure 2).[84] This figure and the guidance on developing and evaluating complex interventions has now been updated (Figure 6).[169] Stage 1 is now titled 'develop or identify interventions' and six core elements have been defined that should be considered at each stage.

Figure 6. Key stages of developing and evaluating complex interventions. Figure updated from the 2019 guidance MRC guidance[84] (see Figure 2), adapted from Skivington et al., 2021.[169]



Context is the first of these core elements and describes how the effects of an intervention may change depending on the setting. The research in this project was based in Denmark, a high income country, with health services funded by the government through taxes. The results in the study may not be generalizable to CA populations in other countries with lower survival from CA, less well-funded health/social support or more rural populations. In these settings, alternative delivery models with lower costs, using digital methods or adapting existing rehabilitation services could be considered.

Programme theory describes the components and mechanism of the intervention.[169] Before conducting Study 3, a Theory of Change model and Logic model were developed to describe how for SCARF would achieve improvements (Figure 2, Appendix 4a and Table 5, Appendix 4b). However, given the new knowledge from this project on the proportion of survivors with problems in the long-term and the heterogeneity of CA survivors these models need further development. In addition, current CA survivor intervention theory does not define how problems are connected through time. The order in which participants receive individual components may affect the success of the intervention, for example, anxiety around CA reoccurrence may need addressing before a survivor can increase their physical activity levels.[34 170]

Pre-project user-involvement activities were used to inform the objectives, outcomes and methods chosen for all three studies. Recent qualitative studies with survivors have explored experiences of rehabilitation after CA[171] and their recommendations for improving post-CA follow-up.[144] The next step would be to develop programme theory with survivors, their relatives and clinicians to identify models and mechanisms of change to inform future post-CA interventions.[172]

Summary of current research gaps

This thesis has identified many gaps in the current research base. These are summarized in Table 8 below.

Table 8. Summary of gaps in CA survivor research evidence

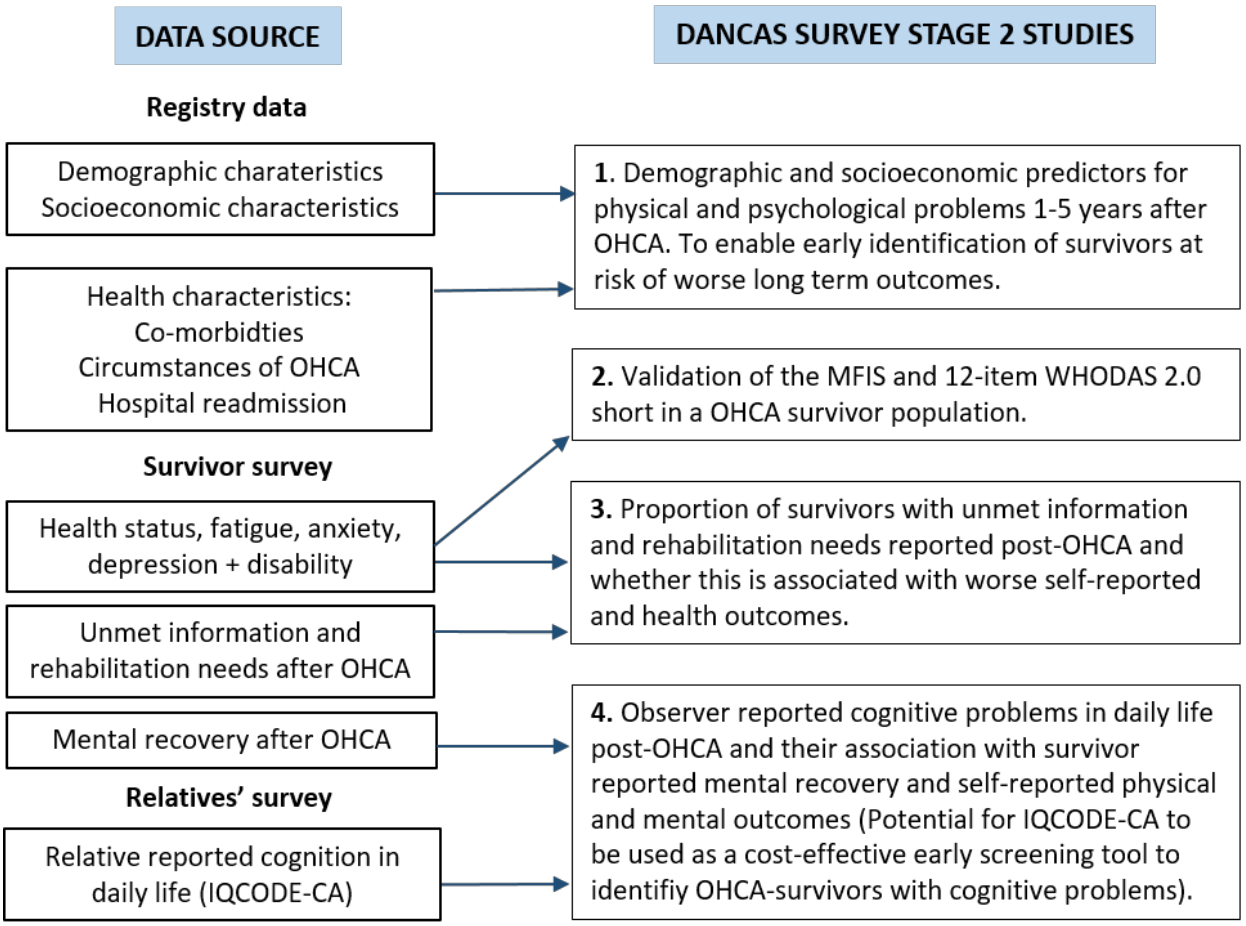
Identification
▪ Methods to identify OHCA and IHCA survivors so they may receive early information, screening and referral to post-CA interventions, and to improve recruitment into research studies.
Standard terminology
▪ Developing standard terminology to describe post-CA survivorship to allow communication of concepts, interventions and outcomes across studies, health fields, and countries; and synthesis of data in meta-analyses.
CA Survivor outcome measures
▪ Develop, validate and test tools for screening CA survivors for common post-CA problems, at a minimum: fatigue, anxiety and cognitive impairment. ▪ Test the implementation of these tools in clinical practice. ▪ Develop and validate a post-CA intervention outcome measures that can be used as a primary outcome in future post-CA intervention effect studies preferably including questions on activity and participation.
Programme theory
▪ Develop programme theory to inform CA interventions that prevent or treat long-term CA problems and the mechanisms that achieve changes within different contexts; using qualitative methods and user-involvement activities with survivors and their relatives.
Post-CA interventions
▪ Investigate association between post-CA needs (information/support/rehabilitation) and long-term outcomes. ▪ Develop or identify existing post-CA interventions and test effect.
Clinicians
▪ Qualitative research to explore facilitators and barriers for screening survivors for post-CA problems, in particular, screening for cognitive impairments by non-clinical psychologists, for example, nurses in hospital ward or out-patient setting. ▪ Strategies for educating all clinicians involved in post-CA survivorship.

Next stage of the DANCAS survey project

Study 3 used a sub-set of the data collected by the DANCAS survey project (described in Paper 1 and summarized in Table 3). Figure 7 sets out how data will be used in stage 2 of the DANCAS survey project to answer some of the research questions set out in Table 8.

We also hope that some of these further research questions will be taken on by the wider CA research community.

Figure 7. DANCAS survey stage 2 research plan



Clinical implications

Given the challenges that have been described and while we await new CA specific outcomes and evidence-based interventions, it is also important to acknowledge that there is a substantial existing knowledge base that can inform how current clinical services could be developed to meet the needs of CA survivors. Three proposals for development of existing services are outlined below.

Pathways for CA survivors

CA survivor pathways through health services have been proposed in existing literature and requested by survivors themselves.[12 80 86 171] This project particularly highlights the importance of identifying CA survivors early in their in-patient admission, providing information on the physical and psychological consequences of CA and how these consequences can be long-standing. Early screening for problems, and referral to rehabilitation may prevent problems becoming chronic. Screening should be followed by referral to appropriate rehabilitation services. Considering that problems can remain in the long term and problems may be very subtle until survivors return home or back to work, survivors should be able to return to the screening and referral process if they or their families identify new problems.

Knowledge sharing with clinicians

For CA pathways to be successful, we need to share research knowledge with clinicians on post-CA problems, how they may persist in the long-term and that survivors may benefit from post-CA interventions. Again, as above, this theme has been raised by survivors in recent qualitative studies.[80 144 171 173] These knowledge sharing activities should include critical care staff, in-patient clinicians, general practioners and those in rehabilitation services that CA survivors may be referred to, for example, CR. CA survivors and their relatives stated in user-involvement activities that improving the knowledge of clinical staff is one their main demands to improve post-CA clinical care.[80]

Integration of CA survivors into existing services.

CA survivors are relatively rare and only a sub-group require post-CA interventions, hence, it might not be feasible for specialist CA rehabilitation services to be implemented in all settings/countries. An alternative solution could be the integration of CA survivors into existing services for similar patient groups, for example, cognitive rehabilitation and fatigue management for people with brain

injuries, or psychological services for anxiety and depression. This process begins with health service managers recognizing CA survivors require these services and then allowing survivors to be referred.

The next step could be the adaptation of existing services to more specifically meet the needs of CA survivors, similar to the combined cognitive/cardiac rehabilitation described by Boyce and Goosens[12] and with healthcare staff educated about the needs of CA survivors.

In addition to these disease or symptom based interventions, survivors should be signposted to peer support and charitable organizations where they have the opportunity to meet other CA survivors.

For those with moderate to severe problems individual specialist psychosocial support or cognitive rehabilitation may be required before CA survivors can participate in group interventions. Lastly, comprehensive interventions such as SCARF should be considered for CA survivors with multiple or long-term rehabilitation needs.

Summary

The number of people surviving a cardiac arrest is increasing due to improvements in pre-and post-resuscitation care. However, survival can come with a range of physical and psychological problems due to hypoxic brain injury, trauma of the event or ongoing cardiac disease. Severe brain injury is rare with most survivors returning home but fatigue, anxiety, depression, cognitive deficits and disability may all be present leading to reduced health related quality of life and participation in society. To date, the majority of studies investigating these problems have focused on the short-term, <12 months after the event while less is known about whether these problems resolve in the long-term.

To treat post-cardiac arrest problems, international guidelines recommend cardiac arrest survivors receive information, support and referral to specialist rehabilitation. However, there is a lack of knowledge on the effectiveness of rehabilitation interventions for cardiac arrest survivors and there are currently no specialist interventions for cardiac arrest survivors in Denmark.

This thesis aimed to meet these gaps in the current evidence base via three studies. Study 1 investigated the physical and psychological problems suffered by cardiac arrest survivors in the long-term via the DANCAS (DANish Cardiac Arrest Survivorship) survey. Study 2 assessed the existing evidence for the effectiveness of rehabilitation interventions for survivors via a systematic review. Study 3 tested the feasibility of a new rehabilitation intervention for cardiac arrest survivors in Denmark: SCARF (Survivors of Cardiac ARest focused on Fatigue.

In the first study, we found up to a third of survivors, 1-5 years after out-of-hospital cardiac arrest, report fatigue, anxiety, depression, reduced mental function and disability and this proportion does not appear to change with time. Hence, our findings support the current guidelines that advocate information provision, screening for problems and referral to tailored interventions to help survivors adapt to their new situation. Future studies, using the DANCAS survey data, will investigate survivors' unmet information and rehabilitation needs, their cognitive status, and the self-reported needs of survivors' relatives.

The systematic review identified fourteen studies involving rehabilitation interventions for CA survivors. However, as overall quality of evidence was low, no conclusions can be drawn on the

effectiveness of these interventions. We recommend existing guidelines on post-cardiac arrest management are followed while we await further high-quality studies.

In the third study, the new rehabilitation intervention, SCARF, was found to be feasible with high participant and clinician satisfaction and with the prospect to change important emotional and life activity related self-reported outcomes. However, study recruitment procedures and methods for collecting final outcome measures need to be amended before a full effect study can be conducted.

There are several challenges in undertaking research with cardiac arrest survivors. These include the wide range of potential problems suffered by survivors, the relative rarity of survivors and the lack of a common language to describe the post-cardiac arrest phase. In the short term, while we await more research evidence, improvements to current healthcare pathways and training for clinical staff on post-cardiac arrest problems may well reduce the long term impact of CA for this growing patient population.

Resumé (Danish summary)

Antallet af mennesker som overlever et hjertestop er stigende på grund af forbedringer i behandlingen før og efter vellykket genoplivning. Overlevelse kan dog for den enkelte medføre en bred vifte af selvrapporterede fysiske og psykologiske problemer grundet hjernepåvirkning forårsaget af iltmangel, traumet fra hjertestoppet eller vedblivende hjertesygdom. Svær hjerneskade er sjælden og de fleste hjertestopoverlevere udskrives til hjemmet, men fatigue, angst, depression, kognitive deficits og funktionsnedsættelse kan alle være til stede, og føre til nedsat livskvalitet og begrænsninger i samfundsdeltagelse. Indtil nu har hovedparten af de studier, som har beskæftiget sig med disse selvrapporterede problemer haft fokus på udfordringer på kort sigt (<12 måneder efter hjertestoppet). Man ved derfor meget lidt om forekomsten af disse selvrapporterede problemer på lang sigt.

Internationale retningslinjer anbefaler i dag, at hjertestopoverlevere modtager information og støtte, samt at udvalgte patienter henvises til specialiseret rehabilitering med fokus på at forbedre patientens problemstillinger. Der mangler imidlertid viden om effekten af rehabilitering til hjertestopoverlevere, ligesom der aktuelt ikke findes specialiserede indsatser til hjertestopoverlevere i Danmark.

Nærværende afhandling havde til formål at udfylde hullerne i den eksisterende viden igennem tre studier. Studie 1 undersøger de selvrapporterede fysiske og psykologiske problemer blandt hjertestopoverlevere på lang sigt baseret på resultater fra DANCAS (DANish Cardiac Arrest Survivorship) survey. Studie 2 gennemgår den eksisterende evidens om effekt af rehabiliteringsindsatser til hjertestopoverlevere igennem et systematisk review. Studie 3 tester gennemførligheden af en ny rehabiliteringsindsats til hjertestopoverlevere i Danmark: SCARF (Survivors of Cardiac ARest focused on Fatigue).

I det første studie fandt vi, at op til en tredjedel af hjertestopoverlevere 1-5 år efter et hjertestop uden for hospitalet rapporterer fatigue, angst, depression, reduceret mental funktion og funktionsnedsættelse, og at denne andel ikke ser ud til at forandres over tid. Vores fund støtter således de nuværende retningslinjer, som advokerer for overlevering af information, screening for problemer og henvisning til individuelt tilpassede indsatser, som hjælper hjertestopoverlevere til at tilpasse sig deres nye situation. Fremtidige studier vil undersøge hjertestopoverleveres uopfyldte

informations- og selvrapporterede rehabiliteringsbehov, deres kognitive status, samt deres pårørendes selvrapporterede behov, ved brug af data fra DANCAS undersøgelsen.

Det systematiske review identificerede 14 studier omhandlende rehabiliteringsindsatser til hjertestopoverlevere. Det var ikke muligt at drage en samlet konklusion om effekten, da studiernes overordnet set havde lav kvalitet. Vi anbefaler, at de eksisterende retningslinjer vedrørende opfølgning efter hjertestop følges, imens man venter på studier af høj kvalitet.

I det tredje studie, som undersøgte rehabiliteringsindsatsen SCARF, fandt vi, at indsatsen var gennemførbar (feasible) med høj deltagelse og tilfredshed blandt sundhedsprofessionelle, og med potentiale til at forbedre vigtige følelsesmæssige og livsaktivitetsrelaterede selvrapporterede effektmål. Dog bør rekrutteringsprocedurer og metode til indsamling af de endelige udfaldsmål ændres, førend et storstilet lodtrækningsforsøg kan gennemføres.

Der er adskillige udfordringer ved at udføre forskning med hjertestopoverlevere. Disse omfatter den brede vifte af potentielle selvrapporterede problemer, som hjertestopoverlevere lever med, den lave forekomst af hjertestopoverlevere, samt manglen på et fælles sprog til at beskrive indsatser rettet mod hjertestopoverlevere. På kort sigt, kan patientforløb på tværs af hjerte- og hjerneskadeområdet optimeres, og uddannelse af det kliniske personale i problemer som følge af hjertestop bidrage til at reducere virkningerne på lang sigt for denne voksende patientgruppe, mens vi venter på mere forskningsbaseret viden.

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Appendix 1a:

Paper 1

BMJ Open

Long-term physical and psychological outcomes after out-of-hospital cardiac arrest—protocol for a national cross-sectional survey of survivors and their relatives (the DANCAS survey)

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To cite: Joshi VL, Tang LH, Borregaard B, *et al*. Long-term physical and psychological outcomes after out-of-hospital cardiac arrest—protocol for a national cross-sectional survey of survivors and their relatives (the DANCAS survey). *BMJ Open* 2021;**11**:e045668. doi:10.1136/bmjopen-2020-045668

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-045668).

Received 07 October 2020
Revised 23 February 2021
Accepted 22 March 2021

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ABSTRACT

Introduction The number of out-of-hospital cardiac arrest (OHCA) survivors is increasing. However, there remains limited knowledge on the long-term physical and psychological problems suffered by survivors and their relatives. The aims of the DANCAS (DANish cardiac arrest survivorship) survey are to describe the prevalence of physical and psychological problems, identify predictors associated with suffering them and to determine unmet rehabilitation needs in order to make recommendations on the timing and content of future rehabilitation interventions.

Methods and analysis The DANCAS survey has a cross-sectional design involving a survey of OHCA survivors and their relatives. OHCA survivors will be identified through the Danish Cardiac Arrest Registry as having suffered an OHCA between 1 January 2016 and 31 December 2019. Each survivor will be asked to identify their closest relative to complete the relatives' survey. Contents of survivor survey: EQ-5D-5Level, Hospital Anxiety and Depression Scale, Two Simple Questions, Modified Fatigue Impact Scale, 12-item WHO Disability Assessment Scale 2.0, plus questions on unmet rehabilitation and information needs. Contents of relatives' survey: World Health Organisation-Five Well-Being Index, Hospital Anxiety and Depression Scale, Informant Questionnaire on Cognitive Decline in the Elderly—Cardiac Arrest and the Modified Caregiver Strain Index. Self-report outcome data collected through the surveys will be enriched by data from Danish national registries including demographic characteristics, circumstances of cardiac arrest and comorbidities. The survey will be completed either electronically or by post December 2020–February 2021.

Ethics and dissemination The study will be conducted in accordance with the Declaration of Helsinki. Surveys and registry-based research studies do not normally require ethical approval in Denmark. This has been confirmed for this study by the Region of Southern Denmark ethics committee (20192000-19). Results of the study will be disseminated via several peer-reviewed publications and will be presented at national and international conferences.

Strengths and limitations of this study

- Denmark has markedly improved the survival rate among out-of-hospital cardiac arrest (OHCA) survivors during the last 5 years.
- This will be one of the largest nationwide surveys of OHCA survivors to date with data collected from survivors and relatives up to 5 years after cardiac arrest.
- Data will be derived from both self-report measures and national registries providing a comprehensive picture of the problems experienced by OHCA survivors and the risk factors associated with suffering them.
- The response rate from OHCA survivors suffering from cognitive problems and/or fatigue may be lower due to difficulties completing the survey compared with those without these problems to counter this, the survey will be available both electronically and on paper.
- The change in physical and psychological problems over time may be influenced by a treatment cohort effect and other unknown time-dependent modifying factors.

INTRODUCTION

The number of people surviving an out-of-hospital cardiac arrest (OHCA) is increasing every year due to advances in prehospital and acute medical care.[1 2] In Denmark, 30-day survival after OHCA improved from 4% to 16% between 2001 and 2018.[3] This amounts to at least 800 new survivors every year.[3] Still, after the acute phase ends, the physical and psychological impacts of OHCA may continue.[4] Most OHCA survivors will have a new or ongoing cardiac condition.[5 6] They may suffer from psychological trauma due to surviving a near-death experience.[7] Furthermore, reduced oxygen levels to the

brain during an OHCA can cause cognitive deficits in up to 50% of survivors.[8–10] Due to this combination of factors, OHCA survivors have been shown to suffer anxiety and depression, fatigue and reduced participation in society.[7 8 11 12] General health, return-to-work rates and quality of life do, however, appear to improve over time,[13–15] but data regarding health measures, return-to-work patterns and unmet rehabilitation needs beyond 12 months after OHCA are limited.[7 11 14 16 17]

As most OHCA occur in private homes, relatives are likely to witness the event.[18] Combined with the changes in both physical and psychological status of many OHCA survivors, quality of life and psychological health among relatives might be influenced. It has previously been described how relatives of OHCA survivors suffer from emotional problems including anxiety, depression and post-traumatic stress, due to becoming a carer for their loved one or fear of the cardiac arrest reoccurring.[19 20] Likewise, lack of control, feelings of insecurity, mood and sleep disturbances have been reported among relatives.[21 22] Yet, very few research studies have investigated the consequences of OHCA for relatives in the longer term,[23 24] or how these are associated with witnessing the event or with the physical and psychological problems suffered by the OCHA survivor.

Rehabilitation for OHCA survivors is recommended in international guidelines,[4 25] but the specific content and timing of these interventions has not been established. Survivors will commonly be offered cardiac rehabilitation related to their new or ongoing cardiac condition,[4 26] but it has been suggested that the psychological and neurological rehabilitation needs of OHCA are not met to the same degree.[27] Hence, the aims of this national cross-sectional study are to (1) describe the long-term prevalence of physical and psychological problems for OHCA survivors and their relatives and how these change over time, (2) identify predictors associated with increased risk of suffering these problems and (3) determine unmet rehabilitation needs in order to make recommendations on the timing and content of future rehabilitation interventions. Specific objectives for each aim will be defined in future publications.

METHODS AND ANALYSIS

Study design

The DANCAS (DANish Cardiac Arrest Survivorship) survey aims will be achieved through a cross-sectional study design.

Setting and participants

In Denmark, prehospital care, hospital care and all cardiac treatment and rehabilitation are funded via the tax system and are free of charge for patients. The Danish Out-of-Hospital Cardiac Arrest (DHRCA) registry will be used to identify the Danish personal identification numbers of people who have suffered an OHCA from 1 January 2016 to 31 December 2019 and were alive 30-days after their cardiac arrest (figure 1). All patients in Denmark who have suffered an OHCA, where bystanders or paramedics attempted treatment are included in the DHRCA registry. Data are recorded electronically immediately after the OHCA in the prehospital patient record by paramedics from one of the five regional ambulance services and collected in the DHRCA. The DHRCA collects data on OHCA in Denmark for the purposes of quality improvement. The prehospital managers of the five Danish regions are responsible for collecting the data, have ownership of their own data and give approval for data access on behalf of OHCA survivors. Access to DHRCA data is granted via approval of a research protocol by the DHRCA steering group.

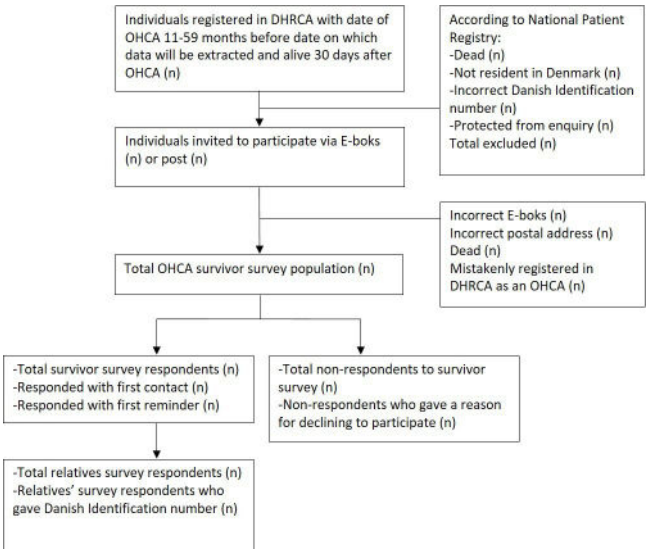

Figure 1 Flow chart of survey population. DHRCA, Danish Out-of-Hospital Cardiac Arrest; OHCA, out-of-hospital cardiac arrest.

The DHRCA started collecting data in 2001, however, before 2016, this was recorded by hand on paper and hence significant gaps in the data exist.[3] In addition, prehospital and medical management of OHCA has changed significantly in the period 2001–2015.[28] Consequently, the proposed timeframe of 1–5 years since OHCA provides both a long-term perspective and ensures data are relevant to the contemporary OHCA survivor population.

The extracted Danish personal identification numbers will be matched by the Danish National Health Digital Board to names, and addresses in the Danish National Patient Registry retrieve.

The information letter received by the OHCA survivors will ask them to identify their closest relative and ask them to complete the relatives' survey. This method of recruitment has been tested in the development of the survey and is feasible. Closest relative is defined as a partner, spouse, sibling or parent that is closest to the survivor.

Eligibility criteria

OHCA survivor participants included in the survey will have a Danish personal identification number, be alive

at least 30-days postcardiac arrest, resident in Denmark, over 18 years of age and able to read and write in Danish and not protected from receiving inquiries during scientific surveys.

Relative participants must have a relative who has survived an OHCA, be over 18 years of age and be able to read and write in Danish. The relatives do not need to have a Danish personal identification number, as they will be invited to complete their survey via the information letter to the OHCA survivor participants. However, they will be asked to provide their Danish personal identification number to allow linkage with Danish national registries.

Data collection

All OHCA survivor participants who meet the eligibility criteria will receive an invitation to participate in the survey via REDCap (Research Electronic Data Capture) software to their e-Boks (government electronic mail account) or via post if they do not have an e-Boks address. Based on the age profile of OHCA survivors over the last 5 years and the age-profile of Danes with e-Boks addresses, it is estimated that 20% of participants will require a postal survey.

The link to complete the separate relatives' survey will be included in the invitation sent to the OHCA survivors' e-Boks. Invitations sent via post to the OHCA survivor will include a paper copy of both surveys, two stamped addressed envelopes (for survivor and relative) and information on how to complete the surveys online rather than by post if they wish. A participant information sheet will be included with all invitations to participate in the survey. This will detail the purpose of the research study, how data will be used and will explain that by returning the survey, they are consenting to take part. The information sheet will include a telephone number to call a member of the research team if participants have any questions. Participants who receive the e-Boks survey will have the option to request a paper survey by post. A reminder invitation will be sent via e-Boks/post after 2 weeks.

Additional data from the DHRCA will provide information on circumstances of the OHCA (box 1).

Development of the DANCAS surveys

The outcome domains for the two DANCAS surveys were developed from a public and patient involvement (PPI) event held in Denmark[29] (see PPI section below) and from the outcomes identified as important by participants in the core outcome set for cardiac arrest initiative.[30] For each of these outcome domains, appropriate existing self-report outcome measures were chosen. For domains where no outcome measure existed, questions from other patient groups were adapted for OHCA survivors or new questions were developed.

The PPI group participants tested individual outcome measures for acceptability and face validity where there was more than one outcome measure available (eg, in the domain 'function and disability'). The PPI group also gave feedback on draft versions of the whole DANCAS surveys, and the participant information sheet. Feedback was received from eight survivors, three relatives and three clinicians with experience of treating OHCA survivors and relatives. Based on this feedback, we reduced the number of questions, removed any outcome measures where the item content overlapped and improved the clarity of the participation information sheet.

Box 1 Data on circumstances of OHCA from DHRCA

Location of cardiac arrest (private/public).
First observed heart rhythm (shockable/not shockable).
Cardiopulmonary resuscitation was given before the arrival of the ambulance (yes/no).
Defibrillated before the arrival of the ambulance (yes/no).
Time to return of spontaneous circulation (minutes: seconds).

DHRCA, Danish Out-of-Hospital Cardiac Arrest; OHCA, out-of-hospital cardiac arrest.

Self-report outcome measures in the DANCAS surveys

Full details on the self-report outcome measures, scoring and Danish translations can be found in the online supplemental data.

The following self-report outcome measures will be completed by OHCA survivors:

EQ-5D-5Level: This is a six-item standardised instrument for measuring current health status.[31] The questionnaire covers five-dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is divided into five-levels: no problems, slight, moderate, severe or extreme problems. The sixth-item, a Visual Analogue Scale, 0–100, allows the respondent to provide a self-rating of his or her health. A higher score signifies a better health status.

Hospital Anxiety and Depression Scale (HADS): The HADS consists of a seven-item subscale measuring symptoms of anxiety (HADS-A) and a seven-item subscale measuring symptoms of depression (HADS-D).[32] Each item has a four-choice response, with scores ranging from 0 (no symptoms) to 3 (maximum number of symptoms). The total scores on each subscale range from 0 to 21. A score of less than 8 indicates no psychological distress, 8–10 mild psychological distress and over 10 definite psychological distress. It has recently been shown to be a valid measure of anxiety and depression in a Danish cardiac disease population.[33]

Two Simple Questions: Consists of three items. Developed to assess the survivor's own perception of mental recovery and dependency in daily activities after cardiac arrest.[34 35]

Modified Fatigue Impact Scale (MFIS): The MFIS assesses impact of fatigue on performance of functional activities and consists of 21-items in three subscales (physical, cognitive and psychosocial). Total scores range from 0 to 84 with a score of 30 or more signifying a fatigued individual. It has been validated in people with multiple sclerosis and traumatic brain injury.[36 37]

12-item WHO Disability Assessment Schedule 2.0 (12-item WHO DAS 2.0): This assesses disability and functioning in the prior month on six adult life tasks. There are 12-items scored from 0=no difficulty to 4=extreme difficulty, total score 0–48 with higher scores indicating greater difficulty. Used extensively to research rehabilitation and disability in a wide range of disease populations[38] and validated in patients with chronic diseases[39] including traumatic brain injury.[40]

REHPA (The Danish Knowledge Centre for Rehabilitation and Palliative Care)) scale: A linear analogue self-assessment scale, where participants indicate how close they are to living the life they desire after their OHCA, indicating rehabilitation need. The scale is rated between 0 (goal reached) and 9 (infinitely far from).

Questions on unmet rehabilitation needs have been adapted from the Danish Cancer Society questionnaire 'The experiences of cancer patients during diagnosis and treatment'.[41 42] Participants are asked if they received the help they needed after their cardiac arrest in six areas: emotional reactions, cognitive problems, physical activity, return-to-work, peer-support and family (online supplemental data). Questions on unmet information needs after cardiac arrest were adapted from a questionnaire evaluating experiences of healthcare quality in Denmark among patients with heart disease.[43] Participants are asked if they felt informed after their cardiac arrest on seven subjects: treatment of heart condition, medication for heart condition, emotional reaction, cognitive problems, physical activity, return-to-work and impact on family.

In addition to the HADS, the relatives' survey includes the following:

WHO Five Well-Being Index: The WHO-5 is a self-report measure of current mental well-being[44] that has been shown to be a valid tool across a wide range of study fields.[45] The tool consists of five statements with six responses on a scale from 'At no time' to 'All of the time' scoring 0–5. Scores are totalled and multiplied by 4 with 0 representing the worst imaginable well-being and 100 representing the best imaginable well-being. The WHO-5 was chosen as a generic global measure of health for the survey, as opposed to using the EQ-5D-5L as in the OHCA survivor survey. This choice was based on feedback from a PPI workshop asking relatives to fill-in and provide feedback on individual questionnaires. The relatives felt the EQ-5D-5L was about medical problems and was for their relative (who had suffered the OHCA) to complete and they were unsure how to answer the questions. Conversely, they understood why the WHO-5 might be relevant to their life situation and felt able to complete it.

The Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest: This is a modified version of the observer-reported questionnaire designed to measure global cognitive decline in the dementia population.[46] Informants, defined as relatives or close friends are requested to compare current cognitive function of the survivor with precardiac arrest cognitive function. The tool contains 26-items scored on a five-point scale with higher scores indicating greater impairment. It has been shown to identify cardiac arrest survivors with possible cognitive problems.[46]

Modified Caregiver Strain Index (MCSI): This is a self-reported questionnaire that screens for caregiver strain in caregivers.[47] The tool has 13 questions scoring 2 points for 'yes', 1 point for 'sometimes' and 0 for 'no'. Scores range from 0 to 26 with higher scores indicating a higher level of caregiver strain. The MCSI has been found to be easily administered and a reliable test of strain in an informal caregiver population.[47]

Furthermore, one question derived from the Danish National Health Survey 2017[48] on loneliness and four questions on support received in the postcardiac arrest period (created for this survey, (online supplemental data). Seven questions on educational level, labour market status and sick leave are also asked in the relatives section as their survey answers can only be connected to Danish labour market registry data if relatives choose to provide their Danish personal identification number in their survey response. One question will ask if they witnessed the OHCA.

Data enrichment from registries

Following data collection via the two surveys, data enrichment will occur via Danish national registries for both survivors and relatives. The Danish Civil Registration System will provide gender, age and marital status. The Danish Education Register:[49] education level and the Danish Register on personal income:[50] income.

The Danish National Patient Register[51] provides data on 19 selected somatic comorbidities scored on a 3-point scale. This data will be used to calculate the Charlson Comorbidity Index,[52] based on the 10 years previous to the date of the surveys. The Charlson Comorbidity Index has three categories: 0, 1–2 and ≥3. This registry will also provide data on hospital admissions and healthcare use for the potential substudy on societal costs after surviving OHCA.

Current and pre-OHCA employment status for the working-age population will be obtained from the Danish Register for Evaluation of Marginalisation (DREAM).[53] Participants who are not on any social benefits or participants who are on State Education Fund grants, maternity leave pay, or leave-of-absence schemes will be classified as being part of the workforce.[54] Accordingly, patients receiving unemployment benefits, being on paid sick leave, on early retirement payment or disability pension will be defined as being on social benefits. Pre-OHCA employment status will be assessed in a 5-week span before cardiac arrest to classify patients as either working or receiving social benefits.

Information from the DHRCA and other national registries will be collected for all eligible study participants both responders and non-responders to the survey (figure 1).

Data handling and record-keeping

The study has been registered on the Region of Southern Denmark's record of data processing activities (19/8559). A license agreement has been made with Odense Patient Data Explorative Network (OP-843) to establish the REDCap system, secure data storage, data analysis and data linkage with national registries. REDCap will be used to import Danish personal identification numbers for survey distribution via E-boks. Postal surveys received will be scanned, and the data imported into REDCap and destroyed.

Sample size considerations

Each year approximately 800 people are alive 30-days after surviving an OHCA in Denmark.[3] Hence, we estimate the survey could be sent to approximately n=3200 survivors. Based on similar studies in heart diseases,[17 55] we are assuming a 20% (n=640) loss due to a person having moved out of Denmark, being protected from inquiries or having died,[16] and a response rate of 60%. Hence, the estimated total study population would be approximately n=1540 OHCA survivors. The response rate to the relatives' survey is likely to be less as not all survivors will have a relative able to complete the survey. Hence, estimated 50% (770) of relatives will respond and 50% (380) of responders will provide Danish personal identification numbers.

Planned analysis

Continuous data will be checked for normality and described as mean and SD or median with 25th and 75th quartiles (IQR), as appropriate. Categorical variables will be described as numbers and percentages (n (%)). To investigate changes in physical and psychological outcomes over time, participants will be stratified into four groups: those suffering an OHCA in 2016, 2017, 2018 and 2019 (figure 2). Differences in the prevalence of self-report problems between the groups will be determined by χ^2 test or Fisher's Exact test as appropriate and time-trend analyses will be performed. The OHCA survivor and relatives' surveys will be linked via a unique identifying number to discover if associations exist between each groups' self-report outcomes.

Predictors of physical and psychological problems will be identified from self-report outcomes, demographic characteristics, circumstances of OHCA and unmet rehabilitation/information needs using univariate binary logistic regression. All univariate predictors with p<0.10 will be entered into a multivariate binary logistic regression, with description of ORs or β and 95% CIs. In all regression analyses, both crude and adjusted models will be presented. Level of statistical significance will be set at p<0.05.

A potential substudy is planned to calculate the total societal costs (healthcare costs and absenteeism from work) of surviving OHCA using the EQ-5D-5L data and registry data (National Prescription Registry,[56] and DREAM database).[53]

Ethics and dissemination

The study will be conducted in accordance with the Declaration of Helsinki. Surveys and registry-based research studies do not normally require ethical approval in Denmark. This has been confirmed for this study by the Region of Southern Denmark ethics committee (20192000-19). Participants will be informed about the study via the participant information sheet. Consent to participate will be implied through the return of the completed survey.

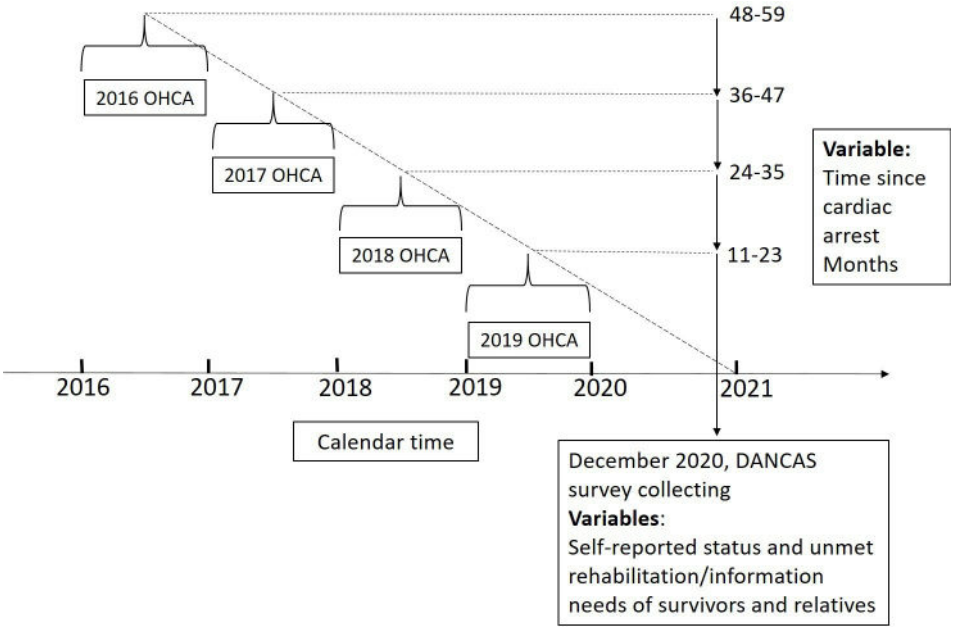

Figure 2 Design of DANCAS survey and grouping according to time since OHCA. DANCAS, DANish cardiac arrest survivorship; OHCA, out-of-hospital cardiac arrest

Results of the study will be disseminated via several peer-reviewed publications and will be presented at national and international conferences. The results of the proposed study will be reported with reference to the international statement in the Strengthening the Reporting of Observational studies in Epidemiology checklist for cross-sectional studies.[57] Health professionals will be informed of the study results through professional literature via new national clinical guidelines on rehabilitation after OHCA. Finally, the survey is part of a larger project on rehabilitation after surviving a cardiac arrest and all results, including the survey results, will be presented at a project-closing event to which all participants, stakeholders and interested parties will be invited.

Patient and public involvement

The themes for the survey were developed from a PPI event involving OHCA survivors, relatives and clinicians.[29] A further group of survivors and relatives have helped to develop the survey by testing individual questionnaires and by providing feedback on the whole survey. At the end of the study, the research advisory group and PPI group will discuss and comment on the findings and contribute to how the results will be disseminated and implemented in the next stage of the research.

DISCUSSION

Recovery after OHCA can be complicated by a new or ongoing cardiac condition, mental trauma from surviving a near-death experience or possible anoxic brain injury. Small scale, short-term studies suggest that these complications can lead to an increased physical and psychological burden for both survivors and their relatives. However, little is known about the long-term prevalence of physical and psychological problems or who is at most risk of developing them. Rehabilitation has been recommended to meet the secondary physical and psychological consequences of OHCA, but more knowledge is needed including establishing the perceived unmet rehabilitation and information needs from OHCA survivors and their relatives themselves.

The results from this study will be used to identify the most prevalent problems suffered by OHCA survivors and their families and those at most risk of suffering them. This will allow researchers and managers within the Danish healthcare system to design assessment tools to ensure that problems are detected early after OHCA, and survivors and relatives are offered rehabilitation plans tailored to their needs. Furthermore, currently, there are few high quality studies investigating the effectiveness of rehabilitation interventions for OHCA survivors. Results from the DANCAS survey will provide researchers with specific information to design the content and timing of new rehabilitation interventions for OHCA survivors and their relatives.

Although this study will be one of the largest surveys involving OHCA survivors and one of the first to survey both survivors and relatives, with the ability to link between the two, there are several potential limitations. The majority of the self-report questionnaires have undergone some validation testing. However, not all these tools have been validated in Danish or in the OHCA survivor population and some questions have been written specifically for this survey (see online supplemental data).

The survey uses questionnaires based on self-report. However, approximately 50% of OHCA survivors suffer from cognitive deficits and/or fatigue, leading to difficulties completing the survey and hence potentially a lower response rate from survivors with these problems. To counter this, the survey will be available both electronically and on paper, survivors will be allowed to have help to complete the survey and asked to state if they had help. In addition, the relatives' section of the survey will include an observer-reported cognitive questionnaire and relatives will be asked to complete this even if the survivor questionnaire is not completed. However, it remains possible that those with cognitive deficits and/or fatigue will be underrepresented in the survey response group and this has to be accepted as a limitation of the self-report method chosen to gain data from as many OHCA survivors as possible. Surveys will only be received by OHCA survivors able to access e-Boks or living at home, so we are very unlikely to receive responses from any survivor living in long-term residential care. Furthermore, the DHRCA only records OHCA and therefore people who have suffered an in-hospital cardiac arrest will not be included in this study. To ensure that the characteristics of the survey population are clear, baseline characteristics of non-responders will also be presented.

One aim of the survey is to describe how the prevalence of physical and psychological problems suffered by survivors and their relatives changes over time since OHCA. Ideally, this would be investigated using a prospective longitudinal study with data from the same population at multiple follow-up points. The disadvantage of this design is the results would not be available for 5 years, and participants are asked to complete multiple surveys. The design of our survey groups participants dependent on time since OHCA to describe changes over time. However, as these are not the same participants in each time interval group, there is a risk of an unknown time-dependent confounding factor effecting one of the groups more than another. Furthermore, the cross-sectional design, by definition, does not allow the formation of solid conclusions but the generation of hypotheses based on associations between variables.

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Acknowledgements We would like to thank the member of the DANCAS network for their support in designing this study: (Anette Marianne Fedder, Annette Rasmussen, Bo Gregers Winkel, Camilla Kofoed Dichman, Charlotte Brun Thorup, Christian Hassager, Christina Marr Andersen, Elin Petersen, Frank Humle, Hanne Balle, Hanne Kruuse Rasmusen, Hanne Skovgaard Petersen, Helle Westberg, Irene Hallas, Jens-Jakob Eifer Møller, Jette Nørr Møllebjerg, Jørgen Feldbeck Nielsen, Klaus Nikolaisen, Lars Thrysøe, Lene Mønsted Nielsen, Lisa Gregersen Østergaard, Lone Andersen, Malene Hollingdal, Malene Missel, Mette Stougaard, Mette Wagner, Mogens Hørder, Morten Jensen, Nina Rottmann, Rikke Mols, Rikke Tornfeldt Martens, Steen Pehrson, Susanne Budin Holst, Susanne S Pedersen, Tina L.B. Andersen, Dorte Qvistgaard). LHT is currently funded by a grant from the Danish Regions and The Danish Health Confederation through the Development and Research Fund for financial support (project nr. 2703) and a grant from Region Zealand, Denmark (Exercise First).

Contributors VLJ, LHT and ADZ conceived the study; VLJ and LHT designed the study with ADZ, BB, LZ, TMB, RST, SRC and JFN. VLJ led the writing of the manuscript, which was revised by all authors. The final manuscript was approved by all authors.

Funding This project will be supported by infrastructure provided by REHPA, Danish Knowledge Centre for Rehabilitation and Palliative Care, Odense University Hospital which receives funding from the Danish Government. This project is part of a PhD partially funded by a PhD Faculty scholarship (no grant number) from the University of Southern Denmark and a stipendium from the Region of Southern Denmark (19/15041).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1b:

Supplementary material for paper 1

Appendix 1b Supplementary material

Table 1. Detailed content of DANCAS surveys

Outcome domain	Outcome measure	Items, scoring	Danish translation	Notes
Survivors				
Generic health	EQ-5D-5L	Five item health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Divided into five levels: 1='No problems' to 5= 'Extreme problems', scores ≥ 2 signifies a problem. Sixth item: Self-rating of health. Visual Analogue Scale, 0-100. Higher scores signify better health status.[1]	Received from the EuroQoL group	
Anxiety and depression	HADS	Seven-item symptoms of anxiety subscale (HADS-A) Seven-item subscale symptoms of depression (HADS-D). Four responses: 0='No symptoms' to 3= 'maximum number of symptoms'. Total subscale scores range: 0-21. <8 = no psychological distress, 8-10 = mild psychological distress, >10 definite psychological distress. It has recently been shown to be a valid measure of anxiety and depression in a Danish cardiac disease population.[2]	Received from DenHeart study group[3]	Valid measure of anxiety and depression in Danish cardiac disease population[3]
Mental recovery/dependency	TSQ	Yes to Q1a + Yes to Q1b signify new problems with dependency after cardiac arrest. No to Q2 indicates problems with mental recovery after cardiac arrest.[4 5]	Received from TTM2 study group[4]	
Fatigue impact on functional activities	MFIS	21 items in three sub-scales (physical, cognitive and psychosocial). Total scores range: 0-84. Total subscale scores: physical= 0 -36; cognitive=0=40; psychosocial= 0-8. ≥30 signify a fatigued individual (Antmann, 2012, Schiehser, 2015)	Translation received from e Provide, Mapi Research Trust.	Validated in people with multiple sclerosis.[6] and mild to moderate brain injury.[7]
Function and disability	12-item WHO DAS 2.0	12-item assessing 6 domains of functioning: 1) Understanding and communication; 2) Self-care; 3) Mobility; 4) Interpersonal	Available from:https://www.etf.dk/ergoterapi-	Used extensively to research neurological conditions including traumatic brain injury and spinal

		relationships; 5) Work and household roles; and 6) Community and civic roles. Scored from 0= 'no difficulty' to 4= 'extreme difficulty or cannot do'. Total scores range: 0-48. Higher score indicating greater difficulty with activity and participation.	og-politik/hverdagsrehabilitering	cord injury,[8] and rehabilitation and disability in a wide range of disease populations.[9] Validated in patients with chronic diseases.[10]
Life satisfaction/rehabilitation need	REHPA scale	A linear analogue scale, participants indicate how close they are to living the life they desire after their OHCA. Scale ranges from 0= 'goal reached' to 9= 'infinitely far from'. Score of ≤3 will be considered as signifying having rehabilitation needs.	By DANCAS study authors	
Unmet rehabilitation needs		6-items asking if rehabilitation needs were met in different domains, for example, emotional reactions. Scored on a 4-point Likert type scale from 'Yes to a high level' to 'No, not at all'.[12]	Adapted by DANCAS authors	Questions adapted from existing survey 'The Experience of Cancer Patients during Diagnosis and Treatment'.[12 13]
Unmet information needs	Adapted from Zinckernagel et al., 2017	7-items asking if information needs were met in different domains, for example, 'treatment of your heart condition' Scored on a 4-point Likert type scale from 'Yes to a high level' to 'No, not at all'.[14]	Adapted by DANCAS authors for OHCA survivors from a Danish survey of patients with heart disease.[14]	
Relatives				
Anxiety and depression	HADS	As above		
Mental well-being	WHO-5	Five items with 6 responses from 0='At no time' to 5='all of the time'. Scores are totaled and multiplied by 4 to give range 0-100. Score <50 signifies poor emotional well-being.[15]	Developed in Denmark.[16]	Valid in multiple patient populations.[17]
Cognitive problems in daily life	IQCODE-CA	26-items scored on a five-point scale, 1= 'much improved' to 5= 'much worse'. Scores are totaled, divided by the number of questions to give a total, range 1-5. Score ≥3.04 signifies cognitive decline after cardiac arrest.[18]	Received from TTM2 study group	Relatives or close friends compare current cognitive function with pre-cardiac arrest cognitive function. Has been shown to accurately identify cardiac arrest survivors with potential cognitive problems.[18]
Caregiver strain	MCSI	13-items, scored: 2= 'Yes, On a Regular Basis', 1= 'Yes, sometimes', 0= 'No'. Range: 0-26, higher scores signify a higher level of carer strain.[19]	Translated by DANCAS study authors[a]	Found to have high internal validity with a population of family caregivers.[19]

Witness to OHCA	Questions designed for this survey	1-item on whether they witnessed the OHCA	Created by DANCAS study authors	
Labour market	Questions designed for this survey	7-items on educational level completed, current labour market status, status in pre-OHCA period and details of any sick leave in post-OHCA period.	Created by DANCAS study authors	These questions are asked of the relatives as their survey answers cannot be connected to Danish labour market registry data unless they provide their Danish personal identification number.
Social isolation	Question from Danish national health survey	One item: Does it ever happen that you are alone even though you would prefer to be with other people?" Answers: "yes, often" and "yes, sometimes" signify loneliness. Other possible responses are "yes, but rarely" and "no.	Available at: http://www.danskernessundhed.dk/Spoergeskema	
Support received post-OHCA	Questions designed for this survey	4-items on: whether relatives feel they have someone to talk to if they need support (yes, always/yes, mostly/yes, sometimes/no never or almost never); who have they received support from (multiple options); if they received the support they needed (Yes, No), and who would they have like to have received support from in the post-OHCA period (free text box).	Created by DANCAS study authors	

Abbreviations: HADS= Hospital Anxiety and Depression Scale; TSQ=Two Simple Questions; TTM2= Targeted Hypothermia versus Targeted Normothermia after OHCA trial 2; MFIS: Modified Fatigue Impact Scale, WHO DAS 2.0= World Health Organisation disability assessment schedule 2.0 Short; REHPA= Danish Knowledge Center for Rehabilitation and Palliative Care; OHCA=Out-of-hospital Cardiac Arrest; DANCAS=DANish Cardiac Arrest Survivorship; WHO-5= World Health Organisation-Five Well-Being index; IQCODE-CA: Informant Questionnaire on Cognitive Decline in the Elderly, Cardiac Arrest Version; MCSI= Modified Carer Strain Index.
[a]Translation, cultural adaption and psychometric testing performed by study authors, results are planned to be available in a future publication.

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Appendix 2a:

Paper 2

Title page

Does time heal fatigue, psychological, cognitive and disability problems in people who experience an out-of-hospital cardiac arrest? Results from the DANCAS survey study

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ABSTRACT

Aims: Out-of-hospital cardiac arrest (OHCA) survivors may suffer short-term fatigue, psychological, cognitive and disability problems, but we lack information on the proportion of survivors with these problems in the long-term. Hence, we investigated these problems in survivors 1-5 years post-OHCA and whether the results are different at different time points post-OHCA.

Methods: All adults who survived an OHCA in Denmark from 2016 to 2019 were identified using the Danish Cardiac Arrest Registry and invited to participate in a survey between October 2020 and March 2021. The survey included the Modified Fatigue Impact Scale, Hospital Anxiety and Depression Scale, "Two simple questions" (everyday activities and mental recovery), and the 12-item World Health Organisation Disability Assessment Schedule 2.0. To investigate results at different time points, survivors were divided into four time-groups (12-24, 25-36, 37-48 and 49-56 months post-OHCA). Differences between time-groups were determined using the Kruskall-Wallis test for the mean scores and Chi-square test for the proportion of survivors with symptoms.

Results: Total eligible survey population was 2116, of which 1258 survivors (60%) responded. Overall, 29% of survivors reported fatigue, 20% anxiety, 15% depression, and 27% disability. When survivors were sub-divided by time since OHCA, no significant difference was found on either means scores or proportion between time groups (p=0.28 to 0.88).

Conclusion: Up to a third of survivors report fatigue, anxiety, depression, reduced mental function and disability 1-5 years after OHCA. This proportion is the same regardless of how much time has passed supporting early screening and tailored post-OHCA interventions to help survivors adapt to their new situation.

INTRODUCTION

Successful advances in community resuscitation and acute hospital interventions have led to increasing numbers of out-of-hospital cardiac arrest (OHCA) survivors.[1] Yet, survival after OHCA can be complicated by fatigue, psychological, cognitive and disability problems.[2-5] The growing focus on life after OHCA has led to 'Recovery' being included in the Chain of survival[6] and international post-resuscitation guidelines now recommend referral to fatigue-, psychosocial- and cognitive-based support/rehabilitation.[2] However, these recommendations are primarily based on studies with survivors <12 months after OHCA[2 6] and it is possible, that with time, the problems described in these short-term studies may improve without the need for specific post-OHCA interventions.

Where surveys have been conducted with survivors >12-months after the event, studies are generally very small, [7-16] or include a highly select group of survivors, for example, as part of target temperature management studies,[11 13 15] or only investigate global measures of neurological status and/or health-related quality of life[7 17-20] (see supplementary Table 1). These global measures are important outcomes for assessing the effect of prehospital or acute hospital interventions, and providing information on overall survivor status. However, to develop, tailor and deliver effective post-OHCA interventions, we need to know what proportion of survivors have domain-specific problems, for example, fatigue or anxiety, and whether this changes with time.

Hence, we investigated fatigue, symptoms of anxiety and depression, mental recovery and disability in survivors 1-5 years since OHCA and, whether the results are different at different time points post-OHCA.

METHODS

Study design, setting and population

This study has a cross-sectional study design using a sub-set of data from the DANCAS (DANish Cardiac Arrest Survivorship) survey described in the published protocol[21] and is reported according to the STROBE guidelines.[22] The Danish Cardiac Arrest Registry was used to identify people, ≥18 years of age and resident in Denmark, who suffered an OHCA from 1 January 2016 to 31 December 2019 and were alive 30-days after OHCA. We chose the 1-5 years timeframe because this provides both a long-term perspective and still takes account for changes to prehospital and medical management of OHCA patients in recent years,[2 23] ensuring data are relevant to the contemporary OHCA survivor population.

Survivors received an electronic version of the survey or a paper version by post if they did not have government electronic mail. Two electronic reminders were sent and one postal reminder. Surveys were completed from 28 October 2020 to 28 March 2021.

Outcome measures

Domains included in the DANCAS survey covered common problems of OHCA described in existing literature.[21]

Fatigue

The Modified Fatigue Impact Scale (MFIS) was chosen as hypoxic brain injury is a potential consequence of OHCA[24] and the MFIS was developed and validated in people with neurological disorders/brain injury.[25-27] It measures how fatigue affects daily life, reported as overall (total) fatigue and as three sub-scales: physical, cognitive and psychosocial fatigue. In total, 21-items ask about frequency of impact of fatigue on functional activities rated from "never" to "almost always".[28] Total scores range 0-84 with higher scores indicating greater impact of fatigue. Scores ≥30 have been proposed to differentiate between fatigued and non-fatigued individuals in a mild-moderate traumatic brain injury population.[27]

Anxiety and depression

Symptoms of anxiety and depression were assessed by the Hospital and Anxiety and Depression Scale (HADS). The HADS has been used in many existing OHCA studies[9 10 12 16] and has been validated in a Danish population of patients with cardiac diseases.[29] HADS consists of 14-items split into two subscales (HADS-A and HADS-D), scores range 0-21 with scores ≥8 indicating probable presence of a mood disorder.[30]

Everyday activities and mental recovery

Two Simple Questions (TSQ) asks about everyday activities and mental recovery. Adapted for use with OHCA survivors from studies with stroke survivors to be a simple test of neurological outcome.[31 32] Question 1a asks: "In the last 2 weeks did you require help from another person for your everyday activities?", if this is answered yes, Question 1b is asked: "Is this a new situation after your cardiac arrest?" Question 2 asks: "Do you feel that you have made a complete mental recovery after the cardiac arrest?"[31 32]

Disability

The 12-item World Health Organisation Disability Assessment Schedule 2.0 (12-item WHODAS 2.0) was developed by the WHO based on the International Classification of Functioning, Disability and Health framework and validated in multiple disease groups and countries.[33 34] WHODAS 2.0 contains 12-items assessing six domains of functioning: understanding and communicating, self-care, mobility,

interpersonal relationships, work and household roles, and community and civic roles. Scored from 0='no difficulty' to 4='extreme difficulty or cannot do'. Total scores range from 0-48. Scores ≥10 indicate significant clinical disability.[35]

Additional sociodemographic and clinical data

Sociodemographic information at the time of OHCA was extracted from Danish national registries as follows: *Civil Personal Registration Register*: age, sex, living arrangements, living with children <25 years, immigration status and Danish region; *Education register*[36]: highest attained educational level; and the *Family income register*[37]: information on combined family income categorized according to combined family income of the total population in the same age group.

The *National Patient Register*[38] provided information on length of hospital admission after OHCA, cardiac diagnoses[39] during hospital admission after OHCA and was used to calculate the Charlson co-morbidity index for the five-year period one year prior to the OHCA.[40 41] *The Danish Cardiac Arrest Registry* provided information on circumstances of cardiac OHCA.

Statistical analyses

Single item missing data in any of the individual questionnaires (outcomes measures) was not possible in the electronic survey. If one or more items were missing in the returned paper surveys, the individual outcome measure was not included in the analysis.

Survey outcome scores were analysed in two ways. Firstly, the mean scores for all survey outcomes including any sub-scales were calculated. Secondly, the proportion of survivors with problems were calculated using cut-off values described above, presented as percentages. The 95% confidence intervals (CI) were calculated for both mean scores and proportions.

To illustrate potential co-occurrence of three of the domain-specific outcomes (fatigue, anxiety and depression), we created a Venn diagram of the domain scores (MFIS, HADS-A and HADS-D) dichotomised using the cut-off scores described above.

To investigate change in outcomes with time since OHCA, survivors were sub-divided into four groups based on months from their OHCA and to the date they completed the survey: 12-24, 25-36, 37-48 and 49-56.

A descriptive analysis was performed of sociodemographic and clinical characteristics of the survey respondents stratified by time since OHCA (time group). Categorical variables are presented as number

and proportions (n, %). Quantitative variables are presented as mean and standard deviation (SD), or as median, interquartile range (IQR) as appropriate.

Differences between time groups were determined using the Kruskall-Wallis test for the mean scores and Chi-square test for proportions. None of the variables available in the study were considered as potential confounders for the association between time groups and the survey outcomes. If large differences between time groups for sociodemographic and clinical characteristics were found, a further regression analysis would be conducted adjusting for these characteristics. All analyses were conducted using STATA V.16 (StataCorp) statistical software. Statistical significance was set at $p < 0.05$.

Ethics and data protection

The study was conducted in accordance with the Declaration of Helsinki. Surveys and register-based research studies do not require ethical approval in Denmark, which was confirmed for this study by the Region of Southern Denmark ethics committee (20192000-19). The study was registered with the Region of Southern Denmark data protection agency (19/8559).

RESULTS

Total eligible survey population was 2116, of which 1258 survivors (59.5%) responded (Figure 1). Survey participant characteristics are described in Table 1. Mean age was 62.4 (SD 12.8) and 80.7% were male. Compared to non-respondents, survey respondents were significantly older, male, with longer education, receiving a higher income; more were Western-born, had an OHCA in a public place, and received bystander resuscitation, and they had shorter hospital length of stay and less co-morbidities (Table 2 Supplementary data). In addition, the response rate was higher for those sent the electronic (66.6%) versus postal survey (25.1%).

Survey outcomes are reported in Table 2. Overall, mean MFIS was 21.1 points (CI 20.0-22.2) with 28.6% of survivors categorized as fatigued individuals. MFIS mean sub-scale scores were 10.9 (CI 10.4-11.4) for physical, 8.2 (CI 7.7-8.7) for cognitive and 2.1 (CI 2.0-2.2) for psychosocial. The mean HADS scores were 4.0 (CI 3.8-4.2) for anxiety and 3.6 (CI 3.4-3.8) for depression, with 19.6% of survivors reporting symptoms of anxiety (HADS-A ≥8) and 14.7% symptoms of depression. For the TSQ, 10.8% of survivors reported requiring help with everyday activities following their OHCA and 33.6% felt they had not made a complete mental recovery. WHODAS 2.0 mean score was 7.7 (CI 7.2-8.2)) with significant disability reported by 27.3% of OHCA survivors.

Co-occurrence of domain-specific outcomes (fatigue, anxiety and depression) is illustrated in Figure 2. In total, 9.4% of the survivors reported symptoms in all three outcomes; 3.5-4.9% of survivors reported

symptoms in two out of the three outcomes with fatigue alone reported by 10.1% of survivors, anxiety 4.9% and depression 1.0%.

No statistically significant difference was found between time groups (p=0.28 to 0.88) for either mean scores or proportions for any outcome (Table 2). Characteristics of survivors sub-divided by time since OHCA also showed no large differences between time groups (Table 1), hence, no further regression analysis was conducted.

DISCUSSION

As far as we know, this is the largest study of OHCA survivors reporting outcomes up to five years after event. Overall, the proportion of survivors reporting fatigue was 29%, anxiety 20%, depression 15%, and 27% disability. When asked specifically about their recovery after OHCA, 11% of survivors felt they now needed help with their everyday activities and a third that they had not fully recovered mentally. As time since OHCA does not seem to change these self-reported problems, our findings stress the provision of early screening and tailored support or rehabilitation to help survivors adapt to their new situation.

Compared to the previous reporting of long-term fatigue in OHCA survivors, our finding of 29% of survivors reporting fatigue was lower than the 52% found by Moulaert et al.[9] at 12 months and 36% Wimmer et al. at mean 5.3 years.[10] Both these previous studies used the 7-item Fatigue Severity Scale and the disparity between our results and theirs could be due to the use of different outcome measures. Comparing the MFIS total score to a normal American population,[42] our results showed OHCA survivors had higher mean fatigue scores: 21.1 versus 15.3 indicating fatigue could be more common in OHCA survivors than in the general population. This is despite the better welfare and labour market support found in Denmark versus the USA that may lead to increased fatigue in the general population.[43] Considering a third of survivors reported they had not fully recovered mentally, we might have expected the mean MFIS cognitive subscale score to be higher than the physical subscale, but the three MFIS subscale scores were fairly evenly represented in the mean total score.

The proportion of symptoms of anxiety and depression reported in our study were in line with findings by Wimmer et al.[10] who also found relatively low proportions of anxiety (14%) and depression (5%) five years after the event. These results vary somewhat from the 12 month studies: Moulaert et al.[9] demonstrated a proportion of 15% for both anxiety and depression, and Viktorrison et al.[16] 23% for anxiety and 5% for depression. These studies and our results are in contrast to Peskine et al.[44] who found proportions of 34% for anxiety and 25% for depression with a small reduction at 18-months (27%

and 22%). This improvement is interesting and was not reflected in our results. However, this could be due to the smaller sample size of the Peskine study (n=70), loss to follow-up at 18-months (n=10), or the case mix. Peskine included survivors only if they had a Glasgow Coma Score ≥12 in the first two weeks whereas we included all survivors alive one-year post-OHCA.

This study is the first time the TSQ was used in a survey of long-term OHCA survivors. Two previous randomized controlled trials[32 45] found a higher proportion of survivors reporting needing help with everyday activities (17-46%) and reduced mental recovery (52-67%) than in our study where it was 11% and 34% respectively. However, both these trials had 6-months follow-up time points and included a highly selective survivor populations enrolled in pre-hospital[45]/acute management[32] intervention effect studies. It is perhaps not surprising that some recovery occurs between 6-12 months, but our results indicate how a high proportion of survivors still do not feel they have returned to pre-OHCA status even five years post-event. The TSQ itself is a rudimentary measure of cognitive function and validity has not been tested in large survivor populations or at time-points beyond 3-months[31]. Determining neurological or cognitive function is inherently difficult in non-interview surveys. The Informant Questionnaire on Cognitive Decline Evaluation for Cardiac Arrest tool was completed by relatives of survivors as part of the larger DANCAS study[21] and will be published in the future. Hopefully, this will give a more in-depth view of the long-term cognitive recovery of OHCA survivors.

Within existing literature, tools for measuring disability in OHCA survivors vary widely with different conceptual frameworks, category definitions and cut-off points[46] so a direct comparison with our results is difficult (see supplementary Table 1). The finding that 27% of survivors were categorized as having significant disability is in agreement with one large previous study[19] but in contrast to several other studies which reported minimal or no long-term disability[14 15 47] (Table 1, Appendix 2b). These studies used clinician-reported measures such as the Cerebral Performance Category, Glasgow Outcome Scale Extended (GOSE) or modified Rankin Scale with broad categories that may lack the sensitivity to identify survivors with long-term disability who could benefit from rehabilitation.

Mean WHODAS 2.0 score in our study was 7.7 (CI 7.2-8.2), more than twice the score of 3.1 found in a normal Australian population[35] and still higher than 5.6 reported for the oldest Australian age group (75-85 years).[35] A German study of long-term myocardial infarction survivors (mean 6.5 years post-event) found similar WHODAS 2.0 scores to our study of 7.9[48] suggesting that disability could be due in part to the cardiac event. However, the reasons for disability in OHCA survivors is likely to be a mix of

physical/emotional/cognitive problems, ongoing cardiac disease or co-morbidities and, hence, requires further investigation.

The illustration of co-occurrence of domain-specific symptoms (Figure 2) shows nearly 10% of survivors suffered significantly from all three symptoms, and only 1% suffered from depression alone. This is perhaps not unexpected given the close association between fatigue and depression[49 50] but it also suggests that effective post-OHCA interventions need be multi-component rather than treating a single problem or symptom in isolation.

Our study's results, with a large population of all-cause OHCA survivors, suggest time does not heal fatigue, anxiety, depression, mental recovery and disability and so are in broad agreement with existing evidence (supplementary table 1) that OHCA survivors can have long-term problems. Hence, it is vital that this is recognized in existing guidelines and survivors with potential problems are identified early and provided with tailored post-OHCA interventions.

Limitations

This study is, we believe, the largest national long-term survey of OHCA survivors to date, however, there are several limitations. Though no large differences were found in survivors' characteristics across the four time groups (see supplementary Table 2), other factors not available to this study, for example, participation in rehabilitation, may potentially have an influence on our findings. Further, the survey outcomes, for example, fatigue, have multiple causes[51-53] and from our observational data it cannot be stated that the OHCA is the causal factor.

The response rate from OHCA survivors with fatigue and/or cognitive problems may have been lower due to challenges with completing the survey leading to an underestimation of the proportion of survivors with problems.[54] We attempted to counter this by using a short survey and providing electronic and paper formats. It is interesting that the response rate for the electronic format was much higher than for the postal survey suggesting that even with hybrid survey methods, outcomes from a sector of society without electronic mail will be missing from the dataset. Survivors in residential or nursing care were not excluded, but they may have been less likely to complete the survey. There are inherent drawbacks to surveys that are simply sent to participants and other methods such as in-person interviews may be needed to collect data from survivors with high levels of fatigue, cognitive problems, living in residential care or who do not use electronic mail.

We considered weighting the survey outcomes to account for non-respondents. However, given the number of factors that could possibly be included in the weighting and the high response rate of 60% we chose simply to present the respondent/non-respondent characteristics for interpretation in addition to the survey outcomes (see supplementary table 2). Non-respondents were more socioeconomically disadvantaged and potentially more 'unwell' with longer hospital stays and more co-morbidities leading to a possible underestimation of survey results.

Further research

Currently, very few outcome measures have been designed specifically for OHCA survivors (in our study only the TSQ). Work on specific outcome measures for OHCA survivors is on-going[55] and the validity of this will need to be tested in both short and long-term survivor populations. Further research is also needed to describe the characteristics of the sub-set of survivors with significant symptoms/disability and so assisting prediction of who is at greater risk of developing long-term problems. Though not the purpose of this study, survey outcomes could be investigated for predictors for mortality in subsequent years. If depression or fatigue results in more death, the later time groups may be missing these survivors, underestimating the proportion of survivors with long-term problems.

Clinical implications

It is recommended that OHCA survivors receive outpatient follow-up at three-months post-event.[2] Given our finding that the same proportion of survivors may have problems a year or more post-OHCA, repeat clinical follow-up at later time points may be necessary. Information material provided to survivors and/or their families should highlight the potential for long-term problems and offer pathways back into clinical assessment/referral to interventions for survivors whose problems have not resolved with time.

CONCLUSION

Up to a third of survivors report fatigue, anxiety, depression, reduced mental recovery and disability 1-5 years after OHCA. This proportion is the same regardless of how much time has passed post-OHCA supporting the need for early screening and tailored post-OHCA interventions to help survivors adapt to their new situation.

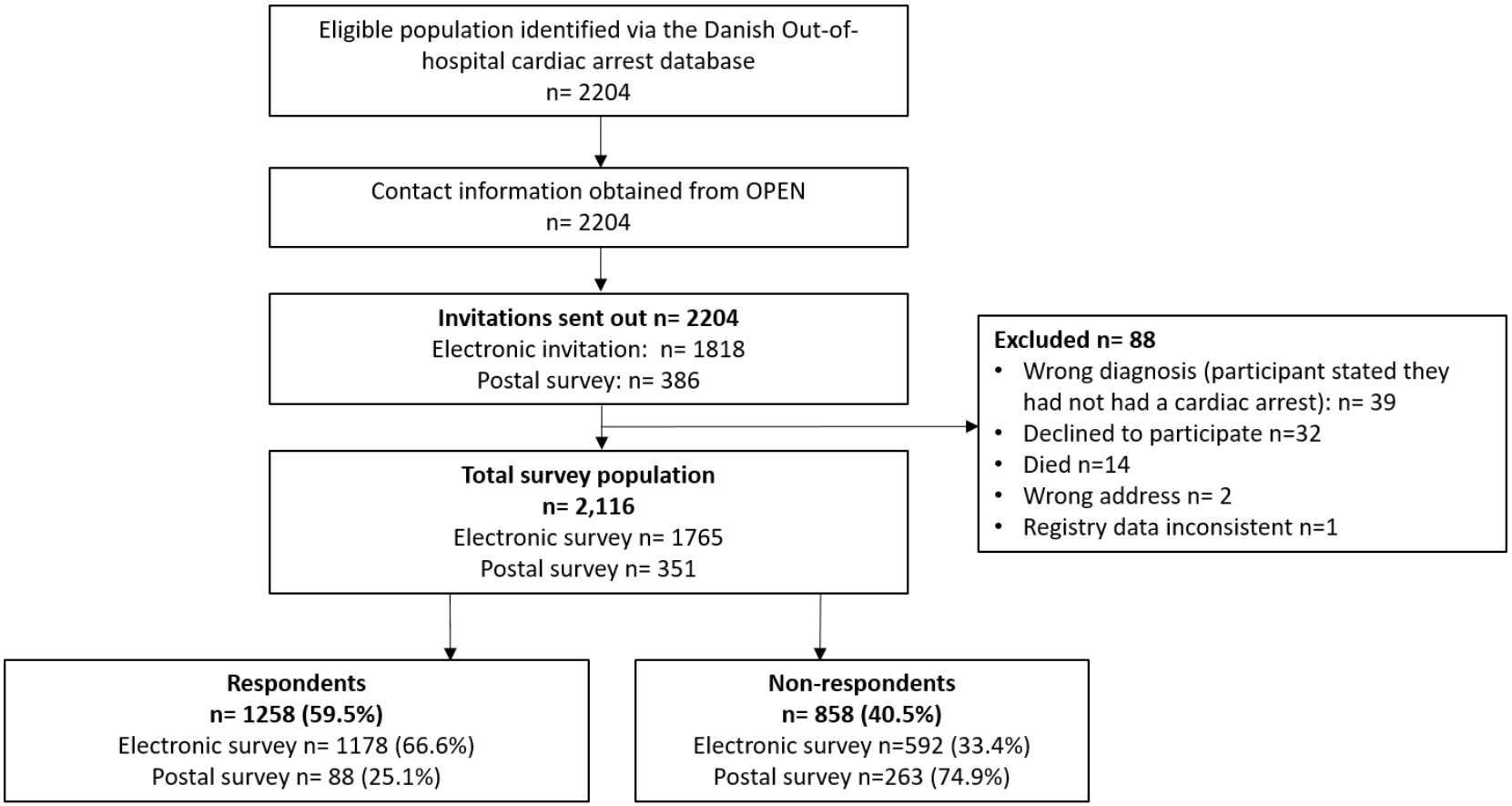
SOURCES OF FUNDING

This project was supported by infrastructure provided by REHPA, The Danish knowledge center for rehabilitation and palliative care, Odense Univeristy Hospital which receives funding from the Danish Government. This project is part of a PhD partially funded by a PhD faculty scholarship from the University of Denmark and a stipendium from the Region of Southern Denmark (19/15041).

ACKNOWLEDGEMENTS

We would like to thank all the OHCA survivors who took the time to complete the survey. Thank you to Helle Collatz Christensen, Kristian Bundgaard Ringgren and everyone involved in the Danish Cardiac Arrest Registy for their help with this project. Thank you to OPEN (Open Patient Data Explorative Network) and Tanja Gram Petersen for their help with the Danish registires. Finally, thank you to Jahan Shabnam, Jens-Jakob Kjer Møller, Josefine Oredson Krone, Nikolaj Nielsen, Sofie Raahauge Christiansen and Henriette Knold Rassau for their help conducting the DANCAS survey.

Figure 1. DANCAS survey study flow diagram



- n=25 participants who received an electronic invite requested a postal survey to complete and of these n=11 were completed.
- n=8 completed an electronic survey after a postal survey was received by following an electronic link in the postal invitation letter.

Table 1. DANCAS survey population sociodemographic and clinical characteristics at the time of OHCA. Values are %, unless otherwise stated.

Characteristic		**Total survey population n,** (% unless otherwise stated)	**Survey population characteristics split by time group (Months after OHCA[a])**			
			1 (12-24)	**2 (25-36)**	**3 (37-48)**	**4 (49-56)**
Participants	n (% of total survey population)	1258	377 (30.0)	306 (24.3)	305 (24.2)	270 (21.5)
Age	median (IQR)	63.9 (54.5-71.8)	64.6	63.4	63.8	64.2
Sex	Male	1015 (80.7)	79.1	80.4	80.7	83.3
Living arrangement	Living alone (versus with someone)	318 (25.3)	23.3	22.9	29.8	25.6
Living with children <25 years	Yes	221 (17.6)	16.2	20.3	19.7	24.1
Education	Elementary school	317 (25.5)	25.8	23.8	26.5	25.8
	Upper secondary/ vocational school	637 (51.2)	50.8	51.5	51.7	50.9
	Higher education	290 (23.3)	23.4	23.4	21.9	23.2
Immigration status	Danish born	1199 (95.3)	94.4	95.4	97.4	94.1
	Western born (not Demark)	32 (2.5)	2.9	3.3	0.0	4.1
	Non-Western born	27 (2.2)	2.7	1.3	2.6	1.9
Income	Low	228 (18.2)	19.9	16.4	18.0	18.0
	Medium	660 (52.6)	49.3	56.4	52.1	53.6
	High	366 (29.2)	30.8	27.2	29.8	28.5
Danish region	Capital Region of Denmark	363 (28.9)	29.4	29.4	26.6	30.0
	Region Zealand	207 (16.5)	25.2	23.5	25.6	21.9
	Region of Southern Denmark	273 (21.7)	8.0	10.8	7.5	9.3
	Central Denmark Region	304 (24.2)	14.6	16.0	17.7	18.2

	Region of Northern Denmark	111 (8.8)	22.8	20.3	22.6	20.7
Place of OHCA	Private (versus public)	579 (46.0)	46.0	51.3	43.7	45.1
Received CPR before ambulance arrived	Yes	919 (73.1)	73.7	71.4	70.8	77.0
Received bystander defibrillation before ambulance arrived	Yes	312 (25.0)	25.9	29.2	21.2	23.3
Total inpatient length of stay (days), median (IQR)[b]		11 (6-18)	12	11	10	11
	Missing		344	18	5	1
Cardiac diagnosis[b,c]	Myocardial infarction	375 (41.9)	-	41.3	43.8	40.7
	Stable angina	223 (24.9)	-	26.4	23.4	26.7
	Heart failure	186 (20.8)	-	18.8	19.4	23.7
	Cardiomyopathy	39 (4.4)	-	3.1	3.3	7.0
	Hypertension	151 (16.9)	-	14.6	16.1	21.5
	Atrial fibrillation	83 (9.3)	-	9.7	9.9	8.5
	VT or VF	171 (19.1)	-	18.1	16.5	24.1
	Valvular heart disease	19 (2.1)	-	3.8	<1.7	1.9
Charlson comorbidity index[d]	None	82.6	81.7	82.0	84.9	81.9
	Mild	15.7	16.5	16.0	13.4	16.7
	Moderate/Severe	1.7	1.9	2.0	1.7	1.4

CPR: Cardiopulmonary resuscitation; OHCA: Out-of-hospital cardiac arrest

[a]Time interval for respondents is interval between OHCA and date survey was answered, time interval for non-respondents is interval between OHCA and the mean date for electronic/postal survey answered by respondents.

[b]Data for 2019 missing due to delays in registration of health data due COVID 19

[c]Cardiac diagnosis(es) recorded for survivor during the hospital admission after OHCA, survivor can have none, one or more diagnoses

[d]Calculated based on health data from the 5-year period starting one year prior to OHCA

Table 2. Self-reported outcomes fatigue, anxiety, depression, mental recover and disability from the DANCAS survey grouped by time since OHCA. Values are mean or % (95% confidence intervals).

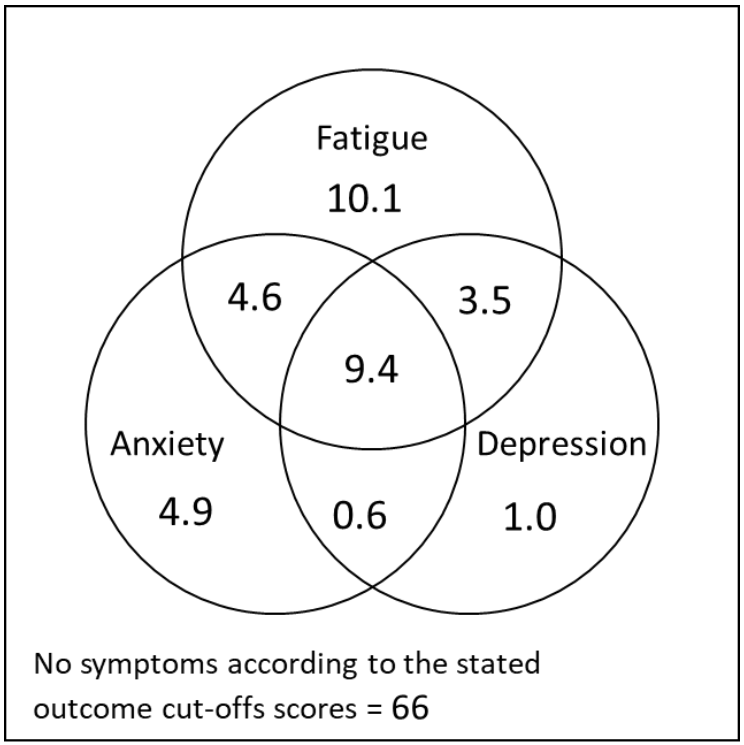
				Survey respondents grouped by time between OHCA and survey completion (months)				
	Outcome measure	**Possible range**	**Total**	**1 (12-24)**	**2 (25-36)**	**3 (37-48)**	**4 (49-56)**	**Difference between time groups p value***
Fatigue	MFIS total, mean (n=1236)	0-84	21.1 (20.0-22.2)	21.8 (20.7-22.9)	20.7 (19.7-21.7)	20.2 (19.2-21.2)	21.7 (20.6-22.8)	0.81
	MFIS total ≥ 30, %	-	28.6 (26.1-31.2)	30.4 (25.7-35.3)	26.7 (21.8-32.1)	26.9 (21.9-32.3)	30.0 (24.6-36.0)	0.61
	MFIS Physical, mean	0-36	10.9 (10.4-11.4)	11.1 (10.6-11.6)	10.7 (10.2-11.2)	10.5 (10.0-11)	11.3 (10.8-11.8)	0.75
	MFIS Cognitive, mean	0-40	8.2 (7.7-8.7)	8.6 (8.1-9.2)	8.0 (7.5-8.5)	7.7 (7.2-8.2)	8.3 (7.8-8.8)	0.80
	MFIS Psychosocial, mean	0-8	2.1 (2.0-2.2)	2.1 (2.0-2.2)	1.9 (1.8-2.0)	2.0 (1.9-2.1)	2.2 (2.1-2.3)	0.56
Anxiety	HADS-A, mean (n=1255)	0-14	4.0 (3.8-4.2)	4.0 (3.8-4.2)	4.1 (3.9-4.2)	4.1 (3.9-4.3)	4.0 (3.8-4.2)	0.96
	HADS-A ≥ 8, %	-	19.6 (17.5-21.9)	20.2 (16.4-24.5)	19.9 (15.8-24.8)	20.7 (16.5-25.6)	17.4 (13.3-22.4)	0.77
Depression	HADS-D, mean	0-14	3.6 (3.4-3.8)	3.5 (3.9)	3.5 (3.3-3.7)	3.6 (3.4-3.8)	3.8 (3.6-4.0)	0.28
	HADS-D ≥ 8, %	-	14.7 (12.9-16.8)	15.7 (12.3-19.7)	14.7 (11.2-19.1)	13.4 (10.0-17.8)	14.8 (11.1-19.6)	0.88
Neurological	TSQ 1. Requires help with everyday activities since OHCA**, % (n= 1243)	-	10.8 (8.8-12.7)	11.9 (9.0-15.6)	11.1 (8.0-15.2)	8.5 (5.9-12.2)	11.5 (8.1-15.9)	0.51
	TSQ 2. Feels mental recovery is not complete after OHCA, % (n= 1243)	-	33.6 (31-36)	36.0 (31.3-41.0)	33.6 (28.5-39.1)	33.0 (27.9-38.5)	30.7 (25.5-36.5)	0.57
Disability	12-item WHODAS 2.0, mean (n=1242)	0-48	7.7 (7.2-8.2)	7.9 (7.4-8.4)	7.3 (6.8-7.8)	7.4 (6.9-7.9)	8.0 (7.5-8.5)	0.76
	12-item WHODAS 2.0 ≥ 10, %	-	27.3 (24.8-39.8)	28.7 (24.0-33.6)	25.6 (20.8-30.9)	24.8 (20.0-30.1)	27.3 (24.7-36.0)	0.43

HADS: Hospital Anxiety and Depression Scale; MFIS: Modified Fatigue Impact Scale; TSQ: Two Simple Questions; WHODAS: World Health Organisation Disability Assessment Scale.

*Differences in means between time groups tested by Kruskall Wallis test. Differences in proportions between time groups tested by Pearson's Chi-squared test.

**Excludes survivors who answered "no" to question 1b, namely they reported needing help for everyday activities but this was not a new situation for them after their out-of-hospital cardiac arrest.

Figure 2. Co-occurrence of symptoms of fatigue, anxiety and depression 1-5 years after OHCA based on cut-off for each outcomes % (see Table 2).



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Appendix 2b:

Supplementary material for paper 2

Appendix 2b Supplementary Materials

Table 1. Studies investigating long term (≥12 months) self-reported domain specific outcomes in CA survivors.

Searches

Pubmed and Web of Science databases were searched as well as the references of relevant literature and existing systematic reviews. Example of search string, in brief form: ((cardiac arrest) AND ((((long term) OR (long-term)) OR (over 12 months)) OR (after 12 months))) AND (((((patient reported) OR (self-reported)) OR (self-report)) OR (survey)) OR (questionnaire)) - Saved search Filters: from 2010 – 2022
Studies were included if they described at least one self-reported outcome completed by CA survivors (or relative) pertaining to a non-HRQoL outcome (ie. physical/psychological/neurological domain specific outcome or measuring function/disability). Outcomes reported as part of effect studies (eg. RCTs were excluded). Searches last conducted July 2022.

Studies needed to include at least one domain specific outcomes. The table below summarizes the included study outcomes with the domain they measure and the results. This includes, where reported, HRQoL measures and clinician reported measures (CPC and mRS) to provide a complete overview of these studies.

Author, year of publication, Country	**Title**	**Study population**	**% Male Age at OHCA (years)**	**Time point(s) post CA**	**Outcome measures (domains)**	**Summary of main results**
Outcomes at 12-month time point						
Nehme, 2015[1] Australia	Comparison of out-of-hospital cardiac arrest occurring before and after paramedic arrival: Epidemiology, survival to hospital discharge and 12-month functional recovery	OHCA survivors n=969	69%, median 70 (IQR: 58.0–80.0)	12 months	GOSE (neurological function) SF-12 (HRQoL EQ5D (HRQoL)	GOSE: Good recovery 54.6%, moderate disability 23.8%, severe disability 12.5 % SF-12 (median, IQR): MCS, 56 (52–59) PCS, 50 (40–56) EuroQol index: 0.82 (SD 0.19)
Moulaert, 2017[2] Netherlands	Long-term Outcome After Survival of a Cardiac Arrest: A Prospective	CA survivors n= 141	84% male, 60 (SD 11)	12 months	NYHA (ADL) Cog-log (cognition) HADS (anxiety + depression)	At 1 year, 14 (13%) survivors scored below cutoff on the Cog-log. HADS: anxiety and depression were present in 15% IES: present in 28%

Steinbusch, 2017[3]	Longitudinal Cohort Study Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: A prospective longitudinal cohort study	(Same study population as Moulaert et., 2017)			IES (post-traumatic stress) FAI (ADL) FSS (fatigue) CIQ (participation) Return to work EQ5D (HRQoL) SF-36 (HRQoL) QLIBRI (HRQoL) Cognitive objective tests (not self-report measure) CFQ (cognition)	FAI: 96% of pre-arrest scores FSS: severe fatigue present in 52% CIQ: 92% of the pre-arrest scores. 41 (72%) returned to work HRQoL: Most recovery of cognitive function and quality of life occurred within the first 3 months. Subjective cognitive complaints were present at two weeks after cardiac arrest in 11%, 12% at three months and 14% at one year. No significant associations between cognitive impairments and cognitive complaints at any time point At one year 10%-22% remained impaired with executive functioning being affected most
Tiainen, 2018[4] Finland	Surviving out-of-hospital cardiac arrest: The neurological and functional outcome and health-related quality of life one year later	OHCA survivors treated in Finnish ICUs n=206	79% male, median 61 (range 18–84)	1 year	CPC (neurological function) BI (ADL) ADL questionnaire (ADL) Lawton IADL (ADL) EQ5D (HRQoL)	CPC: Long-term functional outcome was good in over 90% of patients BI: Median score 100 (IQR 100-100), 88% would be classified as independent ADL: 91% considered themselves independent with ADLs Lawton IADL: 86% scored as independent EQ5D: Similar to that of an age and gender matched population.
Viktorisson, 2019[5] Sweden	One-year longitudinal study of psychological distress and self-assessed health in	OHCA Cerebral performance score	82 % male 63 years (25-89)	at 3 months, 12 months	HADS (anxiety + depression) EQ5D-3L (HRQoL)	HADS: clinically relevant anxiety reported by 23% and depression 5% of survivors at 12 months. Mean anxiety 4.7 (SD 4.3) and depression: 2.6 (SD 2.6)

	survivors of out-of-hospital cardiac arrest	greater than 2 n=74				EQ 5D 3L mean VAS 77 (SD 19), mean index score 0.88 (SD 0.15)
Flickinger, 2021[6] USA	One-year outcomes in individual domains of the cerebral performance category extended	mixed in/out hospital CA as part of a TTM study n=23	63% male, 55 years (SD 16)	discharge, 3,6 and 12 months	mRS (disability) CPC (neurological function) CPC-E (neurological function)	mRS and CPC showed slight to no disability at 12 months CPC-E domains of motor skills and basic ADL were recovered by 12 months. CPC-E domains present in survivors: short term memory (78%), mood (87%), fatigue (22%), complex ADL (78%), Return to work: 65%
Time point greater than 12 months						
Saarinen, 2012[7] Finland	Pulseless electrical activity and successful out-of-hospital resuscitation - long-term survival and quality of life: an observational cohort study	OHCA survivors with initial pulseless electrical activity n=10	30% male, 69 years (at time of study, characteristics include non-survivors)	6.5-7.5 post CA	CPC (neurological function) 15-D (ADL, HRQoL)	7 participants alive after 1 year and 6 at 5 years. CPC: 5/7 same functional level as prior OHCA 15-D: 87% estimated ADL as normal or mildly impaired All normal or mildly impaired function in seeing, hearing, sleeping, eating, speech and in urination or defecation/ energy, distress and depression.
Deasy, 2013[8] Australia	Functional outcomes and quality of life of young adults who survive out-of-hospital cardiac arrest	Young adults, 18-39, registry follow-up n=56	71% male, mean age 35 (29-41)	Median 5 years post CA (range 2.7-8.6) OHCA 2003-2008	GOSE (function) EQ5D (HRQoL) SF-12 (HRQoL)	GOSE: 84% no disability, 29% mild/moderate, 18% marked/severe disability, EQ-5D: Mobility (75%), personal care (75%), usual activities (66%) or pain/discomfort (71%). EQ-5D, anxiety and depression: 61% of respondents reported either moderate (48%) or severe (13%) anxiety.

Kowalik, 2014[9] Poland	Cardiac arrest survivors treated with or without mild therapeutic hypothermia: performance status and quality of life assessment	OHCA patients treated with/without mild therapeutic hypothermia (MTH) MTH n=16 Non-MTH n=15	71% male, 57.5 (SD 2.8)	MTH = mean 290 (14-776 days) Non-MTH= 1409 (1152-1592)	DRS (disability) Barthel Index (ADL) RAND-36 (HRQoL)	Results for Non-MTH only (as time of OHCA was ≥ 12 months) DRS: 33% scored no disability, 67% mild-moderately severe Barthel: 80% none/mild disability, 20% moderately severe RAND-36: Role limitations due to emotional mean scores 18.83, fatigue 10.08, emotional well-being 15.07, social functioning 17.59, general health 17.71
Andersson, 2015[10] Sweden	Life after cardiac arrest: A very long term follow up	OHCA survivors n=8	100% men mean age 53 (at OHCA)	17 (15-19) years	Barthel Index (ADL) MMSE (cognition) MoCA (Cognition) PCL-C (PTSD) HADS (anxiety + depression)	Barthel: 1 major and 3 minor dependency MMSE: 4/8 cognitive impairment MoCA: 7/8 impaired cognitive ability PCL-C: No PTSD HADS: 1/8 mild Anxiety and depression
Geri, 2017[11] France	Predictors of long-term functional outcome and health-related quality of life after out-of-hospital cardiac arrest – a five-year follow-up study	OHCA survivors n=255	74% male, median 55 years (IQR 45-64)	median 38 (IQR 12-78) months	SF-36 (HRQoL) Katz index (ADL)	SF-36: See paper for individual domain scores. Decreased neurological function was associated with lower SF-36 scores Katz ADL index: 83% had ADL above 6 indicating independence with ADL
Caro-Codon, 2018[12] Spain	Long-term neurological outcomes in out-of-hospital cardiac arrest patients treated with targeted-temperature management	OHCA survivors with GCS ≤8 after ROSC and admitted to CCU and received TTM, CPC ≤2 at discharge n=79	90% male, age 53.5 (SD 14.5)	Mean 3.1 years (IQR 1.7-4.4)	Return to work MoCA (cognition) Cognitive tests eg. trail making (objective tests) EQ5D-3L (HRQoL) Modified IQCODE test (relative reported cognition) CPC (neurological function)	37% not able to resume full time work MoCA: 54% scored as mild cognitive impairment Objective cognitive tests: 24% below cut-offs for mild impairment EQ VAS: mean 72.4 (SD 16.1) IQCODE test: 12% 3/25 scored for cognitive impairment CPC: 95% CPC 1

Peskine, 2021[13] France	Long-Term Disabilities of Survivors of Out-of-Hospital Cardiac Arrest The Hanox Study	OHCA survivors with a Glasgow Coma Scale score ≥12 n=74	male 78%, 56 (47-66)	12 months 18 months	GOS-E (function) NIHSS (neurological) MDSUPDRS (neurological) mRS (disability) HADS (anxiety and depression) SF-36 (HRQoL)	GOS-E: 65% good functional outcomes mRS: 58% no disability 12M/18M HADS-A: 34% had symptoms at 12M (n=70), 27% at 18M (n=60) HADS-D: 25% had symptoms at 12 M, 22% at 18M SF-36 physical: median (IQR) 65 (48-81) 12M, 66 (51-83) at 18M SF-36 mental: median (IQR) 69 (46-82) 12M, 67 (48-82) at 18M
Wimmer, 2021[14] Norway	Health-related quality of life after out-of-hospital cardiac arrest a five-year follow-up study	OHCA n=96	84% male, 57 (12.2)	mean 5.3 (range 3.6-7.2) years	CPC (neurological function) EQ-5D (HRQoL) SF-36 (HRQoL) HADS (anxiety + depression) FSS (fatigue)	CPC: 95% CPC 1 or 2 EQ5D Index: 0.78 SF-36: Physical component: 46.5, mental component: 52.1 HADS A-mean 3.7,present in 14% HADS-D mean 2.8,present in 5% FSS: Severe fatigue in 22%; 36% when using the lower cut-off as used by Moulaert et al. 2017. Anxiety and fatigue tended to be lower than general population.

Supplementary Table 1 Abbreviations:

15-D: Fifteen dimensional questionnaire; ADL: Activities of daily living; CFQ: Cognitive Failures Questionnaire; CIQ: Community Integration Questionnaires; CPC: Cerebral Performance Category; DRS: Disability Rating Scale; EQ5D: EuroQoL 5D; FAI: Frenchay Activities Index; FSS: Fatigue severity scale; GOSE: Extended Glasgow Outcome Scale; HADS: Hospital Anxiety and Depression Scale; HRQoL: Health Related Quality of Life; IES: Impact of Event Scale; MDSUPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; Modified IQCODE: Informant; Questionnaire on Cognitive Decline in the Elderly; mRS: Modified Rankin Scale; MTH: Mild therapeutic hypothermia; n/a: not available; NIHSS: National Institutes of Health Stroke Score; NYHA: New York Heart Association Classification; PTSD: Post-traumatic stress disorder; QLIBRI: Quality of Life after Brain Injury questionnaire; SF-36: 36-Item Short Form Survey Instrument

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Table 2. DANCAS survey respondent/non-respondent sociodemographic and clinical characteristics at the time of OHCA

Characteristic		Respondents n, (%)	Non-respondents n, (%)	Difference p value[a]
Total		1258 (59.5)	858 (40.5)	
Age	years, mean, (SD), range	62.4 (12.8), 13.9-92.3	59.2 (17.1), 14-91.6	<0.00
	median (IQR)	63.9 (54.5-71.8)	60.8 (49.1-72.0)	
Sex	Male	1015 (80.7)	642 (74.8)	<0.00
	Female	243 (19.3)	216 (25.2)	
Living arrangement	Living alone	318 (25.3)	407 (47.4)	<0.00
	Living with someone	940 (74.7)	451 (52.6)	
Living with children <25 years	Yes	221 (17.6)	161 (18.8)	0.48
Education	Elementary school	317 (25.5)	382 (46.0)	<0.00
	Upper secondary/vocational school	637 (51.2)	342 (41.2)	
	Higher education	290 (23.3)	106 (12.8)	

Immigration status	Danish born	1199 (95.3)	776 (90.4)	<0.00
	Western born (not Demark)	32 (2.5)	24 (2.8)	
	Non-Western born	27 (2.2)	58 (6.7)	
Income	Low	228 (18.2)	377 (44.0)	<0.00
	Medium	660 (52.6)	364 (42.5)	
	High	366 (29.2)	116 (13.5)	
Danish region	Capital Region of Denmark	363 (28.9)	211 (24.6)	0.03
	Region Zealand	207 (16.5)	155 (18.1)	
	Region of Southern Denmark	273 (21.7)	210 (24.5)	
	Central Denmark Region	304 (24.2)	184 (21.5)	
	Region of Northern Denmark	111 (8.8)	98 (11.4)	
Time since OHCA, months[b]	12-24	377 (30.0)	251 (29.3)	0.52
	25-36	306 (24.3)	191 (22.3)	
	37-48	305 (24.2)	212 (24.7)	
	49-56	270 (21.5)	204 (23.8)	
Place of OHCA	Private (versus public)	579 (46.0)	437 (50.9)	0.03
Received CPR before ambulance arrived	Yes	919 (73.1)	607 (70.8)	0.47
Received bystander defibrillation before ambulance arrived	Yes	312 (24.8)	148 (17.3)	<0.00
Total inpatient length of stay (days), median (IQR)[c]		11 (6-18)	9 (4-18)	<0.00
Cardiac diagnosis[c,d]	Myocardial infarction	375 (41.9)	191 (32.5)	<0.00
	Stable angina	223 (24.9)	103 (17.6)	<0.00
	Heart failure	186 (20.8)	94 (16.0)	0.02
	Cardiomyopathy	39 (4.4)	22 (3.8)	0.57
	Hypertension	151 (16.9)	67 (11.4)	<0.00
	Atrial fibrillation	83 (9.3)	60 (10.2)	0.54
	VT or VF	171 (19.1)	91 (15.5)	0.08
	Valvular heart disease	19 (2.1)	12 (2.0)	0.92

Charlson comorbidity index[e]	None	1039 (82.6)	677 (78.9)	<0.00
	Mild	197 (15.7)	145 (16.9)	
	Moderate	18 (1.4)	32 (3.7)	
	Severe	4 (0.3)	4 (0.5)	

CPR: Cardiopulmonary resuscitation; OHCA: Out-of-hospital cardiac arrest

[a]Differences in means tested by Kruskall Wallis test. Differences in proportions tested by Pearson Chi squared test

[b]Time interval for responders is interval between OHCA and date survey was answered, time interval for non-responders is interval between OHCA mean date for electronic/postal survey answered by respondents.

[c]Data for 2019 missing due to delays in registry data post-COVID 19

[d]Cardiac diagnosis(es) recorded for survivor during hospital admission after OHCA

[e]Calculated based on health data from the 5-year period starting one year prior to OHCA

Appendix 3a:

Paper 3

BMJ Open

Effectiveness of rehabilitation interventions on the secondary consequences of surviving a cardiac arrest: a systematic review and meta-analysis

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To cite: Joshi VL, Christensen J, Lejsgaard E, *et al*. Effectiveness of rehabilitation interventions on the secondary consequences of surviving a cardiac arrest: a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e047251. doi:10.1136/bmjopen-2020-047251

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online. (http://dx.doi.org/10.1136/bmjopen-2020-047251).

Received 24 November 2020
Accepted 29 July 2021

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ABSTRACT

Aim The aim of this systematic review was to assess the effectiveness of rehabilitation interventions on the secondary physical, neurological and psychological consequences of cardiac arrest (CA) for adult survivors.

Methods A literature search of electronic databases (MEDLINE, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, Excerpta Medica database, Psychological Information Database, Web of Science and Cochrane Central Register of Controlled trials) was conducted for randomised controlled trials (RCTs) and observational studies up to 18 April 2021. The primary outcome was health-related quality of life (HRQoL) and main secondary outcome was neurological function with additional secondary outcomes being survival, rehospitalisation, safety (serious and non-serious adverse events), psychological well-being, fatigue, exercise capacity and physical capacity. Two authors independently screened studies for eligibility, extracted data and assessed risk of bias.

Results Three RCTs and 11 observational studies were included (total 721 participants). Study duration ranged from 8 weeks to 2 years. Pooled data from two RCTs showed low-quality evidence for no effect on physical HRQoL (standardised mean difference (SMD) 0.19, (95% CI: −0.09 to 0.47)) and no effect on mental HRQoL (SMD 0.27 (95% CI: −0.01 to 0.55)).

Regarding secondary outcomes, very low-quality evidence was found for improvement in neurological function associated with inpatient rehabilitation for CA survivors with acquired brain injury (SMD 0.71, (95% CI: 0.45 to 0.96)) from five observational studies. Two small observational studies found exercise-based rehabilitation interventions to be safe for CA survivors, reporting no serious or non-serious events.

Conclusions Given the overall low quality of evidence, this review cannot determine the effectiveness of rehabilitation interventions for CA survivors on HRQoL, neurological function or other included outcomes, and recommend further high-quality studies be conducted. In the interim, existing clinical guidelines on rehabilitation provision after CA should be followed to meet the high burden of secondary consequences suffered by CA survivors.

Strengths and limitations of this study

- ► This is the first systematic review and meta-analysis to assess the effectiveness of rehabilitation interventions for cardiac arrest (CA) survivors.
- ► Comprehensive literature searches were conducted with the inclusion of both randomised controlled trial and observational studies, and a wide range of outcomes relevant to CA survivors.
- ► High heterogeneity in intervention design and outcome measures limited the possibility for meta-analysis of study results.
- ► Quality of evidence was generally low with the majority of studies having small or very small sample sizes and insufficient description of the rehabilitation interventions.

PROSPERO registration number CRD42018110129.

INTRODUCTION

The number of people surviving a cardiac arrest (CA) to hospital discharge is increasing due to improvements in postcardiac arrest systems of care.[1] In the USA, survival to hospital discharge is now 11.4% translating to 70 000 new CA survivors each year with this number expected to increase.[1 2] However, after survival, multiple research studies have documented the secondary physical, neurological and psychological consequences for CA survivors.[1 3–6] Rehabilitation helps people to achieve and maintain optimum functioning in interaction with their environments.[7] Rehabilitation interventions have shown benefits for the secondary consequences of brain injury or cardiac events[8 9] indicating the same may be true for CA survivors. Rehabilitation after surviving a CA is recommended in consensus-based international clinical guidelines[1 10 11] but, to date, there has not been a

systematic assessment of the effectiveness of rehabilitation interventions for CA survivors.[12] In previous consensus building research with survivors, relatives and clinicians, quality of life and neurological function were identified as important outcomes after CA.[4 13]

The aim of this systematic review and meta-analysis was to assess the effectiveness of rehabilitation interventions for adult CA survivors. The primary outcome was health-related quality of life (HRQoL) and main secondary outcome was neurological function. Additional secondary outcomes were survival, rehospitalisation, safety (serious and non-serious adverse events), psychological well-being, fatigue, exercise capacity and physical capacity.

METHODS

Protocol and registration

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental file 1).[14]

Eligibility criteria

Studies using randomised controlled trials (RCTs) using individual or cluster randomisation in a parallel or crossover design, pilot studies, non-RCTs and prospective/retrospective observational studies were included. Studies using a case series or case report design were excluded.

The parameters for the systematic review were defined using the Population, Intervention Comparator, Outcome (PICO) framework. The question being: What is the effectiveness among adult (≥18 years) CA survivors (P), of rehabilitation interventions (I) on HRQoL and neurological function (O)? Comparator was defined as no treatment, active control, usual care, additional intervention or no comparator (C). No restriction on publication date, language or length of follow-up was made.

Studies that included both CA survivors and people with cardiac disease without CA were eligible for inclusion if subgroup data for CA survivors were presented or if these specific data could be obtained by contacting the study authors. If separate subgroup data for CA survivors could not be acquired, studies were eligible for inclusion if at least 50% of participants were CA survivors. Studies with mixed CA survivors and non-CA survivors acquired brain injury populations were treated in the same way.

Rehabilitation can be defined as: 'A set of measures that assist individuals, who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments'.[7] To align with this broad definition of rehabilitation and ensure inclusion of all possible rehabilitation interventions, interventions were included if they were not primarily pharmacologically or surgically based or involved invasive technology. Interventions in the emergency room or critical care unit setting were excluded.

The primary outcome was HRQoL. HRQoL outcome measures could include generic or disease-specific patient-reported outcome measures and could be either a single item or multi-item outcome measure. The main secondary outcome was neurological function, defined as measuring the level of disability after a neurological event. Measures may primarily test cognitive ability or may combine cognitive and physical ability hence measuring global disability. Additional secondary outcomes were survival, rehospitalisation, safety (serious and non-serious adverse events), psychological well-being, fatigue, exercise capacity and physical capacity. Measures may be patient reported, clinician reported, observer reported or performance based. The primary and main secondary outcomes were chosen as, alongside survival, HRQoL and neurological function have been identified as important core outcome domains after CA by survivors, relatives and clinicians.[4 13] Choice of secondary outcomes was informed by existing evidence on the secondary consequences of CA[1 3 5 6] and inspired by outcomes in previous systematic reviews on rehabilitation with other cardiac disease populations.[8 15]

Information sources

Preliminary searches were conducted to identify relevant search terms and subject headings. The final systematic search for eligible studies was conducted in the online databases: The National Library of Medicine (MEDLINE), Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, Excerpta Medica database, Psychological Information Database, Web of Science, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled trials were initially searched on 2 December 2019 and updated on 18 April 2021. Abstracts from the 'postcardiac arrest conferences' 2013–2019 were hand searched, and bibliographies of articles included at the full-text stage were reviewed to identify possible additional studies. Ongoing trials were identified by searching clinical trial registries (International Standard Randomised Controlled Trial Number, WHO International Clinical Trials Registry Platform and ClinicalTrials.gov).

Searches

The search matrix consisted of a combination of keywords and synonyms for: (1) CA and (2) non-pharmacological/surgical/invasive technology rehabilitation interventions. The complete search strategy and detailed search matrix is outlined in online supplemental table 1.

Study selection

Using the technology platform Covidence, two authors (VLJ and EL) independently screened all identified studies, first by title and abstract, and then after reading the full-text articles. First and last authors of studies were contacted where full-text articles were unavailable or CA survivors subgroup data were required. Any disagreements in the screening process were discussed between the two authors and if necessary a third author was consulted (JC).

Data collection process

Data were extracted from the included studies independently by two review authors (VLJ and LHT) using a predefined standardised data extraction form. Any inconsistencies between authors in the data extraction process were resolved by discussion and if necessary a third author was consulted (JC).

Data items

Extracted data items included: study characteristics (author, year of publication, country, number of groups, number of participants, inclusion and exclusion criteria, setting, method of recruitment, aim of study, study design, length of study), characteristics of participants (mean age, gender, ethnicity, cause of CA, and comorbidities), description of intervention (duration, timing after CA, provider of intervention, description of control if relevant), theory or mechanism of intervention, outcomes (measured at baseline, hospital discharge, 3 months and final follow-up point and, if present, mortality, rehospitalisation, serious and non-serious adverse events) and results (sample sizes, baseline and all follow-up points, mean, estimate of effect, CI, SD, p value).

Risk of bias in individual studies

Two researchers independently assessed risk of bias for the included studies. RCTs were assessed using the RoB 2: a revised tool for assessing risk of bias in randomised trials,[16] and observational studies were assessed using the National Institutes of Health Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group.[17]

Summary measures

For continuous data, the effectiveness of the rehabilitation interventions was expressed either as mean difference (MD) or as standardised MD (SMD) with 95% CI. For time-to-event outcomes (survival, rehospitalisation), hazard ratios were pooled if presented.

Synthesis of results

If more than one study reported an outcome related to the outcomes of interest, the clinical heterogeneity (similarity in CA survivors population, rehabilitation interventions and outcomes) was assessed. If studies were considered clinically comparable, data were pooled using a random effects meta-analysis. SMD was calculated where the same outcome was reported but using different measurement tools with values of 0.2, 0.5 and 0.8 interpreted as small, medium and large effect sizes, respectively. Separate analyses were conducted for RCTs and observational studies. Study heterogeneity was examined using the Cochran Q test and quantified with I^2 statistic (statistical heterogeneity indicated by χ^2 test, $p<0.10$ and an I^2 statistic >50%). All analyses were conducted using STATA V.16 (StataCrop) statistical software.

Results from the Short Form Health Survey (SF-36 or SF-12) can be reported as either two component scores, (physical/mental) or as eight subscales. To allow synthesis of results, where results were reported as the eight subscales they were transformed into the two component scores following the method used by Matcham *et al*.[18]

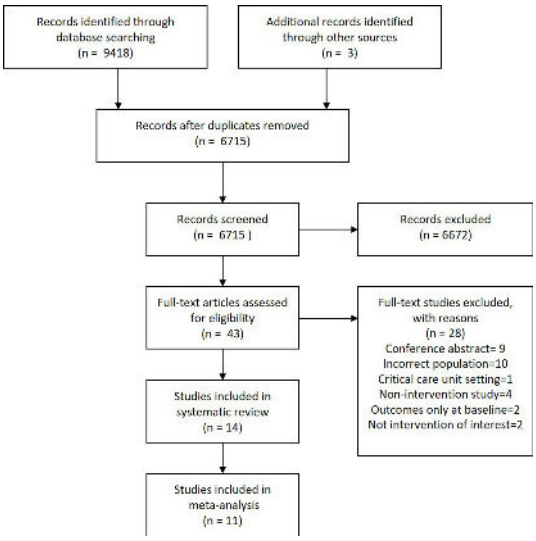

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram describing study selection.

Risk of bias and quality of evidence across studies

Grades of Recommendation, Assessment, Development and Evaluation system (GRADE)[19] was used to assess the overall quality of evidence across studies separately for the primary and main secondary study outcomes.

Additional analyses

If possible, subgroup and stratified analyses, meta-regression and assessment of small study bias will be investigated as prespecified in the protocol (online supplemental file 1).

Patient and public involvement

The need for the systematic review of rehabilitation interventions, and identification of important outcomes for the systematic review, were developed from a patient and public involvement event involving survivors, relatives and clinicians.[13]

RESULTS

Study selection

The search identified 6715 unique articles. After screening titles and abstracts, 43 full-text articles were screened, of which 14 studies were included for analysis.[20–34] Studies excluded at the full-text stage are listed with reasons in online supplemental table 2. Figure 1 presents the study flow chart and reasons for exclusion in the full text screening. Two registered ongoing trials were identified.[35 36]

Study characteristics

Study characteristics of the 14 included studies are described in online supplemental table 1.

Three RCTs (total 393 participants) and 11 observational studies (total 328 participants) were included. Nine studies

A

Study author, year	Risk of bias domains: Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of bias
Cowan, 2001	-	?	-	?	?	-
Dougherty, 2004	+	?	+	-	?	-
Moulaert, 2015	+	+	+	+	?	?

+ = Low risk; ? = Some concerns; - = High risk

B

Study Author, year	Quality assessment domains: Research question	Eligibility criteria	Representativeness of participants	Eligible participants enrolled	Sample size	Intervention	Outcome measures	Blinding of outcome assessors	Loss to follow-up	Statistical measures	Multiple outcome measures taken	Group level statistical analysis
Burke, 2005	+	-	+	-	-	-	+	-	+	-	-	?
Dougherty, 2008	+	+	+	-	-	+	+	-	+	+	-	?
Dougherty, 2019	+	+	+	+	+	+	+	-	+	+	+	?
Fertl, 2000	+	+	+	+	-	-	+	-	?	+	-	?
Howell, 2013	+	+	+	+	+	-	+	-	?	+	-	?
Kim 2014	+	+	+	?	-	+	+	-	+	+	-	?
Kim, 2016	+	+	+	-	-	+	+	-	+	+	-	?
Mion 2019	-	-	+	?	-	+	+	-	+	+	-	?
Schmidt, 1997	+	+	+	-	-	-	+	-	+	+	-	?
Shah 2007	+	+	+	+	-	-	+	-	+	-	-	?
Tazopoulou, 2016	+	+	+	?	-	-	+	-	+	+	-	?

+ = Yes; ? = Cannot determine, not applicable, not reported; - = No

Figure 2 Quality assessment and risk of bias, review authors judgements about quality assessment and risk of bias for each included study. (A) Summary based on 'RoB 2: a revised tool for assessing risk of bias in randomised trials'. (B) Summary based on 'Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group'.

investigated outpatient or community-based rehabilitation interventions of which three were RCTs. Five studies investigated inpatient rehabilitation for acquired brain injury, all were observational studies. Considering the very different CA survivor populations and intervention settings, the results for outpatient or community-based rehabilitation studies and inpatient rehabilitation for acquired brain injury are presented separately. Study follow-up period ranged from 1 to 24 months. One study[25] had CA survivors in both arms of the RCT receiving the same intervention, hence, data from both arms were combined and treated as one observational study (data obtained from study authors).

Risk of bias within studies

Risk of bias assessments are summarised in figure 2A,B. Of the three included RCTs,[21–23 31] Moulaert *et al*[31] was assessed as having 'some concerns' and the two other studies[21–23] were assessed having a 'high risk' of bias in the overall risk of bias assessment. Ten of the 11 observational studies had multiple high risk of bias domains.

Results of individual studies

A summary of the results of the individual studies is reported in online supplemental table 1.

Synthesis of results

Health-related quality of life

In total, two RCTs[22 23 31] and four observational studies[24 25 30 34] measured HRQoL.

HRQoL meta-analysis

Two RCTs[22 23 31] evaluated the effectiveness of a rehabilitation intervention compared with standard care. The

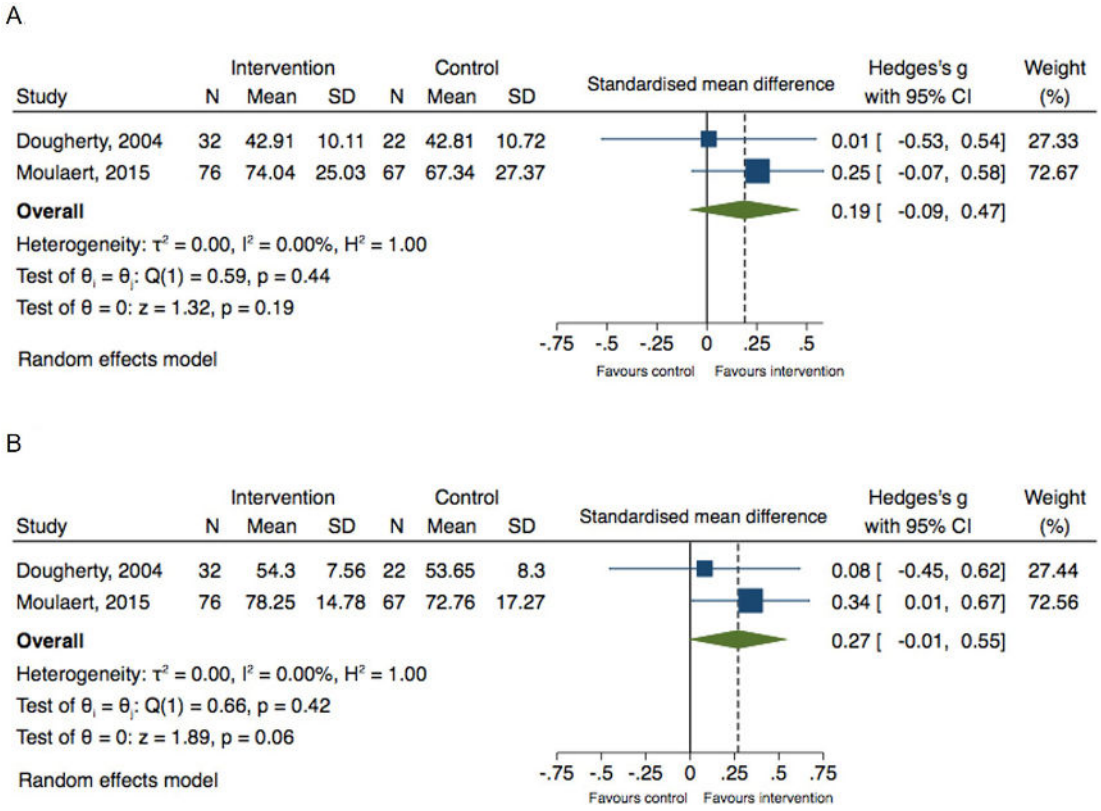

Figure 3 Forest plots for outpatient/community-based rehabilitation for cardiac arrest survivors compared with standard intervention, effect on health-related quality of life as measured by SF-12 or SF-36 (Short Form Health Survey) at 12 months follow-up. (A) Physical Component Score, (B) Mental Component Score

random effects meta-analyses showed from baseline to 12 months follow-up, no statistically significant effectiveness of rehabilitation interventions in physical HRQoL, overall SMD 0.19, (95% CI: −0.09 to 0.47, p=0.19), I^2=00.0% or mental HRQoL, overall SMD 0.27, (95% CI: −0.01 to 0.55, p=0.06), I^2=0.00% (figure 3A,B).

Two observational studies[25 30] could be pooled and a significant improvement in physical HRQoL was observed 6 months after baseline assessment, overall SMD 0.95, (95% CI: 0.64 to 1.27, p<0.001), I^2=0.00%, p<0.001 (figure 4A), however, no improvement in mental HRQoL was observed with an overall SMD 0.80, (95% CI: −0.45 to 2.05, p=0.21), I^2=90.17% (figure 4B).

HRQoL studies not included in meta-analysis

Due to clinical heterogeneity, two observational studies[24 34] reporting on HRQoL were not included in the meta-analysis. One study,[24] involving exercise-based rehabilitation, showed a non-significant increase in physical HRQoL at 8 weeks follow-up (44.33 points (SD 10.77) to 47.19 (SD 9.11), p=0.19) and mental HRQoL (51.33 (SD 11.68) to 55.03 (SD 8.04), p=0.48). A second observational study[34] involving a community-based rehabilitation intervention for CA survivors with acquired brain injury showed a significant increase in HRQoL at 2 months follow-up (Quality of Life after Traumatic Brain Injury Satisfaction scale mean score, 82.25–89.95 points, p=0.015).

Neurological function

Neurological function was used as an outcome in one RCT[31] and six observational studies.[20 26 27 32–34]

The RCT[31] showed an outpatient rehabilitation intervention had no significant effectiveness in improving cognitive function on performance-based cognitive tests compared with standard care at any follow-up point.

Neurological function meta-analysis

Five observational studies[20 26 27 32 33] were included in a meta-analysis. This showed rehabilitation significantly increased clinician-reported function, overall SMD 0.71, (95% CI: 0.45 to 0.96, p<0.001), I^2=17.36%, between admission and discharge for CA survivors with acquired brain injury (figure 5). Howell *et al*[27] was removed in a sensitivity analysis as the population were all in a vegetative or minimally conscious state with the lowest possible Functional Independence Measure (FIM) score of 18. This resulted in a larger overall SMD 0.89, (95% CI: 0.56 to 1.22, p<0.001), I^2=0.00 (online supplemental figure 1). In an analysis with the three observational studies[20 32 33] using FIM as their outcome, rehabilitation interventions showed an improvement in total FIM, overall MD of 28.24 points (95% CI: 16.33 to 40.15, p<0.001), I^2=0.00%, between admission and discharge (figure 6).

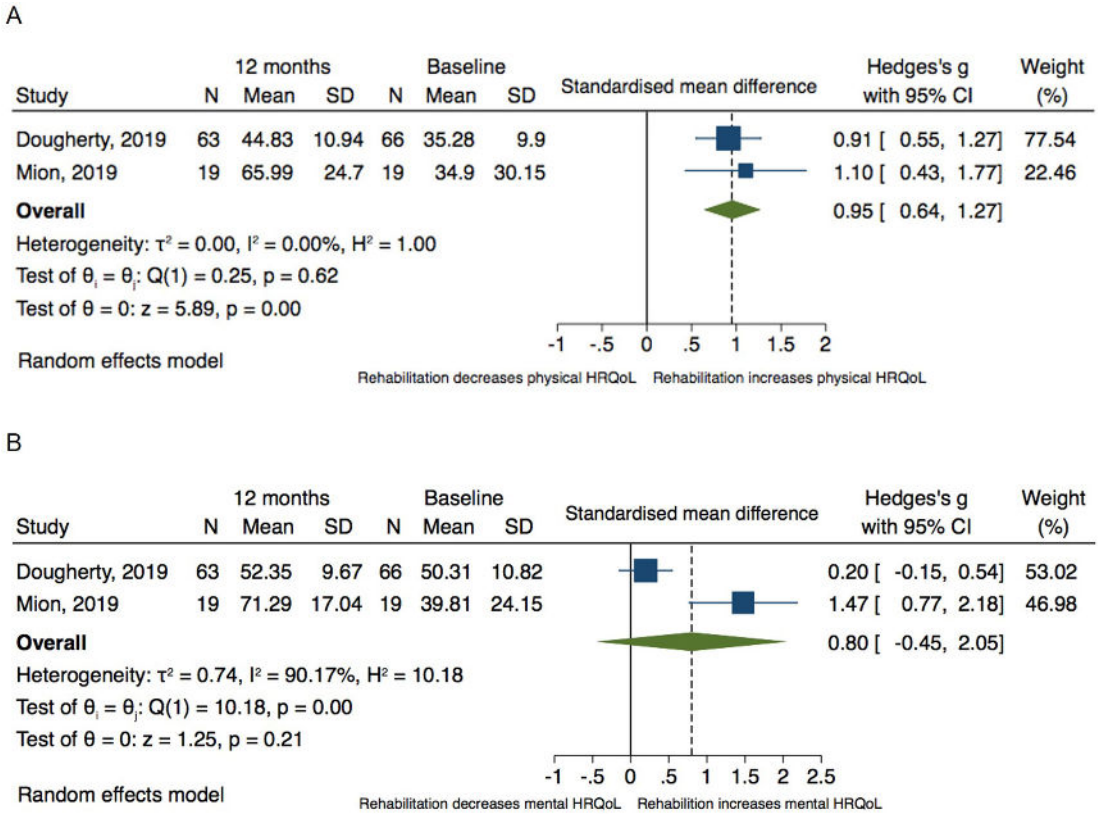

Figure 4 Forest plots for outpatient/community-based rehabilitation for cardiac arrest survivors, effect on health-related quality of life (HRQoL) as measured by SF-12 or SF-36 (Short Form Health Survey) between baseline and 6 months follow-up (A) Physical Component Score, (B) Mental Component Score.

Neurological function data not included in meta-analysis

One observational study[34] showed no significant change in neurological function after a community-based rehabilitation intervention for acquired brain injury. Further, Howell *et al*[27] found by discharge, 6.2% of CA survivors with acquired brain injury in a vegetative or minimally conscious state achieved a good neurological functional outcome (defined as Glasgow Outcome Scale category 4–5). Cognition, specifically executive function, is the primary outcome in one ongoing trial,[36] with results due in 2024.

Survival

Survival was used as an outcome in one RCT.[21] The study found no statistically significant reduction in risk of all-cause mortality (62% risk reduction, p=0.13, CI not stated). However, a statistically significant decrease in risk of cardiovascular death was found in favour of those who were allocated to the rehabilitation intervention (86% risk reduction, HR=0.14; p=0.03, CI not stated) one death in the intervention group due to stroke, six out of seven deaths in control group due to CA.

Rehospitalisation

No study reported on rehospitalisation.

Safety (serious and non-serious adverse events)

Reported in two observational studies[24 28] involving exercise-based rehabilitation. No serious or non-serious events were reported in either study.[24 28]

Psychological well-being

Psychological well-being was reported in one RCT[31] and three observational studies.[24 25 34] No meta-analysis was

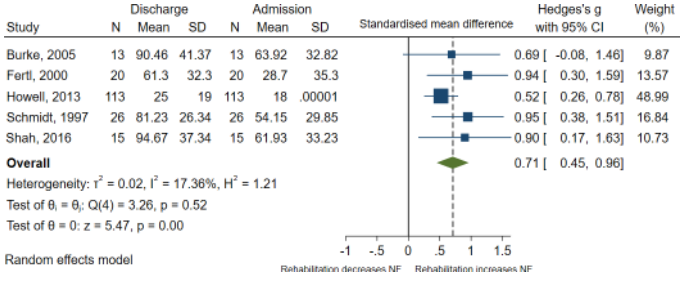

Figure 5 Forest plot for effect of inpatient rehabilitation on neurological function (NF) between admission and discharge.

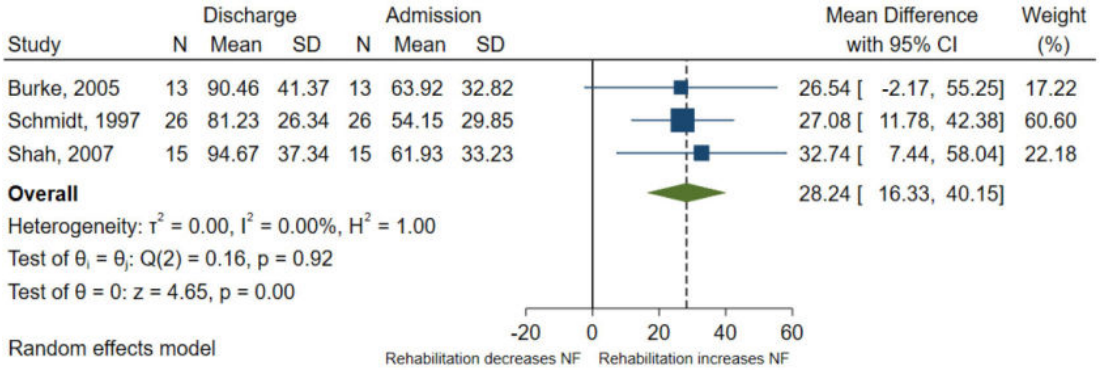

Figure 6 Forest plot for effect of inpatient rehabilitation for cardiac arrest survivors with acquired brain injury on neurological function (NF) between admission and discharge as measured by the Functional Independence Measure (scale: 18–126 points, with higher scores indicating better function).

possible due to clinical heterogeneity between studies. All studies used self-reported symptom measurements and not a medical diagnosis of psychological well-being.

The RCT[31] found that education-based rehabilitation had a positive effect on total anxiety and depression (p=0.002) and anxiety subscale (p<0.001) compared with standard care at 1-year follow-up.

An observational study[25] found that an education/psychological support-based intervention had a reduction in anxiety (32.10 points (SD 11.03) to 28.57 (SD 9.65)) and depression (5.46 points (SD 4.37) to 3.7 (SD 3.89)) between baseline and 3 months. This was maintained at 12 months follow-up (28.87 (SD 10.62) and 3.36 (SD 4.29), respectively). An exercise-based rehabilitation intervention observational study[24] found a non-significant reduction in anxiety (31.56 (SD 11.83) to 28.22 (SD 9.68), p=0.06) and depression (11.00 (SD 13.08) to 9.22 (SD 11.88), p=0.46) from baseline to 8 weeks follow-up . An observational study involving a community-based rehabilitation intervention for acquired brain injury showed no statistically significant change in anxiety or depression from baseline to 2 months follow-up.[34]

Fatigue

One observational study[29] found between baseline and study end (3–5 weeks) of an energy conservation and problem solving therapy intervention, a significant decrease in self-reported total (p<0.001), physical (p=0.001) and cognitive (p=0.006) fatigue, with small to moderate effect sizes (r=0.23–0.25). Fatigue is the primary outcome in one ongoing trial,[35] with results due in 2021.

Exercise and physical capacity

Reported in two observational studies.[24 28] Meta-analysis of the two studies found that an 8-week exercise-based rehabilitation intervention significantly increased exercise duration (MD 3.72 min (95% CI: 0.49 to 6.95, p=0.02), I^2=42.61% but not exercise capacity, overall SMD 0.41, (95% CI: −0.23–1.04, p=0.32), I^2=0.00% (online supplemental figures 2 and 3).

Daily activity was reported in one observational study.[28] Measured by RT3 accelerometer, it increased after an 8-week exercise-based rehabilitation intervention and continued to increase at 6-month follow-up (baseline 143.02 vector magnitude/minute (vm/min) (SD 41.44), 8 weeks 230.0 vm/min (SD 121.78), 6 months 289.89 vm/min (SD 8.99), p=0.17).

Risk of bias and quality of evidence across studies

Quality of evidence (GRADE) for both the primary and main secondary outcomes, HRQoL and neurological function, was assessed as low for the RCTs and very low for the observational studies. Reasons for downgrading of evidence are described in the Summary of findings tables (online supplemental tables 3 and 4).

Heterogeneity between studies

Possibility for meta-analyses in this study was limited due to the heterogeneity in CA survivors populations, rehabilitation interventions and outcomes (online supplemental table 1).

Additional analyses

A priori, we planned several univariate meta-regression analyses,[37] subgroups analyses and investigation of small study bias (see protocol, online supplemental file 1). However, due to the limited number of included studies, all of these analyses were not conducted, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[37]

DISCUSSION

This study systematically investigated the effectiveness of rehabilitation interventions for CA survivors. Overall, quality of the body of evidence of these interventions is low or very low. Eleven of the 14 studies were observational and cannot determine the cause and effect of an intervention, but can only show the associated change in outcomes between one time point and another. The overall risk of bias of the three included RCTs ranged from ‘some concerns’ to ‘high risk of bias’ (figure 2A).

Analysis of these RCTs showed no significant effect on HRQoL or neurological function with one RCT showing a positive effect on anxiety and depression (psychological well-being). The included observational studies suggested some associated positive change in outcomes, but the quality of the body of evidence was generally low (figure 2B) with the majority having small or very small sample sizes and insufficient description of the content of the rehabilitation interventions. Hence, all of the findings should be interpreted with caution as additional evidence is needed and could substantially impact the interpretation of the results.

The meta-analysis of RCTs found no significant effect for rehabilitation interventions on HRQoL. However, it should be noted that only two RCTs[22 23 31] were included in this pooled analysis. The RCT by Moulaert *et al*,[31] taken on its own, reported a significant effect on HRQoL compared with control in three out of eight SF-36 domains (online supplemental table 1). Our findings on HRQoL, being mindful of the low number of included RCTs, are largely in agreement with an earlier systematic review of similar education-based rehabilitation interventions for patients with coronary heart disease.[15] While the review authors found some evidence for greater HRQoL in some domain scores, overall, they found no definite evidence for better HRQoL after education in comparison to control.

A meta-analysis of two observational studies[25 30] showed a significant associated increase in physical HRQoL. However, as is inherent to the study design, neither of the studies had a control group. From the control arms in the two RCTs,[22 23 31] we see that CA survivors receiving standard care also seem to improve over time (mean 12.8 points improvement in physical HRQol, online supplemental table 3). Thus, demonstrating the importance of using control group trial designs to determine the real effectiveness of rehabilitation interventions in this population.

Our main secondary outcome was neurological function. The only RCT[31] to report neurological function found no effect of an outpatient intervention compared with usual care on cognitive function, however, Moulaert *et al*[31] state that this was expected as the intervention did not include cognitive training. In the observational studies, inpatient rehabilitation was associated with improvements in neurological function for CA survivors with acquired brain injury (figure 5). Three of the studies[20 32 33] reported total FIM (figure 6). The total FIM minimal clinically important difference (MCID) has not been described for CA survivors, but in patients who had a stroke, the MCID has been shown to be an improvement of ≥22 points.[38] Hence, the pooled mean improvement of 28.24 points found in this study would indicate inpatient rehabilitation provides a clinically significant improvement in neurological function for CA survivors. However, none of the studies had control arms, and all had several high risk of bias domains including insufficient description of intervention or small sample sizes. This review found very few studies aimed at improving neurological function including cognition for CA survivors. However, one ongoing RCT was found investigating a computer-based intervention to improve executive function with results due in 2024.[36]

Survival was only reported in one study[21] that was judged to be of high risk of bias with missing data, therefore, no conclusions on the effect of rehabilitation on survival can be made. By definition, rehabilitation helps people to achieve and maintain optimum functioning in interaction with their environments.[7] Hence, survival would not seem to be a primary outcome for rehabilitation for CA survivors.

Two small observational studies[24 28] reported exercise-based rehabilitation interventions as safe for CA survivors. The reporting of no serious or non-serious events is in agreement with earlier studies exploring safety during moderate or high intensity exercise training for people with cardiovascular disease[39–41] or implantable cardioverter defibrillators.[42] However, both included studies had very small populations (8 and 10 participants) and much larger study populations are needed to establish the safety of exercise for CA survivors.

Psychological interventions have been shown to reduce anxiety and depression in patients with coronary heart disease.[43] The RCT by Moulaert *et al*[31] found a reduction in total anxiety and depression although their intervention provided primarily education and screening for cognitive/emotional problems rather than psychological focused interventions. Education on the consequences of CA along with insight into their cognitive/emotional problems may have led to the participants' improved psychological state. Alternatively, participants in the intervention group could be referred for additional specialist support. However, we do not know what proportion of participants received additional specialist psychological support or how this may have influenced the results.

This is the first systematic review and meta-analysis to assess the effectiveness of rehabilitation interventions for CA survivors. Its strengths lie in the comprehensive literature searches, inclusion of both RCTs and observational studies, and the included wide range of outcomes relevant to CA survivors. Nevertheless, there are a number of limitations. In order to pool the HRQoL data, the SF-36 scores from two studies[30 31] were transformed from subscales to component scores. Some overlap in physical/mental domains between the eight subscales has been noted when using this transformation method.[18] Therefore, transformed scores may not completely represent the original study results.[18] We included two studies with populations of CA survivors and people with anoxic brain injury due to other causes (45%[34] and 42%[32] participants with anoxic brain injury other causes) where CA survivors subgroup data were not available. Including non-CA survivors may have influenced the results, however, we deemed the inclusion of these studies as important considering the paucity of data available. The effect of including studies with mixed populations on this review's

results is difficult to determine without greater examination of the aetiology and secondary consequences of the other non-CA causes of anoxic brain injury. However, Schmidt *et al*[32] showed a similar change in FIM to two of the studies[20 33] that only included CA survivors (figure 6).

Our primary outcome, HRQoL, is an important outcome in rehabilitation research.[7] However, the choice of generic or disease-specific HRQoL measures may influence the results as generic measures of HRQoL can be crude with important details lost and large sample sizes required to demonstrate effect.[4 44 45] In this review, all studies except one[34] used generic measures of HRQoL.

Another element that potentially influenced our findings may be the standard care received by the RCT control groups. Two[21–23] of the included RCTs provided educational elements to both the intervention and control groups and in a third[46] participants could have received cardiac rehabilitation.

The high heterogeneity found between studies, limiting meta-analysis, may be explained by the wide range of physical, neurological and psychological problems suffered by CA survivors.[1 3–6] Most CA survivors will have a new or ongoing cardiac condition,[1] and therefore, be eligible for cardiac rehabilitation.[47] Neurological rehabilitation has been recommended to meet the 'brain' aspect of CA recovery.[3 48] This can be mild cognitive impairments in self-caring CA survivors[49] or more severe brain injury needing long-term residential care.[3] Hence, different CA survivor populations lead naturally to the selection of different rehabilitation interventions and study outcomes.

Implications for future research and clinical practice

The majority of studies found by this systematic review were observational. Given their potential risk of bias and no control group, we recommend no further observational studies focusing on the question of effectiveness are conducted but instead there is a need for high-quality RCTs comparing rehabilitation interventions for CA survivors to standard care alone. Considering the small population of CA survivors, multicentre RCTs should be considered to achieve a sufficient sample size to determine an effect on specific outcomes. In view of the wide range of potential consequences after CA, future studies might also consider investigating interventions that target a single consequence of CA, for example, fatigue, or whether interventions should be multicomponent. A minimum outcome set for these future rehabilitation RCTs should include those recommended by COSCA (Core Outcome Set for Cardiac Arrest),[4] HRQoL and neurological function, and consider including disease-specific outcomes. However, more research is needed to identify outcomes and measurement tools that reflect the range of rehabilitation needs of CA survivors. Agreement on a CA survivors' rehabilitation core outcome set would facilitate subsequent meta-analysis of study results providing a stronger body of evidence on rehabilitation after CA. Further, it is essential future RCTs use agreed reporting guidelines such as CONSORT (Consolidated Standards of Reporting Trials)[50] or TIDieR (Template for Intervention Description and Replication)[51] to detail the complex rehabilitation interventions under investigation. This systematic review has focused primarily on impairment and function outcomes and less on activity and participation. Hence, future systematic reviews on this subject could consider including these outcomes.

Based on the low quality of the body of evidence, clinical rehabilitation guidelines should continue to be consensus based.[1 10 11] In clinical practice, rehabilitation interventions should be offered based on these consensus-based recommendations with ongoing monitoring of clinical outcomes. The documented secondary physical, neurological and psychological consequences of CA for survivors are so comprehensive[1 3–6] that we as clinicians must meet these needs in current clinical practice.

CONCLUSIONS

Given the overall low quality of evidence, this review cannot determine the effectiveness of rehabilitation interventions for CA survivors on HRQoL, neurological function or other included outcomes, and recommend further high-quality studies are conducted. In the interim, existing clinical guidelines on rehabilitation provision after CA should be followed to meet the high burden of secondary consequences suffered by CA survivors.

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Acknowledgements LHT is currently funded by a grant from the Danish Regions and The Danish Health Confederation through the Development and Research Fund for financial support (project no. 2703) and a grant from Region Zealand, Denmark (Exercise First).

Contributors Conception of study: VLJ, RST, ADZ and LHT. Preparation of protocol: VLJ, JC, RST, ADZ and LHT. Study selection: VLJ, JC, EL and LHT. Data extraction, data analysis and risk of bias assessment: VLJ, JC and LHT. Writing of the manuscript, review and editing: VLJ, JC, EL, RST, ADZ and LHT. The final manuscript was approved by all authors.

Funding This study was supported by infrastructure provided by REHPA, Danish Knowledge Centre for Rehabilitation and Palliative Care, Odense University Hospital which receives funding from the Danish Government. This study is part of a PhD partially funded by a PhD Faculty scholarship (no grant number) from the University of Southern Denmark and a stipendium from the Region of Southern Denmark (19/15041).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Appendix 3b:

Supplementary material for paper 3

Appendix 3b. Systematic review: Supplementary data 1

PROSPERO Protocol

Citation

Vicky Joshi, Jan Christensen, Esben Lejsgaard, Ann-Dorthe Zwisler, Rod Taylor, Jørgen Feldbæk Nielsen, Lars Tang. Non-pharmacological rehabilitation interventions for survivors of cardiac arrest: a systematic review and meta-analysis. PROSPERO 2018 CRD42018110129 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018110129

Review question

What is the effectiveness of non-pharmacological rehabilitation interventions on adult cardiac arrest survivors?

Searches

The following electronic databases will be searched: MEDLINE, EMBASE, CINAHL, PsycINFO, AMED, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled trials (CENTRAL) and Web of Science (up to April 2021 without any restriction in publication date or language).

Trial registries ISRCTN and the WHO ICTRP search portal, and the database ClinicalTrials.gov will be used to search ongoing trials relevant to the review, identify unpublished work, and describe upcoming publications within the studied area. The Cochrane Database of Systematic Reviews will be searched to identify former reviews that identify possible studies for inclusion. These will be screened for eligibility in the same manner as all other studies identified during the database searches.

The search matrix will consist of a combination of relevant indexed terms (e.g. MeSH, Subject Headings or Thesaurus terms), keywords and synonyms for: 1) cardiac arrest, and 2) non-pharmacological rehabilitation interventions.

Title and abstracts from the following conferences will be hand searched: ‘European Resuscitation Council Congress’, ‘American Heart Association’ and American College of Cardiology (all from 2009), and the ‘Post-cardiac arrest conference’ (from 2013).

To identify studies that were not captured by the search matrix, forward and backward citation searching will be conducted on all papers included after full-text screening by two authors (VLJ and MA). Backward citation searching involves screening the references in papers identified after full-text screening. Forward citation searching, searches papers that have cited any papers found after full test screening. References will be hand-searched and citations will be searched for via Web of Science. Titles will be screened for eligibility. Abstracts of possible eligible studies will be screened for eligibility as per all other studies identified during the original database searches.

The first and last authors of unobtainable studies or studies with missing data will be contacted.

Types of study to be included

Included:
- Randomised controlled trials using individual, cluster or any design including parallel group, cross overallocation trials, including pilot studies. - Non-randomised controlled trials
- Prospective and retrospective observational studies with or without a control group.

Excluded:
- Case reports

Condition or domain being studied

The number of people surviving a cardiac arrest is increasing due to improvements in bystander resuscitation and acute hospital care. However, following a cardiac arrest up to half of survivors experience cognitive, psychological and physical problems. These secondary problems plus the underlying cardiac condition present in the majority of cardiac arrest survivors may impact on survivors' well-being and healthrelated quality of life. Non-pharmacological rehabilitation interventions have been recommended in international guidelines but the effect of these interventions remains unknown. A recent investigation into the outcomes for testing effectiveness of interventions for cardiac arrest survivors, by the COSCA initiative (core outcome set for cardiac arrest), recommended three measures be used: survival at 30 days or hospital discharge, neurological function and health-related quality of life (1).

For reference list, see additional information section.

Participants/population

Studies investigating adults, over the age of 18, of both sexes, and all ethnicities who have survived a cardiac arrest will be eligible for inclusion.

Studies that include both survivors of cardiac arrest, and people with cardiac disease without cardiac arrest will be managed in the following way; all trials that present data for cardiac arrest survivors in a subgroup will be included. Where data is not presented in a sub-group, we will contact trial authors to ascertain separate data on the survivors of cardiac arrest. If it is not possible to ascertain subgroup data and only pooled data is available, the study will only be included if at least 50% of participants were survivors of a cardiac arrest.

Intervention(s), exposure(s)

Studies investigating any non-pharmacological rehabilitation intervention for survivors of cardiac arrest, will be considered eligible for inclusion. Non-pharmacological interventions refers to interventions that are not primarily surgically or pharmacologically based or do not involve invasive technology. There will be no restrictions related to length of intervention, timing of intervention or timing of follow-up. The intervention may be a single session or a series of sessions. It may be provided one-to-one or in a group of survivors. Most cardiac arrest survivors have an underlying cardiac condition and hence cardiac rehabilitation intervention studies that include cardiac arrest survivors will be considered as a non-pharmacological intervention and included in this review. The cardiac rehabilitation may be exercise-based, psychological-based, education based or comprehensive in nature.

Exclusion criteria:

1. All studies reporting on effectiveness of medical, surgical or invasive technology interventions will be excluded.

2. Interventions in the emergency room or critical care unit will be excluded.

3. Studies that do not report results at baseline and at minimum one follow-up point after intervention.

Comparator(s)/control

Comparator can include no treatment, active control, usual care, or where the intervention is in addition to another non-pharmacological intervention (for example, as an add on to exercise rehabilitation) or no comparator.

Context

The intervention may take place in any setting: in the hospital (but not while in the emergency room/critical care unit), outside the hospital, at survivors' home or may start in hospital and continue following discharge from hospital or via telemedicine.

Main outcome(s)

The outcomes are based on the those recommended by the COSCA initiative (1). The primary outcome will be health-related quality of life. Measures of health-related quality of life outcomes will include generic or disease-specific patient reported outcome measures. The outcome measure can be a single-item tool (e.g. 'How would you rate your overall quality of life?') or a multi item tool (examples include 36-item Short Form Health survey and EuroQoL five dimensions questionnaire). For multi component/dimensional outcome measures a subscale which contains health-related quality of life will be favoured over the overall score of the measurement even if the overall score reflects health-related quality of life.

Main secondary outcome: neurological function. Measures of neurological function measure the level of disability after a neurological event. Included measures may primarily test cognitive ability (for example the Mini-mental state examination) or may combine cognitive and physical ability hence measuring global disability (for example the Modified Rankin Scale). Measures may be clinician reported (for example the Cerebral Performance Category or Glasgow Outcome Scale –Extended) or observer reported (for example the Informant Questionnaire on Cognitive Decline in the Elderly, completed by relatives or carers) or patient reported (for example Two-simple questions).

Measures of effect

It has been suggested that outcomes for cardiac arrest survivors evolve over time and survivors should be reassessed at 30-days, 60-days and one-year after arrest (1, 2). Hence, data will be extracted at all time points that are the nearest possible to the recommended follow-up points (1) (survival at 30 days or hospital discharge, three-month follow-up and longest follow up point) to discern if outcomes change over time.

Additional outcome(s)

Secondary outcomes:

1. Survival at 30 days or hospital discharge (if both are reported, survival at 30 days will be favoured over survival at hospital discharge), and one year. Mortality due to any cause, but if proportion due to cardiac cause is available this will be reported.

2. Re-hospitalization (all cause and the proportion due to cardiac cause if available)

3. Serious adverse events: defined as resulting in death or re-hospitalization causing significant disability ,including cardiovascular complications such as cardiac arrest or any arrhythmia with hemodynamic compromise.

4. Non-serious adverse events for example musculoskeletal injury, palpitations, or dizziness.

5. Psychological well-being: measured by patient reported symptoms of anxiety, depression, post-traumatic stress disorder or stress. The outcome measure can be a single-item tool (for example 'How would you rate your overall psychological well-being?') or a multi item tool (for example the Hospital Anxiety and Depression Scale).

6. Fatigue outcomes: measured by patient reported outcomes such as the Fatigue impact scale. Measures may be disease specific or generic and multi-component/dimensional. For multi component/dimensional outcome measures a sub-scale which contains fatigue will be favoured over the overall score of the measurement even if the overall score reflects fatigue.

7. Exercise capacity: measured by aerobic fitness. This will include any objective measure of the ability of the heart and lungs to get oxygen to the muscles where it can be consumed. This could be maximal or peak oxygen consumption. A change of the aerobic fitness could be an increase in peak oxygen consumption (VO2peak) obtained from a maximal cardiopulmonary exercise test or as a decrease in sub-maximal oxygen uptake at a given work load, or a decrease of sub-maximal heart rate at a given work load.

8. Physical capacity: measured by self-reported questionnaires, single item questions or objectives measures for example activity monitors or step counters.

Data extraction (selection and coding)

Selection of studies will be done by merging all search results into the technology platform, Covidence. Duplicates will be removed before two authors (VLJ and MA) will independently screen titles and abstracts followed by full-text screening of potentially eligible studies. Any disagreements will be discussed and resolved with a third review author (JC). For randomised controlled crossover trials data will be handled as it would have been a randomised controlled trial and therefore data will be extracted for baseline and from the assessment of effect from the first period (data from after the cross-over will not be extracted).

A standardised pre-piloted form will be used to extract data from all the included studies.

The following data will be extracted if it is relevant in terms of study design (observational vs randomised controlled studies) by two independent reviewers (VLJ & MA):

1. Source of study and author contact details

2. Study design, study duration, setting and country.

3. Participant characteristics: age, sex, cause of cardiac arrest, place of cardiac arrest, cardiac arrest circumstances, health-status of participants including details of any ongoing cardiac condition (for example myocardial infarction), in hospital interventions and whether they received targeted temperature management and/or an implantable cardioverter defibrillator.

4. Number of groups and number of participants in each study, and study arm.

5. Description and components of rehabilitation intervention and any control, length of intervention, dose and frequency.

6. Theory or mechanism of the study intervention.

7. Which primary and secondary outcomes as defined above are present and time points of outcomes.

8. For each outcome of interest: sample size, estimate of effect and confidence interval; p value and subgroup analyses.

9. Information for assessment of risk of bias.

Any discrepancies in data extraction will be investigated and discussed, then if necessary resolved with a third review author (JC).

Risk of bias (quality) assessment

Two review authors (VLJ & MA) will independently assess the risk of bias in included studies. RoB 2.0 tool for randomised controlled trials ROBINS-I (risk of bias in non-randomised Studies – of Interventions) will be used to assess risk of bias in observational studies.

Risk of bias will be assessed for each outcome within each study. While some items are generic across outcomes, where potential differences may occur (for example between subjective and objective measures), outcomes will be assessed separately and may be judged at a different level of bias within the same study.

Any disagreements between review authors will be discussed and resolved with a third review author (JC).

Strategy for data synthesis

Results from the different study designs will be presented and pooled separately.

We will undertake a meta-analysis where two or more trials are similar enough clinically and statistically for pooling of trials to be appropriate. Where there is high heterogeneity between studies or inappropriate quantitative reporting of outcomes, a narrative synthesis of outcomes from included studies will be provided.

If it is possible to conduct a meta-analysis a random effects meta-analysis will be used given the likely presence of some clinical heterogeneity across studies. Continuous data will be expressed as the mean difference (MD) or standardized mean difference (SMD) and their respective confidence intervals (CI) will be calculated.

For dichotomous outcomes (serious and non-serious adverse events) and for outcomes of observational studies relative risk ratios (RR) along with a CI will be calculated using random effects meta-analysis.

For time to even outcome (survival, re-hospitalization) hazard ratios will be pooled if presented.

Statistical heterogeneity of the study results will be examined using Cochran Q test and quantified with I^2 values and the between study variance I^2. Qualitative assessment of heterogeneity will be assessed by comparing the characteristics of included studies. Assessment of small study bias will be assessed by calculating an Egger's test score and illustrated with a funnel plot. If small study bias is present defined by a positive Egger's test, a metatrim analysis will be conducted.

If the included studies need network meta-analysis to be pooled this will be performed, as described in chapter 16.6.3 of the Cochrane Handbook.

The confidence in estimates of the effects of interventions will be assessed using the Grading of Recommendation, Assessment, Development and Evaluation system (GRADE).

The paper will be reported according to the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guidelines.

Analysis of subgroups or subsets

If possible, we will carry out the following subgroup and stratified analyses to explore heterogeneity of the studies. Location of cardiac arrest (in versus out-of-hospital).

1. Mode of delivery of intervention (supervised vs non-supervised).
2. Provision of intervention (individual vs group based).
3. Content of rehabilitation, single component (for example: exercise-based/education-based/psychological based) vs comprehensive.
4. Received an implantable cardioverter defibrillator vs did not receive an implantable cardioverter defibrillator.
5. Random sequence generation (low/some concerns/high); random sequence concealment (low/some concerns/high).
6. Overall risk of bias (low/some concerns/high).
7. Length of intervention (single session vs 1-6-weeks vs over 6-weeks) 8. Duration of trial follow-up (1-12 weeks vs 13-24 weeks vs over 24 weeks).
9. Setting of trials (single vs multicentre).
10. Continent of publication.
11. Self-reported cognitive ability vs self-reported cognitive and physical ability.

12. Clinician reported cognitive ability vs observer reported vs self-reported.

Meta-regression will be carried out to investigate the effect of continuous variables including age, sex distribution and all sub-group analyses listed above.

Contact details for further information

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Organisational affiliation of the review

Danish Knowledge Centre for Rehabilitation and Palliative Care
http://www.rehpa.dk/

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Professor Jørgen Feldbæk Nielsen. Aarhus University, Hammel Neurocenter Denmark
Dr Lars Tang. Danish Knowledge Centre for Rehabilitation and Palliative Care

Type and method of review

Intervention, Meta-analysis, Systematic review

Anticipated or actual start date

01 November 2018

Anticipated completion date

31 July 2021

Funding sources/sponsors

Funding for the writing of the review protocol, data analysis and preparation of the article for publication will be provided by REHPA - Danish Knowledge Centre for Rehabilitation and Palliative Care, University of Southern Denmark.

Conflicts of interest

Language

English

Country

Denmark

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Heart Arrest; Humans; Medicine; Survivors

Date of registration in PROSPERO

11 October 2018

Date of first submission

19 September 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

11 October 2018
07 May 2021
12 May 2021
15 May 2021

Supplementary data Table 1. Search Strategy

MEDLINE	
POPULATION	INTERVENTION
heart arrest [MeSH Terms] out-of-hospital cardiac arrest [MeSH Terms] heart arrest [Title/Abstract] heart arrests [Title/Abstract] cardiac arrest [Title/Abstract] cardiac arrests [Title/Abstract] cardiopulmonary arrest [Title/Abstract]	rehabilitation [MeSH Terms] physical medicine [MeSH Terms] rehabilitation nursing [MeSH Terms] exercise [MeSH Terms] social support [MeSH Terms] psychological adaptation [MeSH Terms] cognitive behavior therapy [MeSH Terms] health education [MeSH Terms] aftercare [MeSH Terms] rehabilitation, vocational [MeSH Terms] rehabilitation [Title/Abstract] vocational [Title/Abstract] aftercare [Title/Abstract] telerehabilitation [Title/Abstract] physical medicine [Title/Abstract] exercise [Title/Abstract] exercises [Title/Abstract] physical activity [Title/Abstract] social support [Title/Abstract] psychological adaptation [Title/Abstract]) coping behavior [Title/Abstract]) coping skills [Title/Abstract]) adaptive behavior [Title/Abstract]) cognitive behavior therapy [Title/Abstract] cognitive behavioral therapy [Title/Abstract] cognitive behavior therapies [Title/Abstract] cognitive behavioral therapies [Title/Abstract] cognitive psychotherapy [Title/Abstract]
	cognitive psychotherapies [Title/Abstract] acceptance and commitment therapy [Title/Abstract] mindfulness [Title/Abstract] health education [Title/Abstract])

AMED 1985 to date	
POPULATION	INTERVENTION
(MH “Heart arrest” explode)	(MH "Rehabilitation+") (MH "Physical Medicine") (MH “Rehabilitation nursing”) (MH Exercise+) (MH Support, Psychosocial+)

	(MH Adaptation, Psychological+) (MH Cognitive therapy+) (MH Health education+) (MH After Care)
TI OR AB	TI OR AB
Heart arrests Cardiac arrest Cardiac arrests Cardiopulmonary arrest	Rehabilitation Vocational Aftercare Telerehabiliation Physical medicine Exercise Exercises Physical activity Social support psychosocial psychological adaptation coping behavior coping skills adaptive behavio* cognitive behavio#r therap* cognitive behavio#ral therap* cognitive behavioral therap* cognitive psychotherap* acceptance and commitment therapy mindfulness health education
CINAHL	
POPULATION	INTERVENTION
(MH “Heart arrest” explode)	(MH "Rehabilitation+") (MH "Physical Medicine") (MH “Rehabilitation nursing”) (MH Exercise+) (MH Support, Psychosocial+) (MH Adaptation, Psychological+) (MH Cognitive therapy+) (MH Health education+) (MH After Care)
TI OR AB	TI OR AB
Heart arrests Cardiac arrest Cardiac arrests Cardiopulmonary arrest	Rehabilitation Vocational Aftercare Telerehabiliation Physical medicine Exercise

	Exercises Physical activity Social support psychosocial psychological adaptation coping behavior coping skills adaptive behavio* cognitive behavio#r therap* cognitive behavio#ral therap* cognitive behavioral therap* cognitive psychotherap* acceptance and commitment therapy mindfulness health education
Embase 1974 to present	
heart arrest Exp out-of-hospital cardiac arrest Exp	Rehabilitation (Exp all) Physical medicine Rehabilitation nursing Exercise Social support Coping behavior Cognitive behavioral therapy Health education
Ti OR Ab Heart arrests Cardiac arrest Cardiac arrests Cardiopulmonary arrest	Ti or Ab Rehabilitation Vocational Aftercare Telerehabiliation Physical medicine Exercise Exercises Physical activity Social support psychosocial psychological adaptation coping behavior coping skills adaptive behavio* cognitive behavio#r therap* cognitive behavio#ral therap* cognitive behavioral therap* cognitive psychotherap* acceptance and commitment therapy mindfulness health education

PsychINFO 1806 to present	
All fields: Heart arrest Heart arrests Cardiac arrest Cardiac arrests Cardiopulmonary arrest	Subject headings: Rehabilitation Exercise Social support Cognitive therapy Health education Ti or Ab Rehabilitation Vocational Aftercare Telerehabiliation Physical medicine Exercise Exercises Physical activity Social support psychosocial psychological adaptation coping behavior coping skills adaptive behavio* cognitive behavio#r therap* cognitive behavio#ral therap* cognitive behavioral therap* cognitive psychotherap* acceptance and commitment therapy mindfulness health education
Web of Science	
Heart arrest Heart arrests Cardiac arrest Cardiac arrests Cardiopulmonary arrest <u>Search string</u>: (TS=Topic) TS=(rehabilitation) OR TS=(vocational) OR TS=(aftercare) OR TS=(telerehabilitation) OR TS=("physical medicine") OR TS=(exercise) OR TS=(exercises) OR TS=("physical activity") OR TS=("social support") OR TS=("psychological adaptation") OR TS=("coping behavio*") OR TS=("coping skills") OR TS=("adaptive behavio*") OR TS=("cognitive behavio*	Rehabilitation Vocational Aftercare Telerehabiliation Physical medicine Exercise Exercises Physical activity Social support psychosocial psychological adaptation coping behavior coping skills adaptive behavio* cognitive behavio#r therap*

therap*") OR TS=("cognitive psychotherap*") OR TS=("acceptance and commitment therapy") OR TS=(mindfulness) OR TS=("health education") AND TS=("heart arrest") OR TS=("cardiac arrest") OR TS=("heart arrests") OR TS=("cardiac arrests") OR TS=("cardiopulmonary arrest") OR TS=("cardiopulmonary arrests")	cognitive behavio#ral therap* cognitive behavioral therap* cognitive psychotherap* acceptance and commitment therapy mindfulness health education
The Cochrane library (SRs and CENTRAL)	
As for Medline but using CENTRAL's search builder syntax.	
International Standard Randomised Controlled Trial Number (ISRCTN)	
Cardiac arrest	
World Health organisation International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov	
(Condition) Cardiac arrest	OR (Other terms) Rehabilitation Vocational Aftercare Telerehabiliation Physical medicine Exercise Physical activity Social support psychosocial psychological adaptation coping behavior cognitive behavio#r therap* cognitive behavio#ral therap* cognitive behavioral therap* cognitive psychotherap* acceptance and commitment therapy mindfulness health education

Sample search matrix:

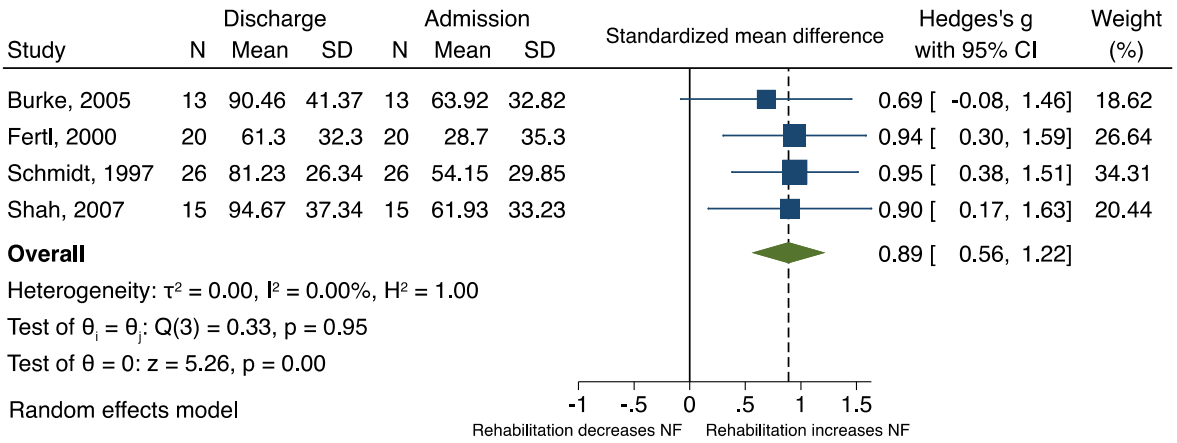
MEDLINE Search matrix:

Search ((((((((((((((((((((((((((((((rehabilitation[MeSH Terms]) OR physical medicine[MeSH Terms]) OR rehabilitation nursing[MeSH Terms]) OR exercise[MeSH Terms]) OR social support[MeSH Terms]) OR psychological adaptation[MeSH Terms]) OR cognitive behavior therapy[MeSH Terms]) OR health education[MeSH Terms]) OR aftercare[MeSH Terms]) OR rehabilitation, vocational[MeSH Terms]) OR rehabilitation[Title/Abstract]) OR vocational[Title/Abstract]) OR aftercare[Title/Abstract]) OR telerehabilitation[Title/Abstract]) OR physical medicine[Title/Abstract]) OR exercise[Title/Abstract]) OR exercises[Title/Abstract]) OR physical activity[Title/Abstract]) OR social support[Title/Abstract]) OR psychological adaptation[Title/Abstract]) OR coping behaviour[Title/Abstract]) OR coping skills[Title/Abstract]) OR adaptive behavior[Title/Abstract]) OR cognitive behavior therapy[Title/Abstract]) OR cognitive behavioral therapy[Title/Abstract]) OR cognitive behavior therapies[Title/Abstract]) OR cognitive behavioral therapies[Title/Abstract]) OR cognitive psychotherapy[Title/Abstract]) OR cognitive psychotherapies[Title/Abstract]) OR ((acceptance[Title/Abstract] AND commitment therapy[Title/Abstract]))) OR mindfulness[Title/Abstract]) OR health education[Title/Abstract])) AND (((((((heart arrest[MeSH Terms]) OR out of hospital cardiac arrest[MeSH Terms]) OR heart arrest[Title/Abstract]) OR heart arrests[Title/Abstract]) OR cardiac arrest[Title/Abstract]) OR cardiac arrests[Title/Abstract]) OR cardiopulmonary arrest[Title/Abstract])

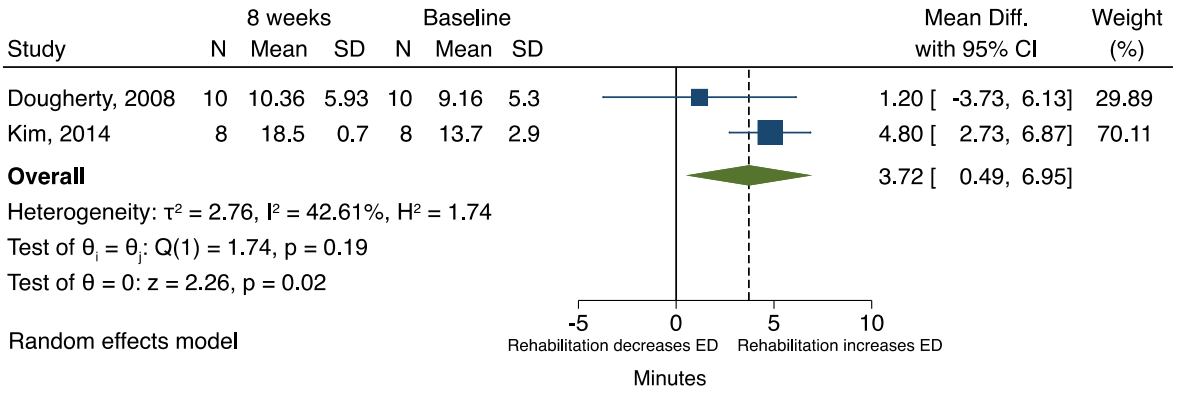
Supplementary data Table 2. Studies excluded at full text stage with reasons

Excluded study	**Reason for exclusion**
Ada, 2018	Conference abstract
Arabia, 2011	Mixed population of people who have suffered a major cardiac event
Baston, 2017	Conference abstract
Berg, 2020	Mixed population of ICDs implanted for primary and secondary prevention and authors did not have separate data on number of cardiac arrest survivors.
Bermejo, 2015	Conference abstract
Boyce, 2017	Outcome data only at baseline
Chanu, 2016	Not survivor of cardiac arrest population
Helmark, 2016	Conference abstract
Choi, 2017	No survivor of cardiac arrest population
Dougherty, 1997	Not an intervention study
Dougherty, 2015	Mixed population of ICDs implanted for primary and secondary prevention and authors did not have separate data on number of cardiac arrest survivors.
Exposito, 2012	Conference abstract
Goldman, 2013	Conference abstract
Harbinson, 2017	Not survivor of cardiac arrest population
Irvine, 2011	Not survivor of cardiac arrest population
Kim, 2017	Not effect study
Ko, 2020	Not survivor of cardiac arrest population
Konh, 2000	Not survivor of cardiac arrest population
Markus, 2017	Not rehabilitation intervention
Mochizuki 2014	Conference abstract
Moroni, 2006	Not survivor of cardiac arrest population
Moulaert, 2016	Economic evaluation
Moulaert, 2011	Study rationale
Moulaert, 2007	Study protocol
Munjal, 2018	Conference abstract
Sears, 2004	Systematic review
Stock, 2019	Not survivor of cardiac arrest population
Takahashi, 2015	Intervention in intensive care unit

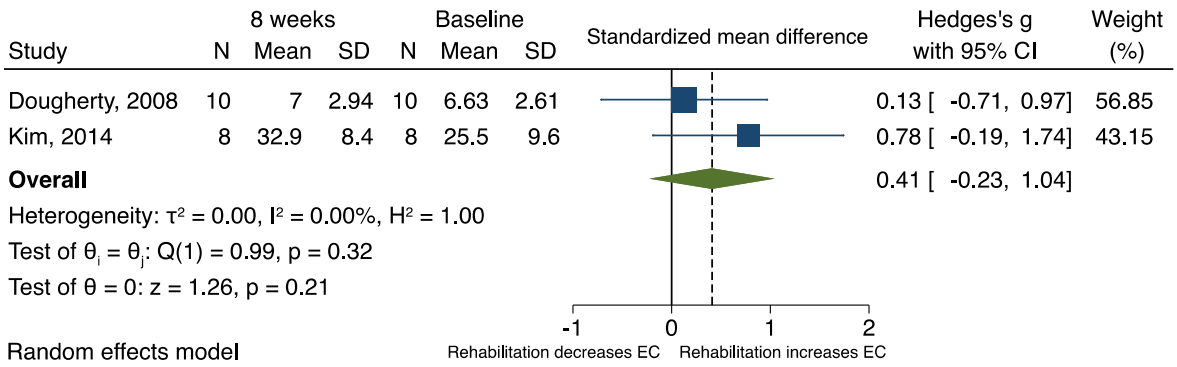
Supplementary data Fig. 1. Forest plot for effect of inpatient rehabilitation for CA-survivors with acquired brain injury on neurological function (NF) between admission and discharge, sensitivity analysis with Howell (2013) removed due to heterogeneity in study population and presence of statistical heterogeneity.



Supplementary data Fig. 2. Forest plot for effect of exercise-based rehabilitation for CA-survivors on exercise duration (ED) (minutes) between baseline and 8 weeks follow-up.



Supplementary data Fig. 3. Forest plot for effect of exercise-based rehabilitation for CA-survivors on exercise capacity (EC) between baseline and 8 weeks follow-up.



Supplementary data Table 3. Summary of findings: HRQoL

Rehabilitation for improving health related quality of life (HRQoL) in survivors of cardiac arrest					
Randomised controlled trials					
Outcome	Standard care	Rehabilitation	Number of participants (studies)	Quality of evidence[a] (GRADE)	Comments
HRQoL Physical component score difference between baseline and 12 months follow-up (0-100 points, higher scores better)	12.8	mean **4.75** points greater compared to standard care	108(2)	++oo Low[b]	
HRQoL Mental component score difference between baseline and 12 months follow-up (0-100, higher scores better)	7.57	mean **3.26** points greater compared to standard care	108(2)	++oo Low[b]	
Prospective observational studies					
HRQoL Physical component score difference between at 6 months follow-up (0-100, higher scores better)	-	mean **20.32** point increase	82(2)	+ooo Very low[c,d]	No comparison arm included in either trial
HRQoL Mental component score at 6 months follow-up (0-100, higher scores better)	-	mean **16.76** point increase	82(2)	+ooo Very low[c]	No comparison arm included in either trial

[a]GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Explanations
[b]High risk of bias in one of the two studies ('some concerns' with criteria: deviations from intended outcomes and selection of the reported results, 'high risk of bias' with criteria: measurement of the outcome), some indirectness of evidence in one study (intervention aimed at people with new ICD implanted) and due to the serious imprecision in both studies (small number of participants).
[c]High risk of bias in one study out of two studies, both studies were observational.
[d]Considerable heterogeneity (I^2=90.17%) (point estimates and confidence intervals vary considerably).

Key: CI: Confidence interval; HRQoL: Health related quality of life; SMD: Standardized mean difference

Supplementary data Table 4. Summary of findings: neurological function

Effect of inpatient rehabilitation on neurological function for survivors of cardiac arrest with acquired brain injury					
All observational studies					
Outcome follow-up	Standard care	Rehabilitation	Number of participants (studies)	Certainty of evidence (GRADE[a])	Comments
Improvement in function between admission and discharge (Functional independence measure and Barthel index)	-	SMD **0.71** effect size (CI 0.45-0.96)	187(5)	+ooo Very Low[d]	No comparison arm included in any included trial
[a]GRADE Working Group grades of evidence **High quality**: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: We are very uncertain about the estimate					
[d]High risk of bias in all studies (multiple domains) and all were observational studies.					

Key: CI: Confidence interval; SMD: Standardized mean difference

Appendix 3c:

Supplementary material for paper 3

Appendix 3c. Supplementary data 2:

Table 1. Characteristics of studies investigating rehabilitation interventions for survivors of cardiac arrest

Study	Title	Population	Rehabilitation intervention	Outcomes		Summary of results
Author, year, country **Study design** **Setting**		**a. Participants** **b. Number of included participants (N)** **c. Age (mean)** **d. Gender (male, %)** **e. Ethnicity (% Caucasian)**	**a. Description** **b. Duration (time period and/or number of sessions)**	**Outcomes of interest**	**Follow-up period**	
Burke, 2005, USA Retrospective chart review Freestanding rehabilitation hospital	Rehabilitation outcomes of cardiac and non-cardiac anoxic brain injury: a single institution experience	a. Acquired brain injury due to cardiac arrest. b. n=13 c. 52.5 d. 54 e. 61	a. Comprehensive, multi-disciplinary inpatient b. rehabilitation services. Admission period mean 69.8 days (SD 59.4)	FIM subscales activities of daily living, mobility, cognition and total	Admission, discharge	Total FIM improved from admission mean 63.92 days (SD 32.82) to mean discharge 90.46 days (SD 41.37).
Cowan, 2001, USA Randomized controlled trial Outpatient clinic	Psychosocial nursing therapy following sudden cardiac arrest: impact on two-year survival.	a. Out-of-hospital cardiac arrest survivors b. n=66 (intervention) n=67 (control) c. NS d. 73 e. 90	a. Three components: 1) physiologic relaxation, 2) Cognitive behavioral therapy and 3) Health education focusing on cardiac risk factors. Delivered by experienced nurses. b. Control received only the health education component. 4 weeks, mean 11 sessions (30 minutes each)	All-cause mortality; Risk of cardiovascular death; Non-Fatal cardiac effects	2 years	Reduction in risk of all-cause mortality for the intervention group was 62%, but this was not statistically significant, (p=0.13). Risk of cardiovascular death was significantly reduced in the intervention group by 86% compared to conventional treatment at two-years follow-up (hazards ratio =0.14; p=0.03; one death in the intervention group due to stroke, six out of seven deaths in control group due cardiac arrest. Confidence intervals for these results were not available).
Dougherty, 2004, 2005, USA Randomized controlled trial Telephone	Short-term efficacy of a telephone intervention by expert nurses after an ICD; Long-Term Outcomes of a Telephone	a. Cardiac arrest survivors with first time ICD implantation for secondary prevention of cardiac arrest b. n=38 (intervention), n=27 (control) c. 63.5	a. 1) Booklet mailed to study participants on strategies to manage recovery, 2) structured information provided by experienced cardiovascular nurses to improve self-efficacy to deal with illness demands, and to	SF-12 Physical + Mental component sub-scale (separate results for other outcomes reported in the paper were not available for CA-survivors)	Baseline, 1, 3, 6, 12 months	Rehabilitation interventions showed no statistical effectiveness on either SF-12 physical or mental subscales at any follow-up point compared to standard care.

	Intervention After an ICD	d. 74 e. 91	reduce anxiety, through identification of illness related problems and behavioral strategies to manage them including role playing, problem-solving, goal-setting and collaborating on the learning b. assignment for the coming week. Usual care participants received treatment as usual from their health care providers and standardized hospital-based education about the ICD in the form of a booklet, videotape, or both. First 8 weeks after hospital discharge and ICD implantation (15-20 minute calls, number of calls NS).			
Dougherty, 2008, USA A single group pre-post test design Outpatient group exercise	Aerobic exercise improves fitness and heart rate variability after an ICD	a. Cardiac arrest survivors with first time ICD implantation for secondary prevention of cardiac arrest b. n=10 c. 54.8 d. 90 e. NS	a. Supervised aerobic exercise plus home walking b. 3 days per week for total of 8 weeks (24 sessions) + 1 hour of home walking twice a week.	SF-12 Physical + Mental component sub-scale; State Trait Anxiety Inventory; Center for Epidemiological Studies–Depression Scale; Total exercise time (minutes); Oxygen pulse (VO2/HR); Metabolic equivalent of task; RT3 accelerometer	Baseline, 8 weeks, 6 months	Quality of life (Short Form–12) showed a non-significant improvement in physical and mental sub-scale scores and non-significant reduction in anxiety and depression. Exercise duration, oxygen uptake at anaerobic threshold, and metabolic equivalents were improved after 8 weeks of exercise. There were no lethal cardiac arrhythmias experienced during exercise testing and no participants required cardioversion. There were no sustained ventricular arrhythmias during supervised exercise or home walking sessions in any of the study subjects.

						SF-12 physical health were sustained at 6 months as well as an increase in daily activity as measured by RT3 accelerometer.
Dougherty, 2019, USA Randomized controlled trial Telephone	Patient plus partner trial: A randomized controlled trial of 2 interventions to improve outcomes after an initial ICD	a. Cardiac arrest survivors with first time ICD implantation for secondary prevention of cardiac arrest b. n=66 c. 62.3 d. 72 e. 94	a. Intervention consisted of 4 elements: 1) Information booklet with strategies for health recovery after ICD implant. 2) Nurse telephone support to improve self-efficacy and problem solve. Components of this support were as per the intervention in b. Dougherty, 2004, 2005. 3) Pager access to a study nurse 4) an informational video provided by the device company. 10 telephone calls over 12 weeks	SF-12 Physical + Mental component sub-scale; State Trait Anxiety Inventory; Patient health questionnaire-9	Baseline, 3, 6, 12 months	All outcomes improved between baseline and 12 months follow-up. No effect sizes available.
Fertl, 2000, Austria Retrospective chart review Inpatient neurological rehabilitation	Neurological rehabilitation of severely disabled cardiac arrest survivors. Part I. Course of post-acute inpatient treatment	a. Out-of-hospital cardiac arrest survivors who suffered anoxic brain injury and required prolonged intensive care treatment b. n=20 c. 47.6 d. 85 e. NS	a. Daily multidisciplinary neurological rehabilitation. Speech therapists and psychologist were available for those needing their service. b. Admission period mean 84 days (SD 57) (minimum 15 sessions per week of physical and occupational therapy)	Barthel Index	Admission + discharge	Mean improvement in Barthel index 3.4 (SD 4.4)
Howell, 2013, Germany Retrospective cohort study	Rehabilitation outcome of anoxic-ischaemic encephalopathy survivors with prolonged	a. Cardiac arrest survivors, direct transfer from intensive care unit, all in coma, vegetative state or minimally conscious state b. n=113 c. 55	a. Daily neurorehabilitation b. Mean 84 days (SD 50)	Glasgow outcome scale; FIM; Coma remission scale	Admission + discharge	Total FIM improved from mean (SD) 18 (0) to 25 (19) points between admission and discharge. 6.2% of patient achieved a good functional outcome defined as Glasgow Outcome Scale 4-5.

Inpatient neuro rehabilitation center	disorders of consciousness	d. 74 e. NS				Coma remission scale improved from mean (SD) change of 9 (5) to 13 (7) points (scale 0-24, higher score indicates better recovery).
Kim, 2014, South Korea Retrospective review of medical records Outpatient hospital-based	Cardiac rehabilitation after acute MI resuscitated from cardiac arrest	a. Cardiac arrest survivors who received successful percutaneous coronary intervention for acute MI b. n= 8 c. 46.8 d. 88 e. NS	a. Cardiac rehabilitation including aerobic exercise, advice on secondary risk factors, diet and lifestyle, advice on medication by a cardiologist. Exercise was b. continued at home at 60% intensity of the heart rate reserve. 6 weeks (3x50-minute per week exercise programs for 6 weeks)	Cardiovascular-related complications during exercise monitoring; Peak oxygen consumption (VO2peak (mL/kg/min)); Exercise duration (minutes)	Baseline + 8 weeks	Significant improvement in exercise capacity. No fatal cardiac complications, such as abnormal ECG, cardiac arrest, death or myocardial infarction observed.
Kim, 2016, USA Prospective, pre-post single group experimental design Telephone	An intervention for cardiac arrest survivors with chronic fatigue: A feasibility study with preliminary outcomes	a. Cardiac arrest survivors at least 3 months post cardiac arrest with chronic fatigue b. n=8 c. 53.2 d. 56 e. 100	a. Energy Conservation and Problem Solving Therapy delivered by an occupational b. therapist. Up to 4 weeks (45 minute sessions twice a week)	Modified Fatigue Impact Scale; Fatigue Severity Scale; Patient Reported Outcomes Measurement Information System-Fatigue scale	Pre-test, post-test (range 3-5 weeks)	Significant decreases on the Modified Fatigue Impact Scale total ($p<0.001$), subscales physical ($p=0.001$) and cognitive ($p = 0.006$) fatigue were observed with small to moderate effect sizes of $r=0.23–0.25$. Change effect sizes were small for the Fatigue Severity Scale ($r=0.11$), Patient Reported Outcomes Measurement Information System-Fatigue scale ($r=0.19$).
Mion, 2019, UK Prospective cohort study In-patient and outpatient clinic	Care After Resuscitation: Implementation of the United Kingdom's First Dedicated Multidisciplinary Follow-Up Program for Survivors of Out-of-Hospital Cardiac Arrest	a. Cardiac arrest survivors with good neurological recovery, Cerebral Performance Scale Category 1-2 n=19 b. 61 c. 84 d. NS e.	a. Inpatient information provided via leaflets, bespoke video and direction to a social media website for cardiac arrest survivors and caregivers; telephone and clinic follow-up with ICU nurse, cardiologist and psychiatrist. If psychological b. issues were identified, patients and caregivers were offered further interventions.	SF-36 physical and mental domain scores	Baseline, 6 months	Significant improvement in all domains of Short-form 36 (except general health) at 6 months.

			In-hospital + clinic follow-up at: 8-weeks, 6-months and 12-months post-hospital discharge.			
Moulaert, 2015, The Netherlands Multicenter randomised controlled trial At clinic or at home	Early neurologically-focused follow-up after cardiac arrest improves quality of life at one year: A randomised controlled trial	a. Survivors of cardiac arrest at least two weeks after event, living at home b. n=97 (Intervention) n=98 (Control) c. 60 (Intervention) 69 (Control) d. 83 (Intervention) 84 (Control) e. NS	a. Intervention for survivors of cardiac arrest and their caregivers provided by specialist nurses including 1. Screening for cognitive and emotional problems. 2. Provision of support and information on cardiac arrest and possible neurological consequences. 3. Promotion of self-management strategies. b. 4. Referral to specialized care if indicated. Control group received standard care with potential for referral to cardiac rehabilitation. 1-6 individual sessions	SF-36 domain scores; EuroQol Visual Analogue Scale; Cognitive log Adult Memory and Information processing battery task A; Verbal fluency; Trail making Test A; Trail making Test B; Paragraph recall direct; Paragraph recall delayed; Cognitive Failures Questionnaire; Hospital Anxiety and Depression Scale (anxiety and depression sub-scales and total); Impact of Event Scale	Baseline, 3 + 12 months	At 12 months there were significant differences in estimated means in favour of the intervention group on three domains of quality of life on the SF-36: Role Emotional (p=0.006), Mental Health (p=0.003) and General Health (p=0.010). No significant effectiveness on cognitive tests compared to standard care at any follow-up point. The intervention group scored significantly better on overall emotional state (anxiety and depression) and anxiety at one year.
Schmidt, 1997, USA Retrospective chart review In-patient rehabilitation unit	Anoxic encephalopathy: Outcome after inpatient rehabilitation	a. Patients admitted to a rehabilitation unit with cerebral anoxia (15 due to cardiac arrest and 11 for other causes) b. n=26 c. 58 d. 66 e. NS	a. In-patient rehabilitation unit b. Admission period mean 59.5 days (SD 41.4)	FIM	Admission + discharge	Total FIM improved from admission mean 54.15 (SD 29.85) to discharge mean 81.23 (SD 26.34).
Shah, 2007, USA Retrospective chart review	A comparison of functional outcomes in hypoxia and traumatic brain injury: A pilot study	a. Survivors of cardiac arrest who suffered anoxic brain injury b. n=15 c. 50.8 d. 60 e. 87	a. In-patient rehabilitation b. Mean 61.2 days (SD 68.4)	FIM subscales activities of daily living, mobility, cognition and total	Admission + discharge	Total FIM improved from admission mean 61.93 (SD 33.23) to discharge mean 94.67 (SD 37.34)

Freestanding rehabilitation hospital						
Tazopoulou, 2016, France Observational single cohort study Residential care	Rehabilitation following cerebral anoxia: An assessment of 27 patients	a. Adults with cerebral anoxia in residential care (11 due to cardiac arrest, 9 due to other cause) b. n=20 c. 46 d. 70 e. NS	a. Psychotherapy, support group, physical activities and cultural and/or artistic activities. Participants could b. choose to be in all or some of the activities. 2-months	Glasgow outcome score extended; Bermont Vost Alexithymia questionnaire; Patient Competency Rating scale (agnosia); Quality of Life After Brain Injury questionnaire; Barrow Neurological Institute screen of higher cerebral functions; Hospital Anxiety and Depression scale	Baseline, 2 + 4 months	Quality-of-life was significantly improved between baseline and intervention end at two months. No change found in neurological function or anxiety and depression.

ICD: Implantable Cardioverter-Defibrillator; FIM: Functional Independence Measure; NS: Not stated; SF: Short form health survey

Appendix 4a:

Paper 4

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Resuscitation

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Clinical paper

Promising results from a residential rehabilitation intervention focused on fatigue and the secondary psychological and physical consequences of cardiac arrest: The SCARF feasibility study

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Abstract

Aims: This study investigated the feasibility and potential effect of SCARF (Survivors of Cardiac ARest focused on Fatigue) a multidisciplinary residential rehabilitation intervention focused on fatigue and the secondary psychological and physical consequences of cardiac arrest (CA).

Methods: This was a prospective one-armed feasibility study. Six progression criteria were identified related to the feasibility of the intervention and viability of a future effect study in terms of: participant recruitment (1), participant retention (2,3,4), and completeness of outcomes (5,6). Data on participant/clinician satisfaction with the intervention was also collected along with self-reported outcomes: fatigue, quality of life, anxiety, depression, function and disability, and physical activity (at baseline, 12 weeks and 6 months) and physical capacity (baseline and 12 weeks).

Results: Four progression criteria were met including retention (87.5%) and completion of baseline outcomes (97.5%). Two criteria were not met: recruitment rate was 2.9 participants per month (estimated rate needed 6.1) and completion of final outcomes was 65% (estimated proportion needed 75%). Participant/clinician satisfaction with the intervention was high. Three months after the SCARF intervention small to moderate effect size changes of $r = 0.18–0.46$ were found for self-reported fatigue, quality of life, anxiety, depression, function and disability and for two of the physical capacity tests ($d = 0.46–0.52$).

Conclusion: SCARF was found to be a feasible intervention with high participant/clinician satisfaction, high participant retention and the possible potential to improve self-reported and physical capacity outcomes. Procedures for study recruitment and collection of final outcomes should be modified before a fully powered randomised controlled trial is conducted.

Keywords: Cardiac arrest, Survivorship, Fatigue, Rehabilitation

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https://doi.org/10.1016/j.resuscitation.2022.02.002
Received 1 December 2021; Received in Revised form 31 January 2022; Accepted 3 February 2022

Introduction

The number of survivors of cardiac arrest (CA survivors) is increasing due to successful improvements in prehospital and acute medical care.[1] While most CA survivors return home and live independently,[2] CA can also cause debilitating long term cognitive, psychological and physical problems.[3] Cognitive impairments caused by hypoxic brain injury include deficits in attention, memory, and executive function.[4–7] Though rarely severely disabling these problems may continue beyond a year for 30–50% of CA survivors.[8,9] Psychological problems such as anxiety[10,11] and depression[11,12] can also be common and persistent. However, the most prevalent symptom is fatigue[2] reported by up to 70% of CA survivors.[13,14]

The specific cause of fatigue in CA survivors is unknown[2] but is likely related to the multiple interconnected secondary consequences of CA such as the increased effort required for cognitive processes,[8,15] psychological distress, sleep disturbances,[15] ongoing cardiac disease[16] and reduced physical activity levels.[17,18] Long-term fatigue after CA is associated with decreased physical activity[18], social participation,[18] and return to work.[14] While rehabilitation for the secondary consequences of CA, including fatigue, is recommended in international guidelines,[3,19,20] evidence is sparse and of low quality.[21] Though, one small (n = 18) existing pilot study did find self-reported fatigue in CA survivors improved with telephone-based energy conservation and problem-solving therapy (EC + PST).[22] Considering brain injury in general, there are no evidence-based treatment recommendations for fatigue.[2,23,24] However, treating modifiable psychological or lifestyle factors through education[25] and behavior change strategies has been shown to reduce fatigue, and improve psychological well-being and social participation,[15,26] suggesting this may also be effective for CA survivors.

Testing the effect of any new rehabilitation intervention is crucial but survival after CA remains relatively rare making recruitment to research studies challenging. Thus, we designed a residential intervention inspired by residential programmes for cancer[27–29] with multiple intervention components in a short time frame enabling national recruitment and participation of survivors. This intervention, SCARF (Survivors of Cardiac ARest focused on Fatigue) was designed through a systematic intervention development process based on our best current knowledge. However, there are key uncertainties to be tested before progressing to a fully powered randomised controlled trial (RCT) if the intervention is to be successfully implemented in the future.[30] Hence, the primary aim of this study was to determine the feasibility of the SCARF intervention and viability of a future RCT in terms of acceptable recruitment rate, retention of participants, and completeness of outcomes with a secondary aim to investigate change from baseline to follow-up in relevant self-reported outcomes and physical capacity tests.

Methods

Study design

A prospective one-armed feasibility study was conducted of the SCARF intervention, a new multidisciplinary residential rehabilitation intervention focused on fatigue and the secondary psychological and physical consequences of CA. A priori, six progression criteria[31] were agreed to provide a transparent decision process on readiness to progress to a fully powered RCT and identify necessary modifications to the intervention and/or study design.[31] The study is reported according to the CONSORT extension for pilot and feasibility trials.[32]

Setting and timeframe

Danish healthcare is universal and tax-funded. There are approximately 800 new CA survivors per year in Denmark. The proportion with rehabilitation needs and eligible for this study was unknown.[33] CA survivors are usually offered cardiac rehabilitation if their cause of CA is ischemic heart disease.[34] They may also be referred to psychological therapies, cognitive rehabilitation or physiotherapy for specific problems. However, this provision is inconsistent across Denmark and there is no specific rehabilitation for CA survivors.[34] The SCARF study was conducted at REHPA, the Danish Knowledge Center for Rehabilitation and Palliative Care in Nyborg, Denmark.

The SCARF programme was delivered on four occasions at REHPA from October 2019 to March 2021 with final follow-up data collected in June 2021. SCARF consisted of an initial five-day residential programme at REHPA followed by 12-weeks at home before returning for a further 2-day programme (Fig. 1).

Study population and recruitment

CA survivors with a self-identified need for rehabilitation could be referred to SCARF by their cardiologist or general practitioner. They must be ≥3 months after their CA, ≥18 years old, and able to speak and understand Danish. Participants must be independent with self-care unless this could be provided by their attending relative. Self-identified rehabilitation need was determined by a score of ≥3 on the REHPA scale. This is a linear analogue scale, where participants indicate how close they are to living the life they desire after their CA.[35] The scale ranges from 0= 'goal reached' to 9= 'infinitely far from'. Participants with no permanent residence in Denmark were excluded.

Study recruitment information was publicised on the websites of REHPA, the Danish Heart Foundation and the Danish Resuscitation Council, via leaflets at the five tertiary cardiac centers in Denmark, and to clinicians with a special interest in post-CA care.[36]

Intervention

The SCARF intervention is described according to the TIDieR guidelines.[37] SCARF was a residential rehabilitation intervention (Fig. 1) including group education and individual activity sessions (Tables S1, S2, S3, supplementary, detail the SCARF intervention programme and components). Participants could choose to attend with a close relative. SCARF's delivery structure was adapted from an existing residential rehabilitation intervention provided by REHPA to people with cancer.[35,38,39] CA and cancer survivors share some similar problems, for example, fatigue,[40] fear,[41] anxiety and depression.[42] Hence, some components were adapted from the existing REHPA intervention and others were developed specifically for SCARF. Intervention development (detailed in Table S4 and Fig. S1, supplementary) was based on current research with CA survivors[21,22] and similar patient groups (Table S2, supplementary) informed by clinical experience and refined through user-involvement activities[36] and feedback from preliminary courses. A theory of change model illustrates how and why the intervention would deliver improvements (Fig. 2) and a logic model identified necessary resources/inputs and activities, expected outputs, outcomes and long term impact[43] (Table S5, supplementary).

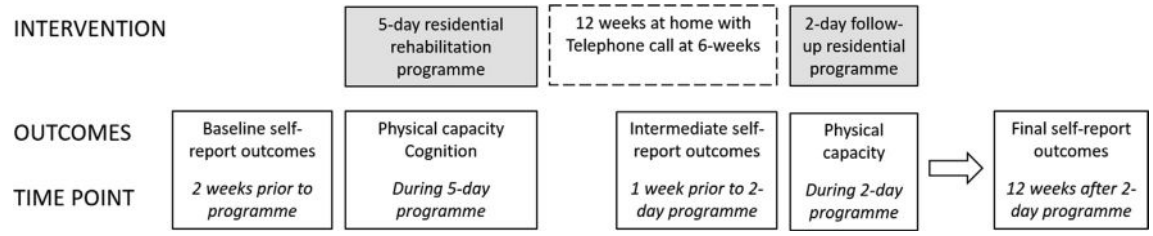

Fig. 1 – Structure of SCARF study.

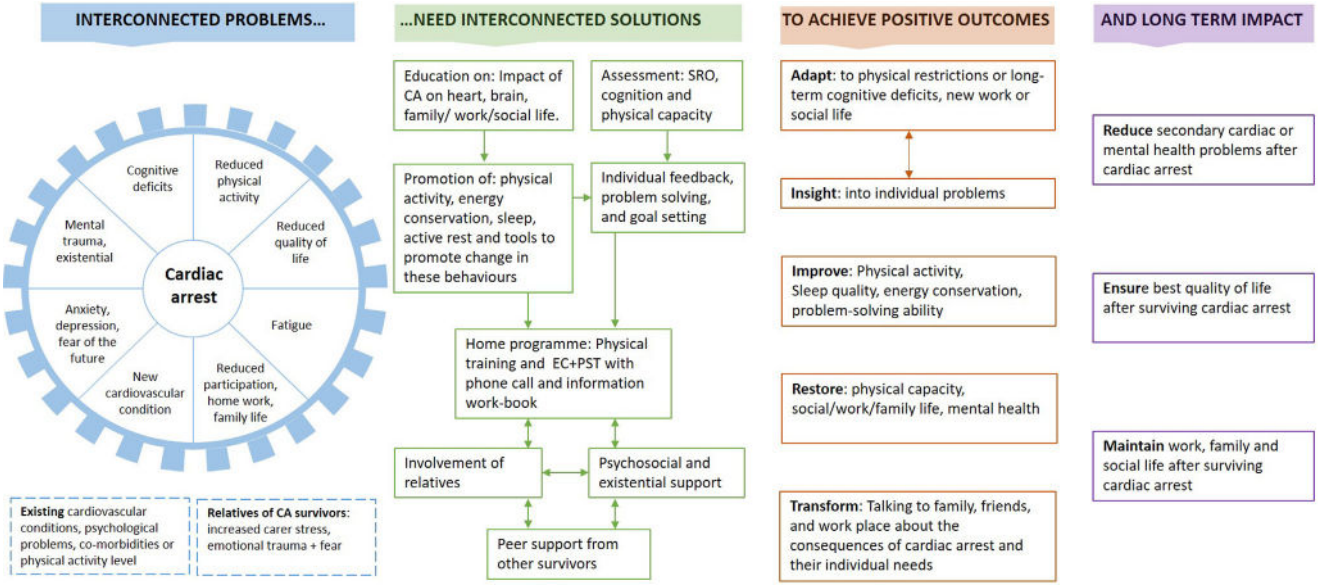

Fig. 2 – SCARF Theory of change model.

Outcomes

Progression criteria

To determine the feasibility of the intervention and study design six progression criteria were identified by the research group based on key uncertainties that could influence the success of a future RCT.[31] Traffic light style categories were defined as stated in Table 1.[31]

A power calculation based on the change in total Modified Fatigue Impact Scale (MFIS) score found in a previous intervention study with CA survivors[22] indicated 124 study participants is needed to have sufficient statistical power to identify a treatment effect.[22] Assuming a recruitment period of three years and a 25% loss from initial application to participation in the intervention (progression criteria 2) and a 25% loss from baseline to completion of final outcomes (progression criteria 6) a future RCT would need to receive 220 applications or 6.1 per month (progression criteria 1).

Further, we were uncertain if participants would be engaged in the intervention and complete the whole programme (retention) (progression criteria 2, 3, 4) or motivated and able to complete the online survey (progression criteria 5, 6).

Participant and clinician satisfaction

Participants rated each session separately on 'relevance' and 'benefit', scored 0–5 on a Likert scale with 0 = no relevance/benefit and 5 = very relevant/beneficial. Clinicians stated their agreement with five statements covering purpose, content, duration, location and adequacy of training, scored 1–5 on a Likert scale with 1 = strongly disagree to 5 = strongly agree (Table S6, supplementary).

Intervention outcomes

To identify a potential primary outcome for a future effect study and provide limited efficacy testing, data was collected on change in self-reported and physical capacity outcomes. Fatigue, as the primary focus of the intervention, was measured by two self-reported questionnaires, MFIS[44,45] measuring impact of fatigue on function and the Multidimensional Fatigue Inventory (MFI-20) measuring fatigue severity.[46] Given the multidimensional nature of fatigue[47] and interconnected secondary consequences of CA[48,49] four further self-reported questionnaires were selected covering health-related quality of life: EQ 5D 5L,[50] anxiety and depression: Hospital Anxiety and Depression Scale[51] (HADS), function and disability: World Health Organisation disability assessment schedule 2.0[52,53] (WHODAS 2.0), and physical activity: International physical activity questionnaire Short Form[54] (IPAQ-SF) (Table S7, supplementary). Physical capacity was measured via the 30-second chair-stand test,[55] 6-minute walk test,[56,57] and hand grip strength[58,59] (Table S8, supplementary).

Data collection

Baseline characteristics came from an initial application form completed by the survivor and their doctor (Fig. 1). Cognitive status was determined by objective cognitive tests administered by a neu-

Table 1 – Progression criteria categories and results.

Progression Criteria		Categories			Result	Category Result
		Green: progress to effect study	Amber: Amend when progressing to effect study	Red: Must be resolved before progression to effect study		
Recruitment and retention:						
1	Initial application recruitment rate (participants per month)	>6.1	4.5–6.1	<4.5	2.9	Red
2	Conversion of applicants to study participants (%)	>75	50–75	<50	93	Green
3	Participation in mid-intervention telephone call (%)	>80	70–80	<70	100	Green
4	Participation in 2-day follow-up (%)	>80	70–80	<70	87.5	Green
Completion of self-report outcomes at:						
5	Baseline (%)	>90	80–90	<80	97.5	Green
6	Final follow-up (26 weeks) (%)	>75	65–75	<65	65	Amber

ropsychologist during the 5-day programme (Tables S2, S9, supplementary). Progression criteria data on recruitment, retention and completion of outcomes were collected from application forms, attendance lists and a telephone call checklist. Participant satisfaction was collected by paper survey on the last day of the 5-and 2-day programmes and clinician satisfaction by email survey after the 2-day programme.

Self-reported outcomes were collected at baseline, at intermediate time point, and at final follow-up online using REDCap (Research Electronic Data Capture). A physiotherapist conducted the physical tests on day two of the 5-and 2-day programmes.

Data analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Data for progression criteria were calculated as proportions and presented as numbers and/or percentages.

Participant satisfaction mean scores for 'relevance' and 'benefit' were calculated for the whole SCARF intervention. Clinician satisfaction mean scores were calculated overall for the intervention and for each statement.

For self-reported outcome scores and physical capacity tests, continuous data was checked for normality and described as mean and SD. Mean difference was determined to investigate change in outcomes from baseline to follow-up time points. Effect size was estimated with Cohen's d[60] for normally distributed data. Non-normally distributed data, where differences were tested with Wilcoxon matched-pairs signed-rank test, effect size (r) was calculated by dividing the test statistic z by the square root of the number of observations. Values of 0.3, 0.5 and 0.8 were interpreted as small, medium and large effect sizes respectively for Cohen's d.[60] while associated values for r were 0.15, 0.24 and 0.37.[61] All analyses were conducted using STATA V.16 (StataCorp) statistical software.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki with informed written consent obtained from all participants. The Region of Southern Denmark ethics committee assessed that according to Danish legislation the study was not subject to ethical notification (journal number 20192000–19). The study was registered with The Danish Data Protection Agency (journal number 19/15603) and in the database Clinical Trials (www.clinicaltrials.gov, NCT04114773) before inclusion of participants.

Results

Participant demographics and CA-related clinical characteristics

The majority of participants were male (62.5%) with a wide age range from 33-79 years (Table 2). Median time since CA was 13 months (IQR 10.5) (Table 2). In total, 43 CA survivors applied for the course of these 40 were included in the study (Fig. 3).

Progression criteria

Progression criteria results were red for initial application recruitment rate, amber for completion of final follow-up self-reported outcomes and green for the other four criteria (Table 1).

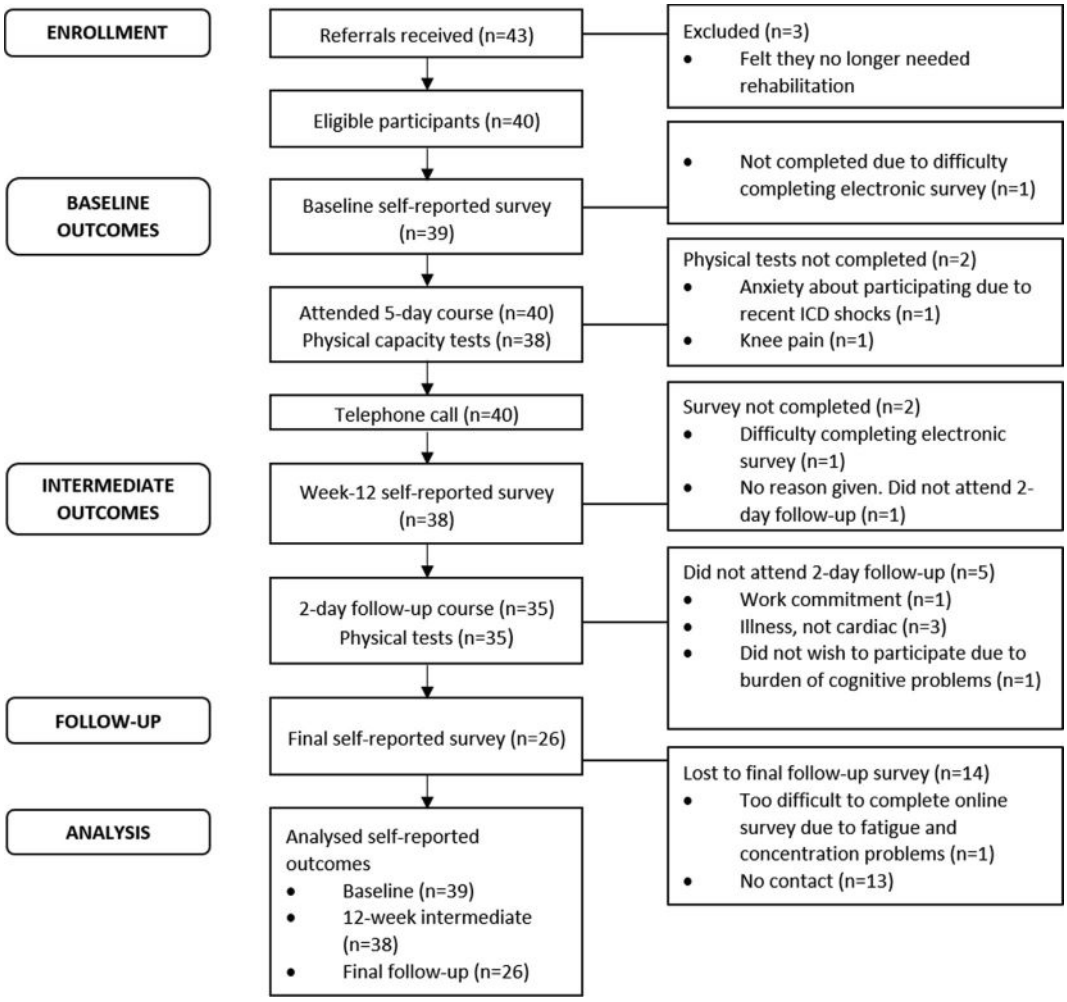

Fig. 3 – Flow of participants through study.

Participant and clinician satisfaction

Overall, participant satisfaction with the SCARF intervention was high with mean scores of 4.5 (SD 0.5) and 4.2 (SD 0.7) out of 5 for relevance and benefit respectively. Clinician overall satisfaction was also high (4.0, SD 0.8) with the statements 'appropriate for participants' (3.6, SD 0.7) and 'enough time' (3.7, SD 0.9) scoring slightly lower than the other three statements.

Intervention outcomes

Neither the total score nor subscales of the MFIS showed an effect size ($r \geq 0.15$) (Table 3). The MFI-20 dimension general fatigue showed a small effect baseline to intermediate follow-up ($r = 0.15$), maintained at final follow-up ($r = 0.18$) with a small effect also found for the MFI-20 dimension physical activity, baseline to final follow-up ($r = 0.15$). Small effect sizes were found, baseline to intermediate follow-up, for the EuroQoL index score ($r = 0.26$), EuroQoL 5D 5L visual analogue scale ($r = 0.27$), HADS-Anxiety ($r = 0.16$) and WHO-DAS 2.0 total ($r = 0.15$) with effect sizes maintained at final follow-up for the EuroQoL index ($r = 0.18$), HADS-Anxiety ($r = 0.17$), and WHODAS 2.0 total ($r = 0.26$). HADS-Depression showed a small effect size baseline to final-follow-up ($r = 0.26$). A moderate effect size was found for WHODAS 2.0 domain 'Life activities' between baseline and intermediate time point ($r = 0.25$) maintained at final follow-up ($r = 0.46$).

A moderate effect size was found for the 30-second chair-stand test ($d = 0.52$) and small effect size for the 6-minute walk test ($d = 0.46$) between baseline and intermediate time points (Table S10, supplementary).

Participants who did not complete the final follow-up self-report outcomes (n = 26) were younger and had a higher burden of self-reported fatigue, depression, and disability (self-care and participation domains) at baseline compared to completers (n = 13) (Table S11, supplementary).

Discussion

This study investigated the feasibility of a residential rehabilitation intervention for CA survivors. We found the intervention was feasible with an 88% completion rate, high participant/clinician satisfaction and showing potential for positive effects bearing in mind the small sample size and one-armed study design. However, two aspects of the study design, recruitment and completion of final outcomes, did not meet the progression criteria and may need to be modified before the intervention is tested in a fully powered RCT.

Recruitment to the SCARF study was primarily via websites connected to CA, relying on clinicians with a special interest[36] or CA survivors/their relatives finding the information. The recruitment rate of

Table 2 – Participant demographics and CA-related clinical characteristics (n = 40).

Demographic/clinical characteristics	Counts (%)
Age (years), mean (range, SD)	57.4 (33–79, 20.72)
Gender, male	25 (62.5)
Body Mass Index, mean (range, SD)	28.2 (18.2–55.0, 7.6)
Marital status	
Single	8 (20.0)
Partner	9 (22.5)
Married	23 (57.5)
Living alone	13 (32.5)
Children < 18 years living at home	13 (32.5)
Time since cardiac arrest (months), median (IQR, range)	13 (10.5, 3–49)
Reason for cardiac arrest[a]	
Ischemic heart disease	20 (50.0)
Arrhythmia	9 (22.5)
Cardiomyopathy	3 (7.5)
Other or unknown	8 (20.0)
Return of spontaneous circulation[b] (minutes) (mean, range)	15 (0.5–87)
Place of cardiac arrest[c]	
Home	15 (37.5)
Public place	14 (35.0)
Hospital	11 (27.5)
Treatment after cardiac arrest[a]	
Percutaneous coronary intervention	20 (50.0)
Implantable cardioverter-defibrillators	28 (70.0)
Coronary artery bypass grafting	3 (7.5)
Rehabilitation need as measured by the	
REHPA scale (points), median (IQR)	5.6 (2.0)
Cognitive status	
Cognitive impairment[d]	11 (28.9)

[a] Information from referring doctor and more than one category may have been recorded.
[b] Return of spontaneous circulation unknown or unrecorded (n = 11).
[c] Public place includes n = 2 in ambulance.
[d] Cognitive impairment was defined as a score less than 1.5 SD of published population norms[6] on two or more cognitive tests (Table S8 supplementary materials) (n = 38).

2.9 per month is half the estimated required rate to show an effect on the MFIS in a full-scale study over a three-year period. Possible modifications to the study design include a more active recruitment process or using a multi-center trial design. Screening CA survivors for fatigue or related secondary problems at outpatient cardiology follow-up may identify those with rehabilitation needs and therefore potential future study participants. A multi-center trial including similar residential facilities in European countries[62,63] may increase pace of recruitment. The residential delivery method used by SCARF meant survivors need only attend twice, improving retention, but possibly reducing recruitment for survivors with work or caring commitments. Recruitment to SCARF could be improved with alternate delivery models, for example, using outpatient centers, as is traditional for cardiac rehabilitation[64] or via tele-rehabilitation whose popularity has accelerated in part due to Covid 19[65] but also due to the potential for reduced resource use[66] and increased participation.[64,66] Telephone-based rehabilitation has successfully been delivered to CA survivors in previous studies[22,67] but this does not allow group-based components. Further, tele-rehabilitation may not suit older CA survivors[68] or provide the social or environmental benefits found with in-person interventions,[69] and the preferences of survivors themselves needs further investigation.

Only 65% of participants completed final outcomes at six months, perhaps due to difficulties with the on-line survey, low motivation, fatigue and/or cognitive problems. Modifications to improve completion could include shortening the self-reported survey,[70,71] providing paper surveys[70] or using additional telephone calls to remind and support participants to complete the final survey.[70,72,73]

Where final outcomes were completed, we found a small effect for MFI-20 general Fatigue score (r = 0.18) but none for the MFIS. Fatigue is the most prevalent symptom after CA but is linked with multiple other secondary problems. Hence, for this feasibility study, we chose a broad recruitment approach based on rehabilitation need. Though we did show a small effect for MFI-20 general fatigue the lack of effect on the MFIS could be due to some participants having low initial fatigue scores. An earlier study testing EC + PST[22] with CA survivors found the MFIS improved significantly, but only included participants with chronic fatigue with a baseline mean MFIS total score of 50.4 (scale 0–84) compared to 29.4 in our study. Further, the MFIS result could have been affected by the poor completion of final outcomes, with the non-completers reporting a significantly higher baseline MFIS score (39.6) than the completers (24.3) (Table S11, supplementary).

Given the multidimensional nature of fatigue and our inclusion based on rehabilitation need,[47] we chose four additional self-reported outcomes. Of these, the WHODAS 2.0 'Life activities' domain showed the largest effect (r = 0.46). SCARF was designed to treat the many interconnected secondary consequences of CA[48,49] with a focus on the causes and consequences of fatigue. Therefore, we included sessions on work and family life as well as

Table 3 – Self-reported outcomes at baseline, intermediate and final follow-up time points.

Time point	Baseline	Intermediate follow-up (11 weeks after baseline)			Final follow-up (6 months after baseline)		
Outcome measure Self-reported	Mean (SD) n = 39	Mean (SD) n = 38	Mean difference baseline to intermediate follow-up (95% CI)[a]	Effect size	Mean (SD) n = 26	Mean difference baseline to final follow-up (95% CI)[b]	Effect size
MFIS total	29.4 (18.9)	29.2 (17.1)	−0.5 (-5.6, 4.6)	0.01	25.1 (16.1)	0.8 (-5.2, 6.8)	0.10
Physical	13.2 (9.0)	13.0 (8.2)	−0.2 (-2.8, 2.3)	0.00	12.2 (8.6)	1.2 (-2.1, 4.5)	0.13
Cognitive	13.6 (10.1)	13.3 (9.4)	−0.5 (-2.8, 1.8)	0.03	10.7 (8.4)	−0.5 (-3.0, 2.1)	0.04
Psychosocial	2.7 (2.4)	2.9 (2.0)	0.2 (-0.6, 1.0)	0.04	2.2 (2.0)	0.0 (-0.9, 0.9)	0.05
MFI-20 General fatigue	13.5 (4.1)	13.1 (3.6)	−0.5 (-1.6, 0.7)	0.15*	12.7 (3.8)	−0.7 (-2.0, 0.5)	0.18*
Physical activity	12.4 (4.9)	12.8 (5.1)	−0.2 (-4.1, 3.7)	0.09	12.2 (5.2)	−1.2 (-2.1, 4.5)	0.15*
Reduced activity	12.2 (4.4)	12.5 (4.1)	−0.2 (-1.3, 0.8)	0.06	11.6 (4.4)	0.1 (-1.4, 1.2)	0.02
Reduced motivation	8.5 (3.4)	8.8 (4.0)	−0.4 (-1.4, 0.7)	0.10	8.0 (2.8)	0.2 (-0.7, 1.2)	0.13
Mental fatigue	11.6 (4.6)	11.7 (4.5)	−0.8 (-0.9, 0.8)	0.01	11.1 (4.7)	0.2 (-1.0, 1.3)	0.07
EuroQoL index	0.72 (0.16)	0.76 (0.11)	0.04 (0.01–0.08)	0.26*	0.79 (0.11)	0.03 (0.15, 0.07)	0.18*
EuroQol 5D 5L VAS	60.2 (21.9)	65.0 (18.7)	5.6 (-0.3, 11.4)	0.27*	65.6 (23.5)	2.1 (-8.4, 12.6)	0.12
HADS Anxiety	7.7 (4.6)	7.4 (4.5)	−0.5 (-1.4, 0.4)	0.16*	6.4 (4.4)	−0.7 (-1.7, 0.3)	0.17*
HADS Depression	5.6 (4.0)	5.4 (4.1)	−0.3 (-1.2, 0.5)	0.11	3.8 (2.8)	−0.8 (-1.7, 0.1)	0.26*
WHODAS 2.0 total	22.1 (14.3)	20.5 (15.3)	−2.0 (-5.1, 1.0)	0.15*	16.8 (12.3)	−2.5 (-6.3, 1.3)	0.26*
Understanding and communication	21.1 (20.1)	20.6 (20.8)	−1.0 (-5.7, 3.8)	0.06	19.4 (20.3)	−0.3 (-8.2, 7.5)	0.04
Getting around	11.6 (14.8)	11.5 (16.7)	0.3 (-4.8, 5.3)	0.08	7.7 (12.3)	−0.8 (-6.1, 4.5)	0.12
Self-care	6.6 (13.7)	4.4 (12.0)	−2.3 (-7.6, 3.0)	0.21*	3.6 (7.3)	0.5 (-0.9, 1.9)	0.07
Getting along with people	20.4 (20.6)	23.6 (21.4)	2.6 (-1.2, 6.5)	0.19*	17.3 (14.2)	−0.2 (-4.21, 4.6)	0.03
Life activities	38.9 (27.9)	29.9 (24.1)	−9.9 (-17.9, −1.8)	0.25*	21.9 (21.3)	−15.4 (-24.1, −6.7)	0.46*
Participation in society	34.4 (18.8)	33.0 (21.9)	−2.0 (-7.5, 3.6)	0.09	30.7 (21.3)	0.7 (-6.3, 7.7)	0.10
IPAQ Short (MET per week)	4237 (3362)	3807 (3181)	−541 (-1840, 757)	0.09	4100 (3362)	107 (-923, 1136)	0.01

MFIS: Modified Fatigue Impact Scale; Multidimensional fatigue inventory; VAS: Visual analogue scale; HADS: Hospital anxiety and depression scale; WHODAS-2.0: World Health Organisation disability assessment schedule 2.0; IPAQ: International Physical Activity Questionnaire; MET: Metabolic equivalent.

capacity measure (n = 33).

* Effect size $\geq$ 0.15.

[a] Change from baseline to intermediate outcome calculated from mean and SD from participants who completed both baseline and intermediate self-report (n = 38) and physical.

[b] Change from baseline to 6 month follow-up calculated from mean and SD from participants who completed both baseline and 6 month follow-up self-report measures (n = 26).

a process for problem solving that could have been used by participants in situations other than for energy conservation. This comprehensive programme might account for the improvement in WHODAS 2.0 'life activities' and suggests a global or composite measure[74] might have been a more appropriate outcome in our study than using a single specific measure such as fatigue. Small effect sizes were found for quality of life (r = 0.18), anxiety (r = 0.17) and depression (r = 0.26) and the 6 minute walk test (d = 0.46) with a moderate effect size for the 30-second chair-stand test (d = 52) again indicating the effect of SCARF may be multi-factorial.

This study successfully identified several modifications required before progression to a SCARF effect study, however, the study had some limitations. We chose not to include a control group with randomization due to the exploratory nature of the study and uncertainty about recruitment. A recent RCT in the same setting[75] successfully demonstrated how SCARF could be tested using a RCT waiting list design.

Participants were included if they had a self-identified rehabilitation need, referred by a medical doctor and were independent with/without a relative, thereby excluding survivors with severe physical/cognitive problems or lacking insight into their rehabilitation needs. However, considering SCARF centers on group education and problem-solving, alternative, one-to-one interventions may be needed to meet the needs of these survivors.

The participant and clinician satisfaction data were limited to the survey questions provided. A parallel qualitative interview study, with both groups, would have increased the depth of information and potentially identified problems and solutions not considered by the research team.[76,77] In a change from the protocol, we were unable to collect information on number of problems solved through the EC + PST due to the complexity of the information needed and the timeframe for the individual conversation. A future study could collect this data via qualitative means.

Except for the recruitment strategy, this study found the SCARF intervention is feasible, but a fully powered RCT is needed to determine the effect. For this to be successful, research is needed to establish the content/face validity and reliability of fatigue measures in CA survivors. Further, developing methods for screening CA sur-

vivors for long term secondary problems would identify those with rehabilitation needs that could benefit from interventions like SCARF. Any future RCT should include a process evaluation to determine if SCARF's mechanism of action is consistent with the presented theory of change and logic models.[76,78]

Conclusions

The SCARF intervention was found to be feasible with high participant/clinician satisfaction, high participant retention and the potential to improve fatigue, quality of life, anxiety, depression, function and physical capacity bearing in mind the small sample size and one-armed study design. Procedures for study recruitment and collection of final outcomes should be modified before a fully powered RCT is conducted.

CRediT authorship contribution statement

Vicky L. Joshi: Conceptualization, Methodology, Investigation. **Lars Hermann Tang:** Conceptualization, Methodology, Investigation. **Young Joo Kim:** Methodology. **Mette Kirstine Wagner:** . **Jørgen Feldbæk Nielsen:** Conceptualization, Methodology. **Morten Tjoernlund:** Methodology, Investigation. **Ann-Dorthe Zwisler:** Conceptualization, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

VLJ received PhD grants from the University of Southern Denmark and the Region of Southern Denmark (19/15041) and this work received partial funding by REHPA, which receives funding from the Danish Government. LHT is currently funded by a grant from the Danish Regions and The Danish Health Confederation through the Development and Research Fund for financial support (project nr. 2703) and a grant from Region Zealand, Denmark (Exercise First). We would like to thank the health professionals and other staff at REHPA who helped to develop and deliver the SCARF intervention. Also, a special thanks to the cardiac arrest survivors who took part in the user-involvment activities and to those who participated in SCARF and to the DANCAS network for their valuable contributions.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.02.002.

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Appendix 4b:

Supplementary material for paper 4

Appendix 4b Supplementary materials

Table S1 SCARF programme

SCARF 5-day programme						SCARF 2-day programme	
DAY 1	**DAY 2**	**DAY 3**	**DAY 4**	**DAY 5**	**12 WEEKS AT HOME**	**DAY 1**	**DAY 2**
	Introduction to cognitive tests (neuropsychologist)	Active rest, yoga and mindfulness (physiotherapist)	Morning exercise, yoga 1 (physiotherapist)		EC+PST session 4 at week 6 over telephone (member of clinical team)		Morning exercise, yoga 2 (physiotherapist)
	Cognitive testing (neuropsychologist)		EC+PST session 2 (nurse and social worker)	EC+PST session 3 (nurse and social worker)		Welcome and presentation of the programme (programme leader)	
Welcome and presentation of the programme (programme leader)		Individual conversation 1 with feedback of cognitive test results and self-reported survey (member of clinical team)	Voluntary sessions on either Working life (social worker) or Intimacy after CA (nurse)			'What has happened since we met last?' EC+PST 5 (nurse)	Individual conversation 2 with discussion of self-reported survey, (member of clinical team)
LUNCH	LUNCH	LUNCH	LUNCH	LUNCH		LUNCH	LUNCH
Presentation on 'life after CA' (consultant cardiologist) Presentation round (programme leader)	Presentation on benefits of physical activity Introduction to the exercise diary (physiotherapist)	CA and psychological reactions 1 (psychologist)	Voluntary session on CA, family and network (nurse)	Closing session, discussion, feedback and farewell (programme leader)		Physical capacity tests. Individual discussion and feedback about results. (physiotherapist)	Closing session, discussion, feedback and farewell (programme leader)
EC+PST session 1 (nurse)	Physical capacity tests (Table 4) (physiotherapist)					CA and psychological reactions 2 (psychologist)	
	Group discussion on existential perspectives (priest)						

CA: Cardiac Arrest; EC+PST: Energy Conservation plus Problem Solving Therapy

Note: Delivery of the SCARF programme required a minimum of 8 participants and group sessions required a minimum of 5 participants.

Table S2. Description of SCARF intervention components

Component	Description	Duration minutes
'Life after CA'	Presentation by a consultant cardiologist on the main causes of CA and frequent secondary problems with time for questions and discussion.	45
Presentation round	Introduction round with each participant explaining their background and hopes for the rehabilitation programme facilitated by the programme leader. Peer support is a frequent wish expressed by CA survivors.[1]	45
Energy conservation and problem-solving therapy (EC+PST)	Previously shown to benefit CA survivors with chronic fatigue.[2] Adaptation of intervention made in consultation with the original study authors.[2] Five sessions: 1. fatigue after CA, treatment for fatigue and sleep hygiene[3]; 2. introduction to EC+PST, identification and analysis of problems; 3. pros and cons of possible solutions and action plan; 4. telephone call (see below); 5. group reflection on EC+PST.	5 sessions 435 in total
Cognitive tests	Cognitive tests (See Table S8), chosen by the clinical psychology team (employed from the Center for Rehabilitation of Brain Injury, Copenhagen) based on known cognitive problems after anoxic brain injury.[4, 5] Test results fed back during the individual conversation. If necessary, the neuropsychologist could refer participants for further cognitive assessment within the Danish health service.	60
Physical activity	Delivered by a physiotherapist, covering benefits of physical activity including for fatigue,[6] adult physical activity guidelines and physical activity with a cardiac condition.[7, 8] Questions relating to a participants specific medical history were answered by the programme cardiologist (ADZ) or they were advised to speak to their own doctor.	120
Physical capacity tests	6-minute walk test, hand grip strength, and 30-second sit-to-stand test (see Table S7)	-
Existential discussion	Group session, facilitated by a priest about existential and spiritual questions after a life-threatening event.[9]	90
Active rest	Yoga and mindfulness may improve quality of life, anxiety and depression for patient with cardiac disease[10] and fatigue following brain injury.[11] The session was delivered by a physiotherapist and certified yoga instructor.	2x75
Individual conversation	A member of the clinical tam discussed the results of the self-reported survey, highlighting potential problem areas and possible solutions, but participants could also decide the topic of the conversation.	2x45
CA and psychological reactions	Education-based psychological interventions for CA survivors have shown improvement in anxiety and depression.[12, 13] This session was led by a psychologist based on a psychoeducational approach in small groups covering frequent psychological reactions to CA and possible coping strategies.	2x90
Morning exercise, yoga	Optional extra session with gentle exercise and yoga as per 'active rest'.	2x30

Working life	Optional group session, led by a social worker, providing advice and information on returning to work, sick-leave and job center support, including rights as per Danish legislation.	90
Intimacy	Optional group session, based on the PLISSET model[14] and led by a sexologist.[15]	90
CA, family and network	Optional group session, led by a nurse, considering the impact of life threatening illness on relationships, family and social lives with advice and facilitated group discussions.	90
6-week telephone call	Call provided encouragement and advice on already identified problems/goals and an opportunity to discuss a new problem/goal. Clinicians were provided with a semi-structured content guide and checklist.	20-40
SCARF booklet	Contents: 2-3 page summaries of education sessions, an optional 12-week exercise diary, and extra EC + PST worksheets.	-
Support from relatives	Participants could choose to attend with a close relative to provide help with self-care if necessary, emotional support and with transfer of new knowledge and behaviors into everyday life.	-

Table S3 Description of intervention materials as per TIDieR guidelines

Materials provided to facilitators of the intervention	Original papers on EC+PST by Kim et al. 2016, 2017.[2, 16] Training video for the original EC+PST intervention provided by Young Kim. Full EC+PST instruction manual in English and the participant sheets translated to Danish (forward backward translation process used). Written descriptions of the psychological tests provided at a training session by the neuropsychologist.
Materials provided to participants	A printed booklet containing photos and titles of all clinicians participating in SCARF, summary of session information, key points and sources of further information alongside extra participant sheets for the EC+PST intervention and a 12-week exercise diary. PowerPoint slides from all the sessions with presentations sent to participants via email after the SCARF programme. Paper copies of the EC+PST sheets filled in by participants for each session. Paper copies of their results for the self-reported and physical tests.

All training and intervention materials can be accessed by contacting the corresponding author.

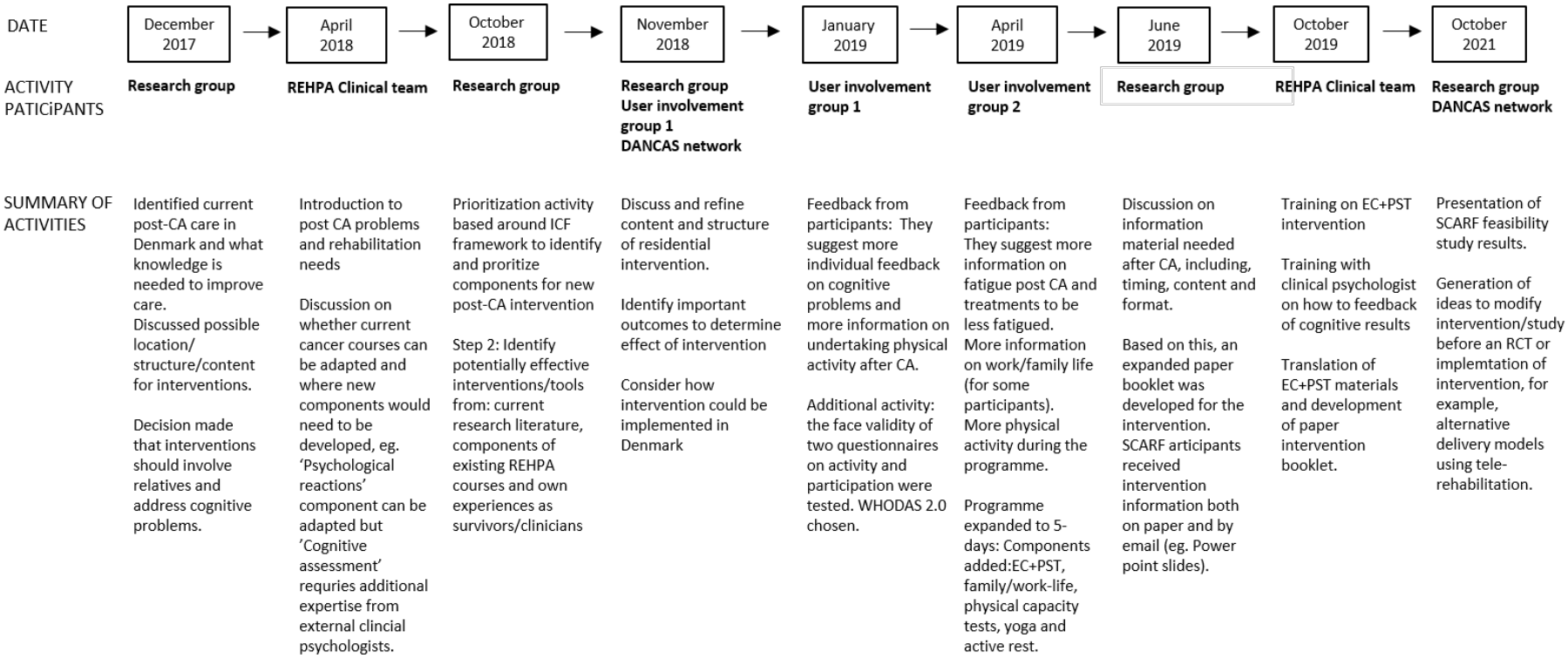
Table S4. Actions to consider for intervention development

Actions to consider	Development of SCARF intervention
Plan the process	Problem identified: more people are surviving cardiac arrest but with secondary problems physical, psychological and cognitive problems (source: personal experience ADZ, VJ and literature.[17-19]) Determine need for development of new intervention in Denmark (size of CA survivor population, prevalence of unmet needs) -Mapping of components of cardiac rehabilitation offered to CA survivors in Denmark.[20] -National survey of CA survivors in Denmark.[21] -Given the national survey will take time and intervention development will need expertise and resources, the DANCAS network was set up in 2018 to share knowledge and support research and clinical practice in the area of post-cardiac arrest care.[22] -Five year plan published to improve post-CA care in Denmark via research and clinical activities which included developing and testing of rehabilitation/support intervention.
Involve stakeholders	Involvement of stakeholders (see Figure S2 for timeline and summary of activities): Research Group: Composed of three CA survivors, one relative of a CA survivor, one representative from the Danish Heart Foundation, five clinicians with an interest in post-CA care, three researchers from the CA survivor rehabilitation project. DANCAS network: Researchers and clinicians with an interest in post-CA clinical care and research in this area (includes REHPA clinical team).[22] User-involvement group 1: CA survivors (n=10) and their relatives who took part in first 3-day preliminary course with 2 day follow-up to test intervention structure, content. User-involvement group 2: CA survivors (n=23) and their relatives (n=18) took part in second and third 3-day courses (no 2 day follow-up) to test intervention structure, content.
Bring together a team	Core research group described above, included acute cardiologists, expert in neurorehabilitation and cardiac rehabilitation. DANCAS network includes clinicians from all five regions and cardiac centers in Denmark. Experts brought in during the development process include Professor Mogens Hoder (expert patient and public involvement in research); neuropsychologists from Center for Rehabilitation of Brain Injury and Dr Young Kim, East Carolina University (expert in EC+PST).
Review published evidence	Published evidence reviewed to identify effective existing interventions for CA survivors. Where this evidence was absent similar patient groups were reviewed, for example, acquired brain injury, cardiac disease and people life threatening diseases, including cancer. Adaptation of an existing rehabilitation intervention for cancer survivors was considered as a delivery method, hence published evidence was reviewed to determine if/where secondary problems suffered by cancer survivors and potential interventions intersect with CA survivors, for example, fatigue,[23] anxiety and depression,[24,

	25] fear for the future,[26] reduced participation,[25] in home, work[27, 28] and family life and overall reduced quality of life.[24] A systematic review and meta-analysis was made of the effectiveness of rehabilitation interventions on the secondary consequences of surviving a cardiac arrest.[29]
Draw on existing theories	Intervention development influenced by the International Classification of Functioning, Disability and Health and specifically the expanded model proposed by Lilja, 2017.[30]
Articulate programme theory	Theory of change and logic modeled developed and refined (Figure 1, Table S5). Danish healthcare is universal and tax-funded. CA survivors are usually offered cardiac rehabilitation if their cause of CA is ischemic heart disease.[31] They may also be referred to psychological therapies, cognitive rehabilitation or physiotherapy for specific problems. However, this provision is inconsistent across Denmark and there is no specific rehabilitation for CA survivors.[31]
Undertaken primary data collection	Qualitative study undertaken with CA survivors involved in early iterations of a residential rehabilitation intervention.[1] Feedback obtained from participants in these preliminary programmes both written and from group discussions at the end of each programme.
Understand context	At the start of development, interventions for CA survivors were recommended in international guidelines[32] but there were no guidelines in Denmark recommending specific follow-up or identifying specific interventions for CA survivors (see figure S1).
Attend to future implementation	Residential rehabilitation enables multiple intervention components in a short time frame enabling national recruitment and participation of survivors. Other delivery methods could include outpatient or online (tele-rehabilitation), however, these may not be appropriate for older participants and require retention of participants for multiple outpatient attendances or 'log ins' to digital method. Intervention for developed deliberately in 'components' or blocks of interventions can be re shaped and delivery over a series of weeks in an outpatient or online intervention.
Design and refine	Two preliminary versions of the intervention were tested and the intervention refined via feedback from participants and clinicians via activities summarized in figure S1.

Table adapted from O'Cathan A, et al., 2019[33] 'Logic model for intervention development'.

Figure S1. Timeline, participants and summary of SCARF intervention development activities



Notes:

Description of participant groups:

Research Group: Composed of three CA survivors, one relative of a CA survivor, one representative from the Danish Heart Foundation, five clinicians with an interest in post-CA care, three researchers from the CA survivor rehabilitation project and one expert patient and public involvement in research.

REHPA Clinical team: Multidisciplinary team with experience of rehabilitation of people with life threatening diseases.

DANCAS network: Researchers and clinicians with an interest in post-CA clincal care and research in this area (includes REHPA clinical team).

User-involvement group 1: CA survivors (n=10) and their relatives who took part in first 3-day preliminary course with 2 day follow-up to test intervention structure, content.

User-involvement group 2: CA-survivors (n=23) and their relatives (n=18) took part in second and third 3-day courses (no 2 day follow-up) to test intervention structure, content.

All activities were facilitated by one or more of the project researchers (ADZ, LHT, VLJ)

Intervention development is illustrated here as a linear process for clarity but was iterative and dynamic with subjects continuously returned to and refined.

CA: Cardiac arrest; ICF: International Classification of Functioning, Disability and Health; EC+PST: Energy conservation and problem-solving therapy; WHODAS 2.0: World Health Organisation Disability Assessment Schedule

Table S5. SCARF logic model

Situation Survivors of cardiac arrest (CA survivors) suffer from interconnected problems: fatigue; impaired cognitive; psychological and physical problems. Different rehabilitation strategies have shown potential benefits to fatigue and other interconnected problems in the non-CA population. In addition, an energy conservation and problem-solving theory intervention (EC+PST) showed a reduction in fatigue in CA survivors. Hence, the design of a comprehensive rehabilitation programme focused on fatigue and secondary physical and psychological consequences of surviving a CA: SCARF (Survivors of Cardiac ARest Focused on Fatigue).			
Resources/Inputs	**Activities**	**Outputs**	**Outcomes**
Project team including experienced researchers and clinicians. Project reference group including experts in CA and rehabilitation research. PPI group including survivors of CA and their relatives. DANCAS network of stakeholders interested in post-CA care including the Danish Heart Foundation. Evidence for the needs of CA survivors and potential solutions from existing evidence and a new qualitative study and a new systematic review on rehabilitation after CA survivors.	PRO data collected from CA survivors and relatives at baseline, 3 months and 6 months. 5-day residential rehabilitation intervention focused on fatigue for CA survivors supported by their relatives. 12-week home programme using EC+ PST and an exercise-training diary including a phone call from clinical team at 6 weeks. 2-day residential follow-up programme. Psychosocial and existential support. Education on: Consequences of CA (the heart and the brain); sleep hygiene, and family/social/work life.	Development of the SCARF intervention programme manual. Development of the SCARF home education and workbook including EC+PST workbook and training diary in Danish. Development of presentations for the education components of SCARF. A telephone script and prompt sheet for clinicians for the Week-6 telephone call to improve adherence to SCARF intervention. Data on 1) recruitment 2) resources required 3) acceptability/satisfaction 4) adherence/completion of outcomes	Improvement in the individual problems suffered by CA survivors attending the SCARF intervention. A rigorously tested intervention for CA survivors that can be revised according to the results and conducted on a larger scale as part of a RCT to test efficacy. A battery of cognitive tests for use with CA survivors after hospital discharge, by clinical staff, to signpost to appropriate rehabilitation or correlation with a PRO outcome to do similar. Data from SCARF study published internationally to inform research and implementation of rehabilitation interventions for SCA globally.

Collaboration with the Center for Brain Injury to develop a battery of cognitive tests suitable for CA survivors. Facilities and funding to carry out 6 residential rehabilitation programmes. REDCap system and appropriate questionnaires to capture PRO data from CA survivors.	Assessment of cognitive problems and physical capacity. Individual feedback and goal setting. Peer support from other CA survivors via group sessions. Support from a relative where possible. Referral by lead physician of any participant found to need specialist intervention (e.g. psychology).	5) variance in outcomes/potential effect Increased knowledge and skills of REHPA clinical on fatigue management, rehabilitation with CA survivors and cognitive tests.	**Long term Impact** Implementation of rehabilitation interventions tailored to the needs of CA survivors in Denmark. CA survivors and their relatives achieve the best possible quality of life after their CA.

Table S6. Clinician satisfaction statements

Clinicians were asked to state their agreement with five statements for each intervention session they took part in.

	Subject of statement	**Clinician satisfaction statement in full**
1	Purpose	The purpose of the activity and my role in the activity was clear
2	Content	The content of the activity was appropriate for the participants
3	Duration	There was enough time to complete all planned activities
4	Location	The location or space was appropriate for the activity
5	Adequacy of training	I had had enough training to be in charge of the activity

Answer categories were ranged 1-5 with 1=strongly disagree to 5=strongly agree.

Table S7. Description of self-reported outcomes

Information on psychometric properties of self-reported outcomes is not available for CA survivors therefore information is presented for patient groups with similar symptoms/experiences, giving preference to acquired brain injury or cardiac disease or, if this is not available, patient groups who have experience a life threatening illness or chronic fatigue.

Outcome domain	Outcome measure	Items, scoring	Notes
Fatigue impact on functional activities	MFIS	The Modified Fatigue Impact Scale assesses impact of fatigue on functional activities in the previous four weeks. There are 21 items in three sub-scales (physical, cognitive and psychosocial). Frequency of impact is rated (never-almost always). Total scores range 0-84. Higher scores indicate greater impact of fatigue. Sub-scale ranges: physical, 0 to 36; cognitive, 0 to 40; and psychosocial, 0 to 8.[34]	Developed from interviews with people with multiple sclerosis (MS) to measure how fatigue affects their daily life activities.[35] In a MS population, content validity found to be excellent for physical and psychosocial subscales and adequate for cognitive subscale.[34] Found to be highly reliable across six months in mildly disabled persons with MS, the physical domain is more reliably captured than the psychosocial and the scale has good precision even with those with high levels of fatigue.[34, 36] Test- retest reliability good.[37] In addition, in people with mild to moderate brain injury, high internal consistency of the total and subscales was found, also strong convergent validity with the Beck Depression Inventory fatigue items and good to excellent accuracy of the MFIS in classifying fatigued versus non fatigued individuals.[38]
Fatigue severity	MFI-20	The Multidimensional Fatigue Inventory measures fatigue severity. Using 20 items rated on agreement with statements (Yes, that is true - No, that is not true) covering five dimensions; general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Range 4-20. Higher scores indicate greater fatigue. Dimension scores cannot be added to give a total score.[39]	Construct validity, internal consistency and convergent validity (with a Visual Analogue Scale of fatigue) originally established in cancer patients and those with chronic fatigue syndrome.[39] This was confirmed in a further study with cancer patients that also demonstrated satisfactory reproducibility and sensitivity to change.[40] In a coronary artery disease population, the MFI-20 showed adequate construct validity and internal consistency.[41]
Generic health	EuroQol 5D 5L	Five items in five health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Divided into five levels: 1='No problems' to 5= 'Extreme problems', scores ≥ 2 signifies a problem. Sixth item for self-rating of	Recommended in the Core Outcomes set for Cardiac Arrest (COSCA) Advisory statement[43] as a measure of Health related quality of life in trials involving cardiac arrest survivors. Excellent reliability and validity has been shown across populations though responsiveness needs further investigation.[44]

		health in Visual Analogue Scale, 0-100. Higher scores signify better health status.[42]	
Mental well-being	HADS	Hospital Anxiety and Depression Survey, 14 items in two sub-scales (anxiety: HADS-A; depression: HADS-D). Total subscale scores range: 0-21. Both subscale scores can be interpreted as follows: 0-7 points is considered within normal range, 8-10 is suggestive of the mood disorder, ≥8 indicating probable presence of the mood disorder.[45]	In a Danish population with cardiac disease evidence was found for convergent validity and high internal consistency for symptoms of both anxiety and depression HADS outcomes.[46] Found to have excellent short term and adequate medium term test re-test reliability in a coronary heart disease population.[47]
Function and disability	WHODAS 2.0	World Health Organisation Disability Assessment Schedule, a generic instrument with 36 items assessing 6 domains of functioning: understanding and communication; self-care; mobility; interpersonal relationships; work and household roles; and community and civic roles. Scored from 0= 'no difficulty' to 4= 'extreme difficulty or cannot do'. Range 0-100. Higher scores indicate greater difficulty with function and disability.	Developed by the World Health Organisation based on the conceptual framework of the International Classification of Functioning, Disability and Health.[48] Multiple studies were carried out during the development phase across countries and patient populations (including 65,000 people) finding high internal consistency, a stable factor structure, high test-retest reliability, good concurrent validity with other recognized disability measurement instruments; and good responsiveness. High construct validity has been confirmed in subsequence studies including acquired brain injury and cardiac conditions.[49]
Physical activity	IPAQ Short Form	The International Physical Activity Questionnaire Short Form, 7 items collecting information on time spent walking, and vigorous- /moderate- intensity physical activity in the last 7 days. Total activity time is reported as metabolic equivalents per week.[50]	Acceptable criterion validity established with comparison with accelerometers in people with multiple sclerosis[51] and adults[50] and acceptable test-retest reliability.[50] Though in other studies (akin to other self-report measures of physical activity) the IPAQ-SF tends to overestimate physical activity when compared to objective measures.[52]

Table S8. Description of physical capacity tests

Test	Test procedure and scoring
30 second chair-stand test	Measures lower body strength. Conducted as described by Jones et al. 1999.[53] Participants stand and sit as many times as possible in 30 seconds without using their hands. Modified version allows use of hands if necessary. Number of full sit-to-stands used for data analysis
6-minute walk test	Tests functional exercise capacity.[54] Participants walk as many laps of a 30m course as possible in 6 minutes.[55] Total distance walked and percentage reference distance (calculated using an age and sex matched reference population) used for data analysis.
Hand grip strength	Grip strength is a common measure of global muscle strength and physical capacity.[56-58] Measured in kg. using a hand dynamometer using the procedure as in Roberts et al. (2011).[56] Mean of three measurements used for data analysis.

Table S9. Cognitive tests conducted by neuropsychologist

Cognitive test
– Trail making test A+B – Wechsler Adult Intelligence Scale (digit span forwards, digit span backwards, digit symbol coding – Five-point test – Repeatable Battery for the Assessment of Neuropsychological Status (word list, recall, recognize) – Word fluency (animals, s and b+k)

All tests are described in Neuropsychological Assessment 5th edition by Muriel Lezak[59]

Table S10. Physical capacity test outcomes at baseline and intermediate follow-up

Time point	**Baseline**	**Intermediate (12 weeks after baseline)**		
Physical capacity test	Mean (SD) n=38	Mean (SD) n=35	Mean difference baseline to intermediate (95% CI)[a]	Effect size Cohen's d
30-second chair-stand test (repetitions)	16.6 (5.0)	19.4 (5.8)	2.7 (1.8, 3.5)	0.52*
6 minute walk test (meters)	575.0 (102.1)	603.6 (100.8)	18.7 (0.1, 37.3)	0.36*
Percentage reference distance (%)[b]	103.8 (15.4)	108.4 (15.3)	3.8 (0.9, 6.7)	0.46*
Hand grip test Right	38.1 (11.0)	39.4 (11.0)	-0.2 (-1.8, 1.3)	0.06
Hand grip test Left	36.4 (10.8)	38.7 (11.3)	2.0 (-2.6, 6.5)	0.14

[a]Change from baseline to intermediate outcome calculated from mean and SD from participants who completed both baseline and intermediate self-report (n=38) and physical capacity measure (n=33)

[b]6 minute walk test distance percentage reference distance for each participant calculated using an age and sex matched reference population.

* Effect size ≥0.3

Table S11. Differences in baseline self-reported outcomes between 6 month (final follow-up) completers and non-completers

Participant characteristic	Baseline 6 month completers Mean (SD) n=26	Baseline 6 month non-completers Mean (SD) n=13	Mean difference (95% CI)	p value[a]
Age (years)	59.5 (2.0)	53.6 (3.0)		0.12
Gender, male (n, %)	19 (73)	9 (70)		0.56
Time since CA (months)	17.9 (12.7)	17.5 (12.5)		0.70
Cognitive deficits (n, %)	6 (24)	5 (38)		0.35
Outcome measure				
MFIS total	24.3 (17.4)	39.6 (18.3)	15.3 (3.1-27.5)	0.02*
Physical	11.0 (8.0)	17.5 (9.5)	6.5 (0.7, 12.4)	0.03*
Cognitive	11.20 (9.7)	18.4 (9.4)	7.2 (0.6, 13.8)	0.03*
Psychosocial	2.2 (2.2)	3.7 (2.6)	1.5 (-0.6, 3.1)	0.06
MFI-20 General fatigue	13.4 (4.5)	13.6 (3.3)	0.2 (-2.6, 3.0)	0.89
EuroQol 5D 5L VAS	63.5 (20.7)	53.7 (23.6)	-9.8 (-24.8, 5.1)	0.19
HADS Anxiety	7.1 (4.5)	9.0(4.8)	1.9 (-1.2, 5.1)	0.22
HADS Depression	4.6 (3.2)	7.7 (4.6)	3.1 (0.5, 5.7)	0.02*
WHODAS 2.0 total	20.6 (13.7)	27.7 (17.0)	8.4 (-1.2, 18.0)	0.08
Understanding and communication	18.8 (17.9)	23.7 (21.3)	4.0 (-10.0, 18.0)	0.56
Getting around	9.4 (11.4)	16.5 (20.0)	8.1 (-1.9, 18.1)	0.11
Self-care	5.3 (12.00)	13.5(20.4)	10.3 (1.4, 19.2)	0.02*
Getting along with people	23.1 (24.1)	26.9 (25.6)	8.1 (-1.9, 18.1)	0.11
Life activities	37.7 (26.1)	42.1 (31.9)	4.8 (-14.6, 24.2)	0.62
Participation in society	29.9 (16.9)	43.3 (20.0)	13.3 (1.0, 25.7)	0.04*
IPAQ	3993 (3502)	4726 (5609)	733 (-2227, 3693)	0.62

[a]Differences in means between completers and non-completers tested by Kruskall Wallis test and differences in proportions tested by Pearson Chi squared test. CA: Cardiac Arrest; MFIS: Modified Fatigue Impact Scale; MFI: Multidimensional Fatigue Inventory; VAS: Visual analogue scale; HADS: Hospital Anxiety and Depression Scale; WHODAS-2.0: World Health Organisation Disability Assessment Schedule 2.0. *p-value <0.05 regarded as significant

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Appendix 5:

Publications and conference contributions during the PhD project

Appendix 5: Publications and conference contributions during the PhD project

Peer-reviewed articles

Stripp KT, Joshi VL. **En oversigt over eksistentielle bekymringer hos hjertestopoverlevere og implikationerne for rehabilitering: Har vi brug for et nyt værktøj i værktøjskassen?** [A review of the existential concerns of cardiac arrest survivors and the implications for rehabilitation: Do we need a new tool in the toolbox?]. Tidsskrift for Forskning i Sygdom og Samfund - Journal of Research in Sickness and Society *(In peer review)*

Rosenkilde S, Missel M, Wagner, MK, Dichman C, Hermansen AS, Larsen MK, Joshi VL, Zwisler AD, Borregaard B. (2022) **Caught between competing emotions and tensions while adjusting to a new everyday life. A focus group study with family caregivers of out-of-hospital cardiac arrest survivors.** Eur J Cardiovasc Nurs: 2022 Jul 8; (00):1-8.

Wagner MK, Kikkenborg Berg S, Hassager C, Joshi VL, Stenbaek DS, Missel, M. (2021). **Feeling understood for the first time: experiences of participation in rehabilitation after out-of-hospital sudden cardiac arrest.** Eur J Cardiovasc Nurs: 20(8):767-74.

Dichman C, Wagner MK, Joshi VL and Bernild C. (2021). **Feeling responsible but unsupported: How relatives of out-of-hospital cardiac arrest survivors experience the transition from hospital to daily life - A focus group study.** Nurs Open: 8(5):2520-27.

Kim YJ, Joshi VL and Wu Q. (2021). **Subjective factors of depressive symptoms, ambulation, pain, and fatigue are associated with physical activity participation in cardiac arrest survivors with fatigue.** Resusc Plus: 5:100057.

Tang LH, Joshi VL, Egholm CL and Zwisler AD. (2020). **Are survivors of cardiac arrest provided with standard cardiac rehabilitation? - Results from a national survey of hospitals and municipalities in Denmark.** Eur J Cardiovasc Nurs: 2021;20(2):115-23

Scientific conferences

Joshi VL, Tang LH, Borregaard B, Wagner M, Guldin MB, Zwisler AD**. Anxiety and depression in relatives of cardiac arrest survivors and whether this is affected by accompanying a survivor to a residential rehabilitation intervention**. *(Poster presented at the ERC Congress, Antwerp, 16-17 June 2022)*

Joshi VL, Tang LH, Borregaard B, Zinckernagel L, Mikkelsen TB, Zwisler AD. **Do Danish healthcare services meet the information and rehabilitation needs of Danish out-of-hospital cardiac arrest survivors?** *(Poster presented at the ERC Congress, Antwerp, 16-17 June 2022)*

Joshi VL, Tang LH, Zwisler AD**. Patient and public involvement in the development of a rehabilitation intervention for survivors of cardiac arrest in Denmark**. (*Presented at the Fourth international symposium on Post cardiac arrest care, Lund, Sweden, May 2019*)