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Cognitive impairment and psychopathology in Out-of-Hospital Cardiac Arrest survivors in Denmark. The REVIVAL cohort study protocol

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ABSTRACT

INTRODUCTION: Cognitive impairment and psychopathology caused by brain hypoxia and the traumatic impact of critical illness are common in cardiac arrest survivors and can lead to negative consequences of everyday life functioning, and further impact mental health in relatives. Most studies have dealt with the mere survival rate after cardiac arrest and not with long-term consequences to mental health in cardiac arrest survivors. Importantly, we face a gap in our knowledge about suitable screening tools in the early post-arrest phase for long-term risk prediction of mental health problems. This study aims to evaluate the feasibility and efficacy of a novel screening procedure to predict risk of disabling cognitive impairment and psychopathology after cardiac arrest. Furthermore, the study aims to evaluate long-term prevalence of psychopathology in relatives.

METHODS AND ANALYSES: In this multicenter prospective cohort study, out-of-hospital cardiac arrest survivors and their relatives will be recruited. The post-arrest screening includes the Montreal Cognitive Assessment (MoCA), the Hospital Anxiety and Depression Scale (HADS), the Impact of Event Scale-Revised (IES-R) and the Acute Stress Disorder Interview (ASDI) and is conducted during hospitalisation. In a sub-sample of the patients, functional magnetic resonance imaging is done, and cortisol determination collected. At 3-months follow-up, the primary study outcomes for 200 survivors include the Danish Affective Verbal Learning Test-26 (VAMT-26), Delis-Kaplan Executive Function System tests (trail-making, colour-word interference, word and design fluency), Rey's Complex Figure and Letter-number sequencing sub-test of Wechsler Adult Intelligence Scale-IV, HADS and IES-R. For the relatives they include HADS and IES-R.

ETHICS AND DISSEMINATION: The study is approved by the local regional Research Ethics Committee (H-18046155) and the Danish Data Protection Agency (RH-2017-325, j.no.05961) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may impact the follow-up of cardiac arrest survivors.

Article summary

Strength and limitations of this study

- A strength of the study is the prospective design and consistent follow-up with the use of standardised and validated measurement tools.
- A limitation of the study is the differential loss to follow-up which can introduce bias and challenge the internal validity of the study.
- A strength of the study is the multicenter approach. This will improve statistical power and generalisability of the results.
- A strength of the study is its potential to contribute to a better referral from cardiac care to targeted rehabilitation services.

INTRODUCTION

The global incidence of cardiac arrest with assumed primary cardiac cause is 55/100,000 inhabitants (1). In Europe approximately 275,000 people with all-rhythm cardiac arrests are treated by the Emergency Medical Systems (EMS) each year (2). Out-of-hospital cardiac arrest (OHCA) is a significant cause of global mortality (3). However, in recent years the survival rates have improved especially in developing countries due to advances in the chain of survival (1). At present the majority of published OHCA studies focus on the acute prehospital and intensive care treatment of OHCA sufferers. Far fewer studies have investigated the period from early recovery to long term return to everyday life. The existing literature on this period highlights two critical challenges for cardiac arrest survivors in the post-arrest recovery process, firstly diminished neurocognitive functions and secondly disabling emotional difficulties (4–8). In these survivors, long-term cognitive impairment and psychopathology constitute both a major personal and family burden, as well as a public health and economic concern (9–16).

Mild to moderate cognitive sequelae are reported in up to 50% of survivors (6,17). Transient or permanent memory loss, attention deficit and executive impairment are the most dominant cognitive impairment found in this population (5,6,18). Importantly, impaired cognitive functioning at 3-months post-arrest has been found to correlate with worse physical and mental Health-related Quality of Life (HRQoL), and not being able to return to work around the first year after OHCA (19). Cardiac-induced cerebral hypoxia cause a diffuse injury that may damage the functional integrity of the brain (20) and cause cognitive impairment (21,22). Resting state functional magnetic resonance imaging (fMRI) is an informative imaging method that assays functional integrity and level of communication within the brain (3, 11). In a recent study, patients with increased within-network and decreased between-network functional connectivity in the acute phase after cardiac arrest survival had a favorable outcome (FO) one year later compared to patients with a non-favorable outcome (nFO) (13), suggesting higher functional integrity in patients with a FO. This increased within-network functional connectivity was also observed in a smaller study of cardiac arrest patients with good outcome at hospital discharge (14). To date, no reliable cognitive screening or imaging method for use during the in-patient hospitalisation that can detect risk of long-term cognitive impairment in cardiac arrest

patients exist. A post-arrest screening model may contribute to prompt initiation of relevant follow-up and targeted cognitive rehabilitation.

A cardiac arrest is a severe and traumatising life event and long-term post-arrest psychopathology is prevalent (5,23–25). Processing near-death experiences, coping with prolonged preoccupation with somatic symptoms and fear of a second cardiac arrest is a burden to many cardiac arrest patients (5,23). Up to 61% of cardiac arrest patients experience anxiety, up to 45% depression and up to 27% post-traumatic stress disorder (PTSD) (5). In particular, anxiety and depression have been found to negatively impact Health-related Quality of Life (HRQoL) and physical health in patients up to several years after survival (26). Furthermore, a cardiac arrest yields the highest prevalence of PTSD among cardiac disease categories (23), and PTSD is reported to double the overall risk of mortality, recurrence of a new cardiac event, and causing long-term diminished mental health and quality of life (8,27). Little is currently known about the role of acute emotional reactions for developing long-term psychopathology in cardiac arrest survivors, but high acute stress reactions in other patient populations appear to be associated with worse long-term outcomes (28–30). Elucidating the role of acute emotional reactions may serve to support and advice the patients about future challenges, and to initiate targeted psychological interventions.

Being the close relative of a cardiac arrest survivor can cause enduring psychological strains (31–33). Research indicates that these psychological strains are caused by a burden of witnessing the cardiac arrest, having to care for the patient and from the emotional stress of living with someone who is at risk of another cardiac arrest (34). At 1-year post-arrest, 40% of the close relatives of patients with brain injury are still experiencing a high impact of the cardiac event and display a more severe traumatic stress level than the patient (Armand S. The acute traumatic stress response is associated with long-term post-traumatic stress in cardiac arrest survivors and their close relatives, Unpublished, March, 2020) , and after 2 years these caregivers show a higher level of trauma-related stress than that observed in the general population (35). As a growing number of patients are surviving cardiac arrest it is crucial to focus more attention on psychological challenges in relatives in the aftermath after surviving cardiac arrest.

The overall aim of the current study is therefore to evaluate and test a novel screening procedure during hospitalisation for its feasibility and ability to predict at-risk patients for disabling cognitive impairment and psychopathology at 3-months. The incidence of psychopathology in close relatives 3-months post-arrest will also be explored. Overall, we hypothesise that the screening procedure will be feasible and able to identify at-risk patients for disabling cognitive impairment and psychopathology at 3-months follow-up. In particular that:

Hypothesis 1: Lower level of cognitive impairment during hospitalisation (screening) is positively associated with cognitive outcome at 3-month follow-up.

Hypothesis 2: The strength of discrete resting-state networks in the brain assessed with fMRI during hospitalisation (screening) is positively associated with cognitive outcome at 3-months follow-up.

Hypothesis 3: Higher level of acute emotional reactions during hospitalisation (screening) is positively associated with psychopathology outcome at 3-months follow-up.

Hypothesis 4: Higher level of cognitive impairment and emotional reactions during hospitalisation in patients is positively associated with psychopathology outcomes in relatives at 3-months follow-up.

METHODS AND ANALYSIS

Study design, setting and population

The REVIVAL (REcovery after cardiac arrest surVIVAL) study is designed as a multicenter, prospective cohort study in which first-time out-of-hospital cardiac arrest (OHCA) survivors are followed for up to 1 year after the event (flowchart presented in figure 1). The study settings are three highly specialized heart centers at university hospitals in Denmark: Rigshospitalet and Herlev-Gentofte Hospital in the Capital Region of Denmark and Odense University Hospital, in the Southern Region of Denmark. All cardiac arrest patients will be approached for study participation and approximately 250 in-hospital patients (≥18 years of age) with a first-time OHCA admission diagnosis will be recruited. Only patients with a presumed cardiac cause for their cardiac arrest will be included. Both cardiac arrests as primary and secondary diagnosis will

be included. Furthermore, the closest relatives will be identified and included during hospitalisation for a 3-months follow-up. Patients are excluded if they have a serious not treatable other somatic or psychiatric illness or previous cerebrovascular events or traumatic brain injury and those unable to speak and understand Danish. The cognitive screening and neuropsychological testing require the patients to follow verbal instructions and to see the tasks presented. Therefore, patients with solid hearing or visual impairments are excluded. In a sub-study exploring resting state fMRI and stress reactivity, respectively 40 patients without contraindications to MR will be included from Rigshospitalet. The REVIVAL study is described in accordance with the current Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Guidelines for reporting observational studies) (36).

Patient selection and recruitment

All the patients and relatives are selected and recruited in the three Danish cardiology wards. OHCA survivors transferred from the intensive care unit (ICU) to the ward will be included four to nine days after termination of analgo-sedatives to ensure no residual sedation used during therapeutic hypothermia. The survivors from the coronary care units will be included immediately after coronary intervention in cardiac catheterisation laboratory (figure 1). This subgroup of cardiac arrest survivors will be included although they are awake or only had a brief period of coma after admission to the hospital and presumably recover earlier to their premorbid cognitive functioning than the critically ill patients. The patients and relatives at the included sites follow the same protocol.

A trained cardiac nurse will collect most of the clinical data from the patients' charts. The same nurse will approach eligible patients during hospital admission on the cardiology ward and invite them to participate in the study. The patients will be assessed clinically and provided with oral as well as written information about the study. The patients are given the opportunity to read and consider the study information leaflet carefully. If the patients agree to participate, they will be asked to provide written informed consent in consultation with their closest relative prior to inclusion. This is justified in ethical issues as some patients with cognitive impairment may not feel empowered to refuse participation.

Collection of data and measures

Screening model during hospitalisation

A team of certified nurses with a background in cardiology will screen the patients. Administration and interpretation of data will take place under supervision by a trained psychologist.

C**ognition:** The cognitive screening is conducted using the Danish version of the *Montreal Cognitive Assessment tool* (MoCA), version 7.0 (37). The MoCA is a brief cognitive screening test designed to identify mild cognitive impairment. The MoCA covers six cognitive domains: Attention, visuospatial construction, executive functioning, memory, language and orientation (table 1), and is rated from 0-30. A cut-off ≥26 is considered as normal cognitive function level. In the summary score a level of education ≤12 years is given an extra point as education level has shown to decrease the overall score (37). The MoCA is suggested for use in the post cardiac arrest settings (38,39), however, it remains to be evaluated in a Danish patient population with possible hypoxic-ischaemic brain injury. The MoCA has shown high level of internal reliability with Cronbach's $\alpha = 0.83$ in detection of mild cognitive impairment (37).

Mood and delirium: As symptoms of delirium often are subtle but still can have an impact on cognition, the cognitive screening is initiated with a rapid clinical assessment of delirium, using 4AT scale (40). Furthermore, the mood state and functional independence of the patients is collected (table 2). If the study nurse is in doubt regarding patients functioning, an informed nurse or relative is asked (41).

Resting state fMRI: Patients who meet inclusion criteria for MRI will undergo structural and functional brain imaging on a 3 Tesla Siemens Prisma MRI scanner at Rigshospitalet. Trained personnel will perform MRI scans; during transport and scanning, a trained nurse will monitor the patients. We will obtain high-resolution structural T1- and T2-weighted images and T2*-weighted BOLD fMRI resting state scans (~10 minutes of resting state fMRI). During resting state fMRI, patients are asked to lie still with eyes closed and let their mind wander freely. Resting state fMRI data will be processed using canonical brain imaging tools, e.g. SPM (42) and Conn (43) to establish region-to-region connectivity estimates while accounting for

motion, physiological and other noise sources. Resting state networks will be defined based on *a priori* connectivity networks descriptions (44).

Psychopathology: Self-rated symptoms of depression and anxiety and trauma reactions will be collected using the Hospital Anxiety and Depression Scale (HADS-D and HADS-A) (45), and the Impact of event Scale-revised (IES-R) (46). The Hospital Anxiety and Depression Scale (HADS) is a valid and internally consistent 14 items instrument to measure anxiety and depression. Each item is scored from 0-3 with a summary score between 0 and 21 for either anxiety or depression. Scores of 11 and above indicate the probable presence of a mood disorder. HADS has shown a mean α of 0.83 and 0.82 for the HADS-A and HADS-D, respectively (47). Impact of Event Scale - revised (IES-R) measures distress caused by a traumatic event is a widely used measures to assess traumatic stress symptoms with a maximum score of 88. The IES-R consist of 22-items measuring subjective distress caused by a traumatic event scored on a Likert scale from 0 (not at all) to 4 (extremely) and includes subscales for avoidance, intrusions and hyperarousal. The IES-R has shown high internal consistency with coefficient alphas ranging from 0.84 to 0.85 for avoidance, 0.87 to 0.92 for intrusion, and 0.79 to 0.90 for hyperarousal (46).

Acute Stress disorder: The Acute Stress Disorder Structured interview (ASDI) is a 19-item clinical interview which investigates the incidence and severity of acute stress responses operated as acute stress disorder (ASD) in DSM-5 in the month following trauma exposure (48,49). Acute stress disorder is divided into five symptom clusters: intrusive memories or revival, negative mood, dissociation, avoidance and arousal. To meet the criteria for acute stress disorder, the patient must have experienced a traumatic event (in this case a cardiac arrest) during the past month (criteria A) as well as the presence or deterioration of at least nine symptoms independent of the associated category after the onset of episode (Criterion B), which should occur within three days to one month (Criterion C) (50).

Cortisol Awakening Response: At the same day as the structured clinical interview (i.e. ASDI) is performed, saliva samples for determination of the Cortisol Awakening Response (CAR) will be obtained from eligible patients. Five samples are collected during awakening and three saliva samples will also be

collected during the day at 12 at 18 and at 23 o´clock. The total amount of saliva per patient is 16 ml. After collecting the saliva, the samples will be stored and analysed at the Department of Clinical Biochemistry, Rigshospitalet, Glostrup.

Sociodemographic variables and several clinical pre- and inhospital data were obtained from electronic medical records (see table 2).

At 3-months follow-up

The patients included at Rigshospitalet and Herlev-Gentofte Hospital will undergo a detailed and individual neuropsychological assessment at the Neurobiology Research Unit at Rigshospitalet, and patients included at Odense University Hospital will be assessed with a similar test battery at the University of Southern Denmark. The cognitive assessment of the patient's cognitive functions will be given, administered and interpreted by a clinical and trained psychologist or psychology student under supervision. The patients and their relatives will furthermore complete a package of self-reported questionnaires.

The neuropsychological assessment: The tests used are a carefully selected neuropsychological test battery comprising the same subcomponents as for the MoCA; *attention, visuospatial construction, executive functioning, memory, language and orientation*. The tests used are all validated in clinical settings for a variety of populations and have shown good test-retest reliability. To address a source of bias, all tests are conducted by a psychologist, who is kept blind of the clinical data as well as the results of the previous brief cognitive screening. A detailed outline of the neuropsychological tasks includes: Danish Affective Verbal Learning Test-26 (VAMT-26) (51) and Delis-Kaplan Executive Function System tests (D-KEFS) comprising trail-making, colour-word interference, design fluency and word fluency (52) together with the Rey's complex figure test (53) and Letter-number sequencing test from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (54) (table 1).

Psychopathology in patients: Furthermore, the patients will repeat the self-reported questionnaires identical to the questionnaires completed during hospitalisation: HADS-D, HADS-A and IES-R.

Psychopathology in relatives: The relatives are also asked to complete the HADS-D, HADS-A and IES-R. The questionnaires for both patients and their relatives are sent via e-mail two weeks before the 3-months follow-up.

At 1-year follow-up

The 1-year follow-up is designed as register-based (table 2). To investigate whether baseline data are associated with morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure and with mortality and health care utilisation, the collected data will be linked with data from national administrative registers; the Danish National Patient Register (55), the Danish Civil Registration System (56), the Danish National Prescription Registry (57), the Danish education registers (58), and the Danish registers on personal income and transfer payments (59).

Primary and secondary study outcome measures

Primary outcome measures for patients

The primary outcome is whether the patients present a favourable outcome (FO) or a non-favourable outcome (nFO) at 3-month follow-up. To elucidate cognition and psychopathology separately, primary outcomes will be established for each of these domains.

Cognition: As primary cognitive outcome the patients will be divided into two groups, FO and nFO, based on their performance in the neuropsychological tasks. The subset with an nFO is defined as minimum 1.5 standard deviation (SD) under the norm or reference data (52,53,60,61) on minimum one test or 1 standard deviation on two or more tests. The rest of the patients fall into the FO group.

Psychopathology: As primary psychopathology outcome the patients will be divided into two groups, FO and nFO, based on their scores on the HADS and IES-R. The subset with an nFO is defined one or more scores above cut-off for psychopathology on the HADS and IES-R: HADS-D and HADS-A >8 and IES-R >24. The rest of the patients fall into the FO group.

Secondary outcome measures for patients

As secondary outcomes for patients are self-reported measures of sleep quality, fatigue, executive functioning, and health-related quality of life at 3-months of follow-up (table 2). A detailed description of the secondary outcomes is described in the supplementary material 1. Secondary outcomes for patients also include register-based information of morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure, mortality and healthcare utilisation at 1-year post-arrest (table 2).

Primary outcome measures for relatives

The primary outcomes for the relatives include HADS-D, HADS-A and IES-R (45,62) (table 3).

Secondary outcome measures for relatives

Secondary outcome measures for relatives include self-reported health-related quality of life, experience of cognitive changes in the patient after the cardiac arrest, social support, major depression, the quality in the relationship with the cardiac arrest survivor, and the extent to which the cardiac arrest is viewed as being central to one´s identity (table 3).

Several exploratory outcomes will also be collected (figure 1).

Data analysis plan

The collected socio-demographic data will be presented as means ± standard deviation (SD) or percentages, respectively and group differences will be calculated by t-tests (continuous data) or χ^2 (categorical data). Appropriate regression models will be used to examine the associations between screening performance during hospitalisation and the primary and secondary study outcomes. In all model's relevant covariates e.g. sex, age, comorbidity, time to return of spontaneous circulation, coma duration time, time at intensive care unit, time of hospitalization, etc. will be included (table 2). A formal power calculation of sample size has not been performed due to the several aims and potential analyses of this study. With no comparative patient groups and only few small existing studies, we aim for a sample size of 200 cardiac arrest survivors at three months follow-up for the primary outcome to be statistically and clinically significant.

Patient and Public Involvement

As a patient involvement method, two theme-based sessions involving *direct patient feedback* have been carried out in the early pilot and design phase of the study. The aim of these sessions was to 1) identify patient preferences regarding the cognitive screening procedure (figure 2), and 2) develop the research priorities including implementation of possible changes based on the patient's feedback. Data derived from the theme-based patient feed-back sessions provides the basis for the cognitive screening procedure in the REVIVAL study. To ensure further patient involvement, we plan to engage the patients in the planning phase of disseminating the results.

ETHICS AND DISSEMINATION

There is little to no discomfort for the patients and their relatives in this study. Due to the weakened constitution of the patients, the neuropsychological test at 3-months post-arrest could be experienced as taxing and can be divided into two days. The study complies with the Declaration of Helsinki and has been approved by the Danish national committee on health research ethics (H-18046155) and the Danish Data Protection Agency (RH-2017-325, I-Suite no: 05961). Patients and their relatives will receive oral and written information about the study and inclusion will require obtained written consent for all participants before enrolment. Results from this study will be disseminated at regional, national and international conferences and in peer-reviewed journals.

Authors' contributions

Department of Cardiology, Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Copenhagen University Hospital Rigshospitalet (Wagner, Berg, and Hassager) and Neurobiology Research Unit, Rigshospitalet (Stenbæk, Fisher and Knudsen) has full access to all the data in the study and takes responsibility for the integrity of the data and the following analysis.

Study concept and design: Wagner, Berg, Hassager and Stenbæk

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Wagner and Stenbæk

Critical revision of the manuscript for important intellectual content: All authors

Obtained funding: Wagner, Berg, Hassager and Stenbæk

Statistical analysis: Wagner, Stenbæk and Ekholm.

Administrative, technical, or material support: Wagner and Stenbæk.

Furthermore, Jensen PS Database Manager at Neurobiology Research Unit, Rigshospitalet and Britt Corfixen, Project Coordinator, clinical biochemistry department, Glostrup, Rigshospitalet.

Study supervision: Berg, Hassager and Stenbæk

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Competing interest statement

On behalf of all authors, the corresponding author states that there are no conflicts of interest related to this study. The funding sources have no role in the design and conduct of the study.

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The cognitive assessment		
	During hospitalisation	**3-months follow up**
Target cognitive domain	**MoCA**	**Neuropsychological tests**
Attention	Number sequence Letter list	D2 (visual attention) (Trail-making + stroop)
Visuospatial construction	Cube copying	Rey's figure
Episodic memory	Verbal memory test	VAMT-26
Working memory	Serial subtraction	Letter-number sequence
Executive functioning	Trail making B Clock drawing Abstraction	Trailmaking B D-KEFS colour-word interference
Psychomotor Processing speed	Trail making B	Trail making A and B
Language	Naming Repeating Word mobilization	
Orientation	Orientation	

MoCA: Montreal Cognitive Assessment**, D2**: D2 test of attention, **VAMT-26**: Danish Affective Verbal Memory Test-26 (VAMT-26), **D-KEFS**: Delis Kaplan Executive Function System

Table 1

Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors		
Outcome domains and measurement instruments	**Time of measure**	**Type of quantity**
Sociodemographic variables		
Age	T0	Continuous
Sex	T0	Binary
Marital status, type of occupation, employment status, living situation	T0	Categorical
Medical variables		
Known IHD, hypertension, previous MI, PCI or CABG, chronic heart failure, diabetes mellitus, COPD and chronic kidney disease	T0	Binary
Clinical variables related to the cardiac arrest		
Place of OHCA, aetiology of cardiac arrest, initial rhythm, TTM, medication during ICU stay, LVEF	T0	Categorical
Bystander witnessed cardiac arrest, bystander performed CPR, Use of AED, shockable rhythm, awake at arrival to hospital, TTM, intubated, medication during ICU, delirium at ICU	T0	Binary
Time to ROSC, intubation time, length of stay at ICU	T0	Continuous
Consious state GCS	T0	Categorical
Neurological outcome CPC	T1	Categorical
Length of stay at hospital	T1	Continuous
Performance based variables		
Delirium score 4AT	T1	Categorical
Functional independence Barthel Index- 20	T1	Categorical
Cognitive status MoCA	T1	Binary
Brain activity while resting rsfMRI	T1	Continuous
Neuropsychological outcome VAMT-26, D- KEFS trail-taking, D-KEFS colour-word interference, D-KEFS design fluency, Rey's complex figure and Letter-number sequencing: sub-test of WAIS-IV	T2	Binary
Cortisol Awakening response	T1	Continuous
Patient-reported outcome measures		
POMS	T1	
HADS, IES-R, CSS	T1, T2	Continuous
B-IPQ, FSS, HeartQoL, SF-12, PSQI, CISS, BRIEF-A, ECR-R, AMCQ, CES-S, MTEQ, PTGQ, ACQ, NDEQ	T2	Continuous
Lifestyle changes, Health profile	T2	Categorical
Register based		
Depression, anxiety, dementia, chronical fatigue syndrome and heart failure, mortality and health care utilisation	T3	Continuous

T0: Pre-arrest, medical and clinical data, T1: During hospitalisation, T2: 3 months follow-up, T3: 1 year follow-up

ICU: Intensive Care Unit, **LVEF**: Left Ventricular Ejection Fraction, **OHCA**: Out-of-hospital Cardiac Arrest, **CPR**: Cardiopulmonary resuscitation, **AED**: Automated External Defibrillator, **ROSC**: Return of spontaneous circulation, **TTM**: Targeted Temperature Management, **IHD**: Ischemic Heart Disease, **MI**: Myocardial infarction, **PCI**: Percutaneous coronary Intervention, **CABG**: Coronary Artery Bypass Surgery, **COPD**: Chronic Obstructive Pulmonary Disease, **GCS**: Glasgow Coma Scale, **CPC**: Cerebral Performance Category, **MoCA**: Montreal Cognitive Assessment, **rsfMRI**: resting state functional magnetic resonance imaging, **VAMT-26**: Danish Affective Verbal Learning Test-26, **D- KEFS**: Delis–Kaplan Executive Function System,, **POMS:** Profile of Mood States, **HADS**: Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event- Revised, **CSS**: Crisis Support Scale, **B-IPQ**: Brief Illness Perception Scale, **FSS**: Fatigue Severity Scale, **SF-12**: 12-item short Form Survey, **PSQI**: Pittsburgh Sleep Quality Inventory, **CISS**: Coping Inventory for Stressful Situations, **BRIEF-A**: Behavior Rating Inventory of Executive Functions, adult version, **ECS-R**: Experience in close relationships, **AMCQ**: Autobiographical Memory Characteristics Questionnaire, **CES-S:** Centrality of Events – Short, **MTEQ**: Memory of Event Scale, **PTGQ:** Post Traumatic Growth Questionnaire, **ACQ**: Attribution, **NDEQ:** Near-death Experience Questionnaire,

Table 2

Outcome domains, measurement instruments and measurement time for the relatives		
Outcome domain	**Measurement instruments**	**Time**
Demographic variables and psychiatric medical history		T2
Health-related quality of life	**SF-12**	
Anxiety and Depression	**HADS**	
Distress caused by a traumatic event	**IES-R**	
Experience in close relationships	**ECR-R**	
Social support after a crisis	**CSS**	
Major depression	**MDI**	
The extent to which an **event** is viewed as being central to one's identity	**CES-S**	
Cognitive decline reported by informants (relatives or close friends)	**IQ-CODE**	

T2: 3 months follow-up

SF-12: 12-item Short Form Survey, **HADS**: Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event- Revised, **ECR-R**: Experience in close relationships, **CSS**: The Crisis Support Scale, **MDI:** Major Depression Inventory, **CES-S**: Centrality of Event short, **IQ-CODE**: The Informant Questionnaire on Cognitive Decline in the Elderly.

Table 3

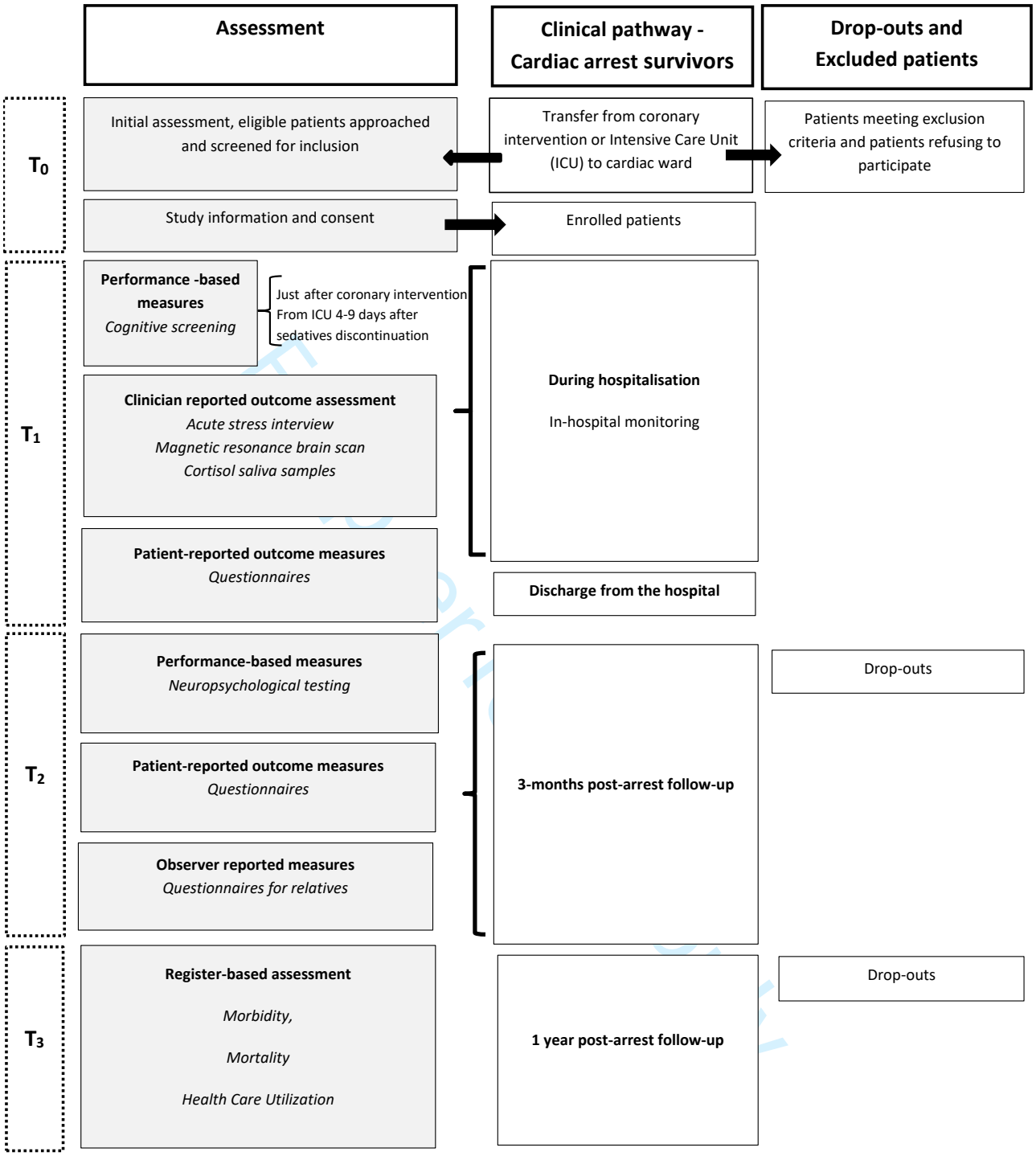

Figure 1: Flowchart of study assessment

T0: Study inclusion, **T1**: During hospitalisation, **T2**: 3 months follow-up, **T3**: 1-year follow-up

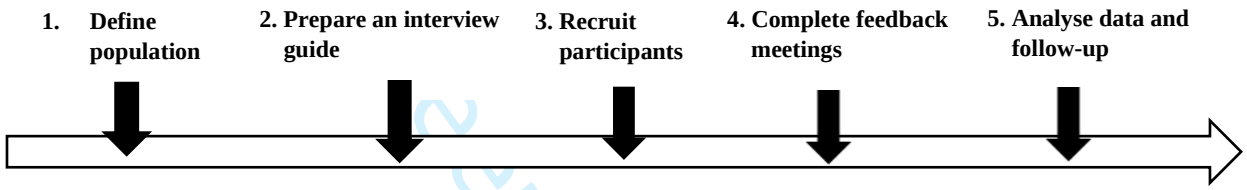

Figure 2

Direct patient-feed back

Supplementary material 1: Description of secondary outcomes

Sleep quality

The Pittsburgh Sleep Quality Inventory (**PSQI**) is a 19-item measure which assesses sleep quality and disturbances over the last months. The items generate a seven-component score each weighted equally on a 0-3 scale. The sum of these scores provides a global score. Higher scores indicate worse sleep quality. A cut-off score of >5 indicates poor sleep quality (64). The PSQI has demonstrated internal consistency reliability with Cronbach's α 0.83 (65).

Fatigue

Fatigue Severity Scale **(FSS)** is a nine-item questionnaire that measures experienced severity of fatigue symptoms in daily activities on a seven-point scale. A mean score is calculated (range 1–7) with higher scores reflecting greater fatigue. The FSS has shown construct validity with correlation coefficient of 0.68 with the visual analogue scale as external criterion and a Cronbach´s α of 0.90 in stroke patients (66).

Executive functioning

Behaviour Rating Inventory of Executive Function **(BRIEF-A)** is a nine-item measure suitable for assessing adults executive functioning in everyday life. BRIEF-A measures different aspects of the executive functioning which are part of three overall clinical indices; *behavioral regulation*, *metacognition* and *general executive function*. Among others the BRIEF-A has been shown sensitive to assess executive function deficiencies in adults with a traumatic brain injury (67). The instrument has shown high internal consistency in clinical populations with a Cronbach´s α ranging from 0.93 to 0.96 (68).

Health-related quality of life

The Medical Outcomes Study 12-item Short Form Health Survey **(SF-12)** is an abbreviated version of the SF-36 and a generic health-related quality of life measure. SF-12 measures eight domains of health on 2 domains, respectively physical health and mental health. The scores ranges from 0-10 with higher scores indicating a higher level of health-related quality of life (69). The instrument has been extensively validated in several populations and has shown good reliability when used in a stable coronary population (70).

Quality of life

The **Heart-QoL** is a 14-item heart disease-specific questionnaire that measures the Quality of life in cardiac patients. The scale is divided into a global, physical (10 items) and emotional (four items) component. Items are answered on a four-point Likert scale (range 0–3) with higher scores indicating better HRQoL. Heart-QoL has shown satisfactory internal consistency Cronbach's α > 0.90 in Danish implantable cardioverter defibrillator recipients (71).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page and abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page 3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 5-7	
Objectives	3	State specific objectives, including any prespecified hypotheses	page 6-7	
Methods				
Study design	4	Present key elements of study design early in the paper	page 7-8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 7-12	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	page 11-13	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 9-13	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	page 8-13	
Bias	9	Describe any efforts to address potential sources of bias	page 7-8	
Study size	10	Explain how the study size was arrived at	page 13	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 13
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			N/A
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Cognitive impairment and psychopathology in Out-of-Hospital Cardiac Arrest survivors in Denmark. The REVIVAL cohort study protocol

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Cognitive impairment and psychopathology in Out-of-Hospital Cardiac Arrest survivors in Denmark. The REVIVAL cohort study protocol

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Supplementary material 1: Description of secondary outcomes

ABSTRACT

INTRODUCTION: Cognitive impairment and psychopathology caused by brain hypoxia and the traumatic impact of critical illness are common in cardiac arrest survivors and can lead to negative consequences of everyday life functioning, and further impact mental health in relatives. Most studies have dealt with the mere survival rate after cardiac arrest and not with long-term consequences to mental health in cardiac arrest survivors. Importantly, we face a gap in our knowledge about suitable screening tools in the early post-arrest phase for long-term risk prediction of mental health problems. This study aims to evaluate the efficacy of a novel screening procedure to predict risk of disabling cognitive impairment and psychopathology 3-months after cardiac arrest. Furthermore, the study aims to evaluate long-term prevalence of psychopathology in relatives.

METHODS AND ANALYSES: In this multicenter prospective cohort study, out-of-hospital cardiac arrest survivors and their relatives will be recruited. The post-arrest screening includes the Montreal Cognitive Assessment (MoCA), the Hospital Anxiety and Depression Scale (HADS), the Impact of Event Scale-Revised (IES-R) and the Acute Stress Disorder Interview (ASDI) and is conducted during hospitalisation. In a sub-sample of the patients, functional magnetic resonance imaging is done, and cortisol determination collected. At 3-months follow-up, the primary study outcomes for 200 survivors include the Danish Affective Verbal Learning Test-26 (VAMT-26), Delis-Kaplan Executive Function System tests (trail-making, colour-word interference, word and design fluency), Rey's Complex Figure and Letter-number sequencing sub-test of Wechsler Adult Intelligence Scale-IV, HADS and IES-R. For the relatives they include HADS and IES-R.

ETHICS AND DISSEMINATION: The study is approved by the local regional Research Ethics Committee (H-18046155) and the Danish Data Protection Agency (RH-2017-325, j.no.05961) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may impact the follow-up of cardiac arrest survivors.

Article summary

Strength and limitations of this study

- A strength of the study is the prospective design and consistent follow-up with the use of standardised and validated measurement tools.
- A limitation of the study is the differential loss to follow-up which can introduce bias and challenge the internal validity of the study.
- A strength of the study is the multicenter approach. This will improve statistical power and generalisability of the results.
- A strength of the study is its potential to contribute to a better referral from cardiac care to targeted rehabilitation services.

INTRODUCTION

The global incidence of cardiac arrest with assumed primary cardiac cause is 55/100,000 inhabitants (1). In Europe approximately 275,000 people with all-rhythm cardiac arrests are treated by the Emergency Medical Systems (EMS) each year (2). Out-of-hospital cardiac arrest (OHCA) is a significant cause of global mortality (3). However, in recent years the survival rates have improved especially in developing countries due to advances in the chain of survival (1). At present the majority of published OHCA studies focus on the acute prehospital and intensive care treatment of OHCA sufferers. Far fewer studies have investigated the period from early recovery to long term return to everyday life. The existing literature on this period highlights two critical challenges for cardiac arrest survivors in the post-arrest recovery process, firstly diminished neurocognitive functions and secondly disabling emotional difficulties (4–9). In these survivors, long-term cognitive impairment and psychopathology constitute both a major personal and family burden, as well as a public health and economic concern (10–17).

Mild to moderate cognitive sequelae are reported in up to 50% of survivors (6,18). Transient or permanent memory loss, reduced visual–motor skills, attention deficit and executive impairment are the most dominant cognitive impairment found in this population (5,6,19,20). Importantly, impaired cognitive functioning at 3-months post-arrest has been found to correlate with worse physical and mental Health-related Quality of Life (HRQoL), and not being able to return to work around the first year after OHCA (21). Cardiac-induced cerebral hypoxia cause a diffuse injury that may damage the functional integrity of the brain (22) and cause cognitive impairment (23,24). Resting state functional magnetic resonance imaging (fMRI) is an informative imaging method that assays functional integrity and level of communication within the brain (3, 11). In a recent study, patients with increased within-network and decreased between-network functional connectivity in the acute phase after cardiac arrest survival had a favorable outcome (FO) one year later compared to patients with a non-favorable outcome (nFO) (13), suggesting higher functional integrity in patients with a FO. This increased within-network functional connectivity was also observed in a smaller study of cardiac arrest patients with good outcome at hospital discharge (14). To date, no reliable cognitive screening or

imaging method for use during the in-patient hospitalisation that can detect risk of long-term cognitive impairment in cardiac arrest patients exist. A post-arrest screening model may contribute to prompt initiation of relevant follow-up and targeted cognitive rehabilitation.

A cardiac arrest is a severe and traumatising life event and long-term post-arrest psychopathology is prevalent (5,25–27). Processing near-death experiences, coping with prolonged preoccupation with somatic symptoms and fear of a second cardiac arrest is a burden to many cardiac arrest patients (5,25). Up to 61% of cardiac arrest patients experience anxiety, up to 45% depression and up to 27% post-traumatic stress disorder (PTSD) (5). In particular, anxiety and depression have been found to negatively impact Health-related Quality of Life (HRQoL) and physical health in patients up to several years after survival (28). Furthermore, a cardiac arrest yields the highest prevalence of PTSD among cardiac disease categories (25), and PTSD is reported to double the overall risk of mortality, recurrence of a new cardiac event, and causing long-term diminished mental health and quality of life (8,29). Little is currently known about the role of acute emotional reactions for developing long-term psychopathology in cardiac arrest survivors, but high acute stress reactions in other patient populations appear to be associated with worse long-term outcomes (30–32). Elucidating the role of acute emotional reactions may serve to support and advice the patients about future challenges, and to initiate targeted psychological interventions.

Being the close relative of a cardiac arrest survivor can cause enduring psychological strains (33–35). Research indicates that these psychological strains are caused by a burden of witnessing the cardiac arrest, having to care for the patient and from the emotional stress of living with someone who is at risk of another cardiac arrest (36). At 1-year post-arrest, 40% of the close relatives of patients with brain injury are still experiencing a high impact of the cardiac event and display a more severe traumatic stress level than the patient (Armand S. The acute traumatic stress response is associated with long-term post-traumatic stress in cardiac arrest survivors and their close relatives, Unpublished, March, 2020) , and after 2 years these caregivers show a higher level of trauma-related stress than that observed in the general population (37). As a growing number of patients are surviving cardiac arrest it is crucial to focus more attention on

psychological challenges in relatives in the aftermath after surviving cardiac arrest.

The overall aim of the current study is therefore to evaluate and test a novel screening procedure during hospitalisation for its ability to predict at-risk patients for disabling cognitive impairment and psychopathology at 3-months. The incidence of psychopathology in close relatives 3-months post-arrest will also be explored. Overall, we expect that the screening procedure will be able to identify at-risk patients for disabling cognitive impairment and psychopathology at 3-months follow-up. In particular that:

Hypothesis 1: Lower level of cognitive impairment during hospitalisation (screening) is positively associated with cognitive outcome at 3-month follow-up.

Hypothesis 2: The strength of discrete resting-state networks in the brain assessed with fMRI during hospitalisation (screening) is positively associated with cognitive outcome at 3-months follow-up.

Hypothesis 3: Higher level of acute emotional reactions during hospitalisation (screening) is positively associated with psychopathology outcome at 3-months follow-up.

Hypothesis 4: Higher level of cognitive impairment and emotional reactions during hospitalisation in patients is positively associated with psychopathology outcomes in relatives at 3-months follow-up.

METHODS AND ANALYSIS

Study design, setting and population

The REVIVAL (REcovery after cardiac arrest surVIVAL) study is designed as a multicenter, prospective cohort study in which first-time out-of-hospital cardiac arrest (OHCA) survivors are followed for up to 1 year after the event (flowchart presented in figure 1). The study settings are three highly specialized heart centers at university hospitals in Denmark: Rigshospitalet and Herlev-Gentofte Hospital in the Capital Region of Denmark and Odense University Hospital, in the Southern Region of Denmark. All cardiac arrest patients will be approached for study participation and approximately 250 in-hospital patients (≥18 years of

age) with a first-time OHCA admission diagnosis will be recruited, starting January 1, 2018 and ending December 31, 2021 Only patients with a presumed cardiac cause for their cardiac arrest, as defined by Utstein template (38) will be included. Both cardiac arrests as primary and secondary diagnosis will be included. Furthermore, the closest relatives will be identified and included during hospitalisation for a 3-months follow-up. Patients are excluded if they have a serious not treatable other somatic or psychiatric illness or previous cerebrovascular events or traumatic brain injury and those unable to speak and understand Danish. The cognitive screening and neuropsychological testing require the patients to follow verbal instructions and to see the tasks presented. Therefore, patients with solid hearing or visual impairments are excluded. In a sub-study exploring resting state fMRI and stress reactivity, respectively 40 patients without contraindications to MR will be included from Rigshospitalet. The REVIVAL study is described in accordance with the current Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Guidelines for reporting observational studies) (39).

Patient selection and recruitment

All the patients and relatives are selected and recruited in the three Danish cardiology wards. OHCA survivors transferred from the Intensive Care Units (ICU) to the ward will be included four to nine days after termination of analgo-sedatives to ensure no residual sedation used during therapeutic hypothermia. The survivors from the Coronary Care Units (CCU) who undergo percutaneous coronary intervention after a brief cardiac arrest without ICU admission will be included after intervention in the cardiac catheterisation laboratory (figure 1). This subgroup of cardiac arrest survivors will be included although they are awake or only had a brief period of coma after admission to the hospital and presumably recover earlier to their premorbid cognitive functioning than the critically ill patients. The patients and relatives at the included sites follow the same protocol.

A trained cardiac nurse will collect most of the clinical data from the patients' charts. The same nurse will approach eligible patients during hospital admission on the cardiology ward and invite them to participate in the study. The patients will be assessed clinically and provided with oral as well as written information about

the study. The patients are given the opportunity to read and consider the study information leaflet carefully. If the patients agree to participate, they will be asked to provide written informed consent in consultation with their closest relative prior to inclusion. This is justified in ethical issues as some patients with cognitive impairment may not feel empowered to refuse participation.

Collection of data and measures

Screening model during hospitalisation

A team of certified nurses with a background in cardiology will screen the patients. Administration and interpretation of data will take place under supervision by a trained psychologist.

Cognition: The cognitive screening is conducted using the Danish version of the *Montreal Cognitive Assessment tool* (MoCA), version 7.0 (40). The MoCA is a brief cognitive screening test designed to identify mild cognitive impairment. The MoCA covers six cognitive domains: Attention, visuospatial construction, executive functioning, memory, language and orientation (table 1), and is rated from 0-30. A cut-off ≥26 is considered as normal cognitive function level. In the summary score a level of education ≤12 years is given an extra point as education level has shown to decrease the overall score (40). The MoCA is suggested for use in the post cardiac arrest settings (41), however, it remains to be evaluated in a Danish patient population with possible hypoxic-ischaemic brain injury. The MoCA has shown high level of internal reliability with Cronbach's $\alpha = 0.83$ in detection of mild cognitive impairment (40).

-Insert Table 1: **The cognitive assessment** about here-

Mood and delirium: As symptoms of delirium often are subtle but still can have an impact on cognition, the cognitive screening is initiated with a rapid clinical assessment of delirium, using 4AT scale (42). Furthermore, the mood state and functional independence of the patients is collected (table 2). If the study nurse is in doubt regarding patients functioning, an informed nurse or relative is asked (43).

Resting state fMRI: Patients who meet inclusion criteria for MRI will undergo structural and functional brain imaging on a 3 Tesla Siemens Prisma MRI scanner at Rigshospitalet. Trained personnel will perform MRI scans; during transport and scanning, a trained nurse will monitor the patients. We will obtain high-resolution structural T1- and T2-weighted images and T2*-weighted BOLD fMRI resting state scans (~10 minutes of resting state fMRI). During resting state fMRI, patients are asked to lie still with eyes closed and let their mind wander freely. Resting state fMRI data will be processed using canonical brain imaging tools, e.g. SPM (44) and Conn (45) to establish region-to-region connectivity estimates while accounting for motion, physiological and other noise sources. Resting state networks will be defined based on *a priori* connectivity networks descriptions (46).

Psychopathology: Self-rated symptoms of depression and anxiety and trauma reactions will be collected using the Hospital Anxiety and Depression Scale (HADS-D and HADS-A) (47), and the Impact of event Scale-revised (IES-R) (48). The Hospital Anxiety and Depression Scale (HADS) is a valid and internally consistent 14 items instrument to measure anxiety and depression. Each item is scored from 0-3 with a summary score between 0 and 21 for either anxiety or depression. Scores of 11 and above indicate the probable presence of a mood disorder. HADS has shown a mean α of 0.83 and 0.82 for the HADS-A and HADS-D, respectively (49). Impact of Event Scale - revised (IES-R) measures distress caused by a traumatic event is a widely used measures to assess traumatic stress symptoms with a maximum score of 88. The IES-R consist of 22-items measuring subjective distress caused by a traumatic event scored on a Likert scale from 0 (not at all) to 4 (extremely) and includes subscales for avoidance, intrusions and hyperarousal. The IES-R has shown high internal consistency with coefficient alphas ranging from 0.84 to 0.85 for avoidance, 0.87 to 0.92 for intrusion, and 0.79 to 0.90 for hyperarousal (48).

Acute Stress disorder: The Acute Stress Disorder Structured interview (ASDI) is a 19-item clinical interview which investigates the incidence and severity of acute stress responses operated as acute stress disorder (ASD) in DSM-5 in the month following trauma exposure (50,51). Acute stress disorder is divided

into five symptom clusters: intrusive memories or revival, negative mood, dissociation, avoidance and arousal. To meet the criteria for acute stress disorder, the patient must have experienced a traumatic event (in this case a cardiac arrest) during the past month (criteria A) as well as the presence or deterioration of at least nine symptoms independent of the associated category after the onset of episode (Criterion B), which should occur within three days to one month (Criterion C) (52).

Cortisol Awakening Response: At the same day as the structured clinical interview (i.e. ASDI) is performed, saliva samples for determination of the Cortisol Awakening Response (CAR) will be obtained from eligible patients. Five samples are collected during awakening and three saliva samples will also be collected during the day at 12 at 18 and at 23 o´clock. The total amount of saliva per patient is 16 ml. After collecting the saliva, the samples will be stored and analysed at the Department of Clinical Biochemistry, Rigshospitalet, Glostrup.

Sociodemographic variables and several clinical pre- and inhospital data were obtained from electronic medical records (see table 2).

-Insert Table 2**: Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors** about here-

<u>At 3-months follow-up</u>

The patients included at Rigshospitalet and Herlev-Gentofte Hospital will undergo a detailed and individual neuropsychological assessment at the Neurobiology Research Unit at Rigshospitalet, and patients included at Odense University Hospital will be assessed with a similar test battery at the University of Southern Denmark. The cognitive assessment of the patient's cognitive functions will be given, administered and

interpreted by a clinical and trained psychologist or psychology student under supervision. The patients and their relatives will furthermore complete a package of self-reported questionnaires.

The neuropsychological assessment: The tests used are a carefully selected neuropsychological test battery comprising the same subcomponents as for the MoCA; *attention, visuospatial construction, executive functioning, memory, language and orientation*. The tests used are all validated in clinical settings for a variety of populations and have shown good test-retest reliability. To address a source of bias, all tests are conducted by a psychologist, who is kept blind of the clinical data as well as the results of the previous brief cognitive screening. A detailed outline of the neuropsychological tasks includes: Danish Affective Verbal Learning Test-26 (VAMT-26) (53) and Delis-Kaplan Executive Function System tests (D-KEFS) comprising trail-making, colour-word interference, design fluency and word fluency (54) together with the Rey's complex figure test (55) and Letter-number sequencing test from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (56) (table 1).

Psychopathology in patients: Furthermore, the patients will repeat the self-reported questionnaires identical to the questionnaires completed during hospitalisation: HADS-D, HADS-A and IES-R.

Psychopathology in relatives: The relatives are also asked to complete the HADS-D, HADS-A and IES-R. The questionnaires for both patients and their relatives are sent via e-mail two weeks before the 3-months follow-up.

At 1-year follow-up

The 1-year follow-up is designed as register-based (table 2). To investigate whether baseline data are associated with morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure and with mortality and health care utilisation, the collected data will be linked with data from national administrative registers; the Danish National Patient Register (57), the Danish Civil Registration System (58), the Danish National Prescription Registry (59), the Danish education registers (60), and the Danish registers on personal income and transfer payments (61).

Primary and secondary study outcome measures

Primary outcome measures for patients

The primary outcome is whether the patients present a favourable outcome (FO) or a non-favourable outcome (nFO) at 3-month follow-up. To elucidate cognition and psychopathology separately, primary outcomes will be established for each of these domains.

Cognition: As primary cognitive outcome the patients will be divided into two groups, FO and nFO, based on their performance in the neuropsychological tasks. The subset with an nFO is defined as minimum 1.5 standard deviation (SD) under the norm or reference data (53,54,55,62) on minimum one test or 1 standard deviation on two or more tests. The rest of the patients fall into the FO group.

Psychopathology: As primary psychopathology outcome the patients will be divided into two groups, FO and nFO, based on their scores on the HADS and IES-R. The subset with an nFO is defined one or more scores above cut-off for psychopathology on the HADS and IES-R: HADS-D and HADS-A >8 and IES-R >24. The rest of the patients fall into the FO group.

Secondary outcome measures for patients

As secondary outcomes for patients are self-reported measures of sleep quality, fatigue, executive functioning, and health-related quality of life at 3-months of follow-up (table 2). A detailed description of the secondary outcomes is described in the supplementary material 1. Secondary outcomes for patients also include register-based information of morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure, mortality and healthcare utilisation at 1-year post-arrest (table 2).

Primary outcome measures for relatives

The primary outcomes for the relatives include HADS-D, HADS-A and IES-R (47,63) (table 3).

-Insert Table 3**: Outcome domains, measurement instruments and measurement time for the relatives** about here-

Secondary outcome measures for relatives

Secondary outcome measures for relatives include self-reported health-related quality of life, experience of cognitive changes in the patient after the cardiac arrest, social support, major depression, the quality in the relationship with the cardiac arrest survivor, and the extent to which the cardiac arrest is viewed as being central to one´s identity (table 3).

Several exploratory outcomes will also be collected (figure 1).

Data analysis plan

The collected socio-demographic data will be presented as means ± standard deviation (SD) or percentages, respectively and group differences will be calculated by t-tests (continuous data) or χ^2 (categorical data). Appropriate regression models will be used to examine the associations between screening performance during hospitalisation and the primary and secondary study outcomes. In all model's relevant covariates e.g. sex, age, comorbidity, time to return of spontaneous circulation, coma duration time, time at intensive care unit, time of hospitalization, etc. will be included (table 2). A formal power calculation of sample size has not been performed due to the several aims and potential analyses of this study. With no comparative patient groups and only few small existing studies, we aim for a sample size of 200 cardiac arrest survivors at three months follow-up for the primary outcome to be statistically and clinically significant.

Patient and Public Involvement

As a patient involvement method, two theme-based sessions involving *direct patient feedback* have been carried out in the early pilot and design phase of the study. The aim of these sessions was to 1) identify patient preferences regarding the cognitive screening procedure (figure 2), and 2) develop the research

priorities including implementation of possible changes based on the patient's feedback. Data derived from the theme-based patient feed-back sessions provides the basis for the cognitive screening procedure in the REVIVAL study. To ensure further patient involvement, we plan to engage the patients in the planning phase of disseminating the results.

DISCUSSION

To the best of our knowledge, the present study will be the largest study evaluating and testing a novel screening procedure for cognitive impairment and emotional reactions during hospitalisation in a population of OHCA survivors. As the incidence of cardiac arrest survival is increasing, establishing a standardized approach to screening in OHCA survivors will be critical in the future. Following the aims of the study and to strengthen the standardization of the results, only patients with a presumed cardiac cause for their cardiac arrest as defined by Utstein template will be included. Since a common single etiology of cardiac arrest is respiratory failure, it could be considered to include this population in a future study. Although cognitive and mental health outcomes in OHCA survivors may be comparable to other medical populations (7,64,65), the study does not contain a comparative arm as it does not aim to investigate a specific intervention. Instead the study seeks to investigate OHCA survivors after standard treatment in a naturalistic setting. Due to the nature of the study and the vulnerable state of the patients, differential loss to follow-up is expected in the study. To elucidate data missing not at random, we plan to conduct phone calls to non-responders at 3-months follow-up regarding their withdrawal from the study. We expect that results from the REVIVAL study will inform an early screening procedure of OHCA survivors in clinical settings as well as inform future targeted rehabiliation in survivors who are likely to develop protracted cognitive impairment and psychopathology.

ETHICS AND DISSEMINATION

There is little to no discomfort for the patients and their relatives in this study. Due to the weakened constitution of the patients, the neuropsychological test at 3-months post-arrest could be experienced as taxing and can be divided into two days. The study complies with the Declaration of Helsinki and has been

approved by the Danish national committee on health research ethics (H-18046155) and the Danish Data Protection Agency (RH-2017-325, I-Suite no: 05961). Patients and their relatives will receive oral and written information about the study and inclusion will require obtained written consent for all participants before enrolment. Results from this study will be disseminated at regional, national and international conferences and in peer-reviewed journals.

Authors' contributions

Department of Cardiology, Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Copenhagen University Hospital Rigshospitalet (MKW, SKB, and CH) and Neurobiology Research Unit, Rigshospitalet (DSS, PMF and GMK) has full access to all the data in the study and takes responsibility for the integrity of data. MKW, SKB, CH and DSS contributed to the study concept and design. MKW, SKB, CH, SA, JEM, PMF, GMK and DSS contribute to the data acquisition. Analysis will be performed by MKW, SKB, CH, OE and DSS, MKW and DSS drafted the manuscript with critical input from SKB, CH, SA, JEM, OE, TBR, PMF and GMK. All authors approved the final version of the manuscript.

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Competing interest statement

On behalf of all authors, the corresponding author states that there are no conflicts of interest related to this study. The funding sources have no role in the design and conduct of the study.

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Table 1: The cognitive assessment

The cognitive assessment		
	During hospitalisation	**3-months follow up**
Target cognitive domain	**MoCA**	**Neuropsychological tests**
Attention	Number sequence Letter list	D2 (visual attention) (Trail-making + stroop)
Visuospatial construction	Cube copying	Rey's figure
Episodic memory	Verbal memory test	VAMT-26
Working memory	Serial subtraction	Letter-number sequence
Executive functioning	Trail making B Clock drawing Abstraction	Trailmaking B D-KEFS colour-word interference
Psychomotor Processing speed	Trail making B	Trail making A and B
Language	Naming Repeating Word mobilization	
Orientation	Orientation	

Table 2: Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors

Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors		
Outcome domains and measurement instruments	**Time of measure**	**Type of quantity**
Sociodemographic variables		
Age	T0	Continuous
Sex	T0	Binary
Marital status, type of occupation, employment status, living situation	T0	Categorical
Medical variables		
Known IHD, hypertension, previous MI, PCI or CABG, chronic heart failure, diabetes mellitus, COPD and chronic kidney disease	T0	Binary
Clinical variables related to the cardiac arrest		
Place of OHCA, aetiology of cardiac arrest, initial rhythm, TTM, medication during ICU stay, LVEF	T0	Categorical
Bystander witnessed cardiac arrest, bystander performed CPR, Use of AED, shockable rhythm, awake at arrival to hospital, TTM, intubated, medication during ICU, delirium at ICU	T0	Binary
Time to ROSC, intubation time, length of stay at ICU	T0	Continuous
Consious state GCS	T0	Categorical
Neurological outcome CPC	T1	Categorical
Length of stay at hospital	T1	Continuous
Performance based variables		
Delirium score 4AT	T1	Categorical
Functional independence Barthel Index- 20	T1	Categorical
Cognitive status MoCA	T1	Binary
Brain activity while resting rsfMRI	T1	Continuous
Neuropsychological outcome VAMT-26, D- KEFS trail-taking, D-KEFS colour-word interference, D-KEFS design fluency, Rey's complex figure and Letter-number sequencing**:** sub-test of WAIS-IV	T2	Binary
Cortisol Awakening response	T1	Continuous
Patient-reported outcome measures		
POMS	T1	
HADS, IES-R, CSS	T1, T2	Continuous
B-IPQ, FSS, HeartQoL, SF-12, PSQI, CISS, BRIEF-A, ECR-R, AMCQ, CES-S, MTEQ, PTGQ, ACQ, NDEQ	T2	Continuous
Lifestyle changes, Health profile	T2	Categorical
Register based		
Depression, anxiety, dementia, chronical fatigue syndrome and heart failure, mortality and health care utilisation	T3	Continuous

T0: Pre-arrest, medical and clinical data, T1: During hospitalisation, T2: 3 months follow-up, T3: 1 year follow-up

ICU: Intensive Care Unit, **LVEF**: Left Ventricular Ejection Fraction, **OHCA**: Out-of-hospital Cardiac Arrest, **CPR**: Cardiopulmonary resuscitation, **AED**: Automated External Defibrillator, **ROSC**: Return of spontaneous circulation, **TTM**: Targeted Temperature Management, **IHD**: Ischemic Heart Disease, **MI**: Myocardial infarction, **PCI**: Percutaneous coronary Intervention, **CABG**: Coronary Artery Bypass Surgery, **COPD**: Chronic Obstructive Pulmonary Disease, **GCS**: Glasgow Coma Scale, **CPC**: Cerebral Performance Category, **MoCA**: Montreal Cognitive Assessment, **rsfMRI**: resting state functional magnetic resonance imaging, **VAMT-26**: Danish Affective Verbal Learning Test-26, **D- KEFS**: Delis–Kaplan Executive Function System,_ **POMS:** Profile of Mood States, **HADS**: Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event- Revised, **CSS**: Crisis Support Scale, **B-IPQ**: Brief Illness Perception Scale, **FSS**: Fatigue Severity Scale, **SF-12**: 12-item short Form Survey, **PSQI**: Pittsburgh Sleep Quality Inventory, **CISS**: Coping Inventory for Stressful Situations, **BRIEF-A**: Behavior Rating Inventory of Executive Functions, adult version, **ECS-R**: Experience in close relationships, **AMCQ**: Autobiographical Memory Characteristics Questionnaire, **CES-S:** Centrality of Events – Short, **MTEQ**: Memory of Event Scale, **PTGQ:** Post Traumatic Growth Questionnaire, **ACQ**: Attribution, **NDEQ:** Near-death Experience Questionnaire,

Table 3: Outcome domains, measurement instruments and measurement time for the relatives

Outcome domains, measurement instruments and measurement time for the relatives		
Outcome domain	**Measurement instruments**	**Time**
Demographic variables and psychiatric medical history		T2
Health-related quality of life	**SF-12**	
Anxiety and Depression	**HADS**	
Distress caused by a traumatic event	**IES-R**	
Experience in close relationships	**ECR-R**	
Social support after a crisis	**CSS**	
Major depression	**MDI**	
The extent to which an **event** is viewed as being central to one's identity	**CES-S**	
Cognitive decline reported by informants (relatives or close friends)	**IQ-CODE**	

T2: 3 months follow-up

SF-12: 12-item Short Form Survey, **HADS**: Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event- Revised, **ECR-R**: Experience in close relationships, **CSS**: The Crisis Support Scale, **MDI:** Major Depression Inventory, **CES-S**: Centrality of Event short, **IQ-CODE**: The Informant Questionnaire on Cognitive Decline in the Elderly.

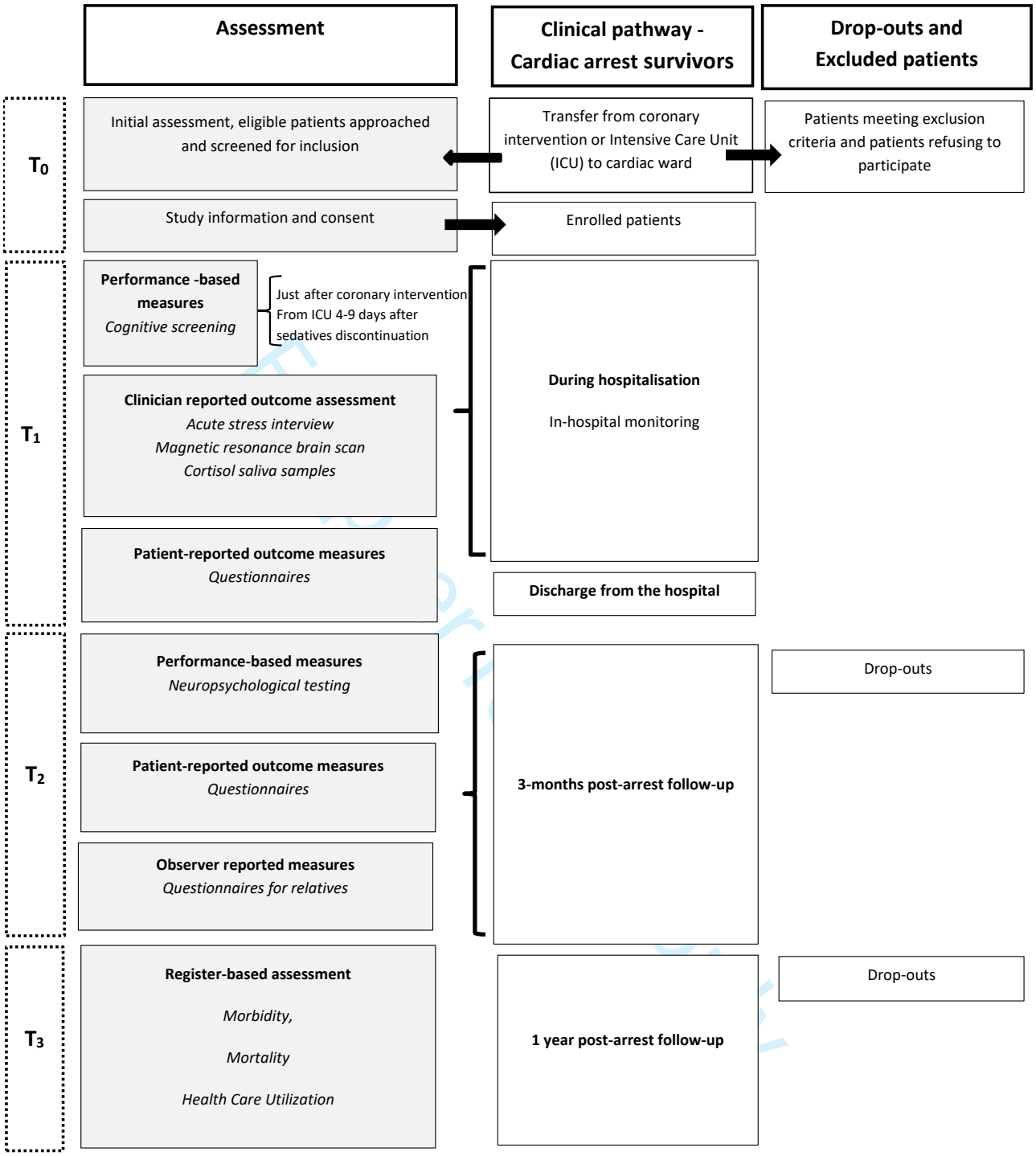

Figure 1: Flowchart of study assessment

T0: Study inclusion, **T1**: During hospitalisation, **T2**: 3 months follow-up, **T3**: 1-year follow-up

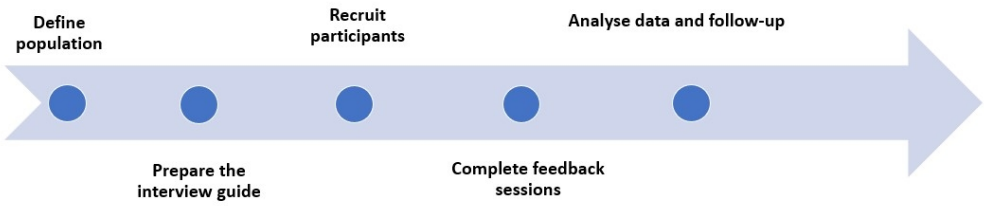

Figure 2
Direct patient-feed back

279x82mm (96 x 96 DPI)

Supplementary material 1: Description of secondary outcomes

Sleep quality

The Pittsburgh Sleep Quality Inventory (**PSQI**) is a 19-item measure which assesses sleep quality and disturbances over the last months. The items generate a seven-component score each weighted equally on a 0-3 scale. The sum of these scores provides a global score. Higher scores indicate worse sleep quality. A cut-off score of >5 indicates poor sleep quality (64). The PSQI has demonstrated internal consistency reliability with Cronbach's α 0.83 (65).

Fatigue

Fatigue Severity Scale **(FSS)** is a nine-item questionnaire that measures experienced severity of fatigue symptoms in daily activities on a seven-point scale. A mean score is calculated (range 1–7) with higher scores reflecting greater fatigue. The FSS has shown construct validity with correlation coefficient of 0.68 with the visual analogue scale as external criterion and a Cronbach´s α of 0.90 in stroke patients (66).

Executive functioning

Behaviour Rating Inventory of Executive Function **(BRIEF-A)** is a nine-item measure suitable for assessing adults executive functioning in everyday life. BRIEF-A measures different aspects of the executive functioning which are part of three overall clinical indices; *behavioral regulation*, *metacognition* and *general executive function*. Among others the BRIEF-A has been shown sensitive to assess executive function deficiencies in adults with a traumatic brain injury (67). The instrument has shown high internal consistency in clinical populations with a Cronbach´s α ranging from 0.93 to 0.96 (68).

Health-related quality of life

The Medical Outcomes Study 12-item Short Form Health Survey **(SF-12)** is an abbreviated version of the SF-36 and a generic health-related quality of life measure. SF-12 measures eight domains of health on 2 domains, respectively physical health and mental health. The scores ranges from 0-10 with higher scores indicating a higher level of health-related quality of life (69). The instrument has been extensively validated in several populations and has shown good reliability when used in a stable coronary population (70).

Quality of life

The **Heart-QoL** is a 14-item heart disease-specific questionnaire that measures the Quality of life in cardiac patients. The scale is divided into a global, physical (10 items) and emotional (four items) component. Items are answered on a four-point Likert scale (range 0–3) with higher scores indicating better HRQoL. Heart-QoL has shown satisfactory internal consistency Cronbach's α > 0.90 in Danish implantable cardioverter defibrillator recipients (71).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page and abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page 3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 5-7	
Objectives	3	State specific objectives, including any prespecified hypotheses	page 6-7	
Methods				
Study design	4	Present key elements of study design early in the paper	page 7-8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 7-12	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	page 11-13	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 9-13	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	page 8-13	
Bias	9	Describe any efforts to address potential sources of bias	page 7-8	
Study size	10	Explain how the study size was arrived at	page 13	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 13
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			N/A
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Cognitive impairment and psychopathology in Out-of-Hospital Cardiac Arrest survivors in Denmark. The REVIVAL cohort study protocol

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Cognitive impairment and psychopathology in Out-of-Hospital Cardiac Arrest survivors in Denmark. The REVIVAL cohort study protocol

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Direct Patient Feed-back

Supplementary material 1: Description of secondary outcomes

ABSTRACT

INTRODUCTION: Cognitive impairment and psychopathology caused by brain hypoxia and the traumatic impact of critical illness are common in cardiac arrest survivors and can lead to negative consequences of everyday life functioning, and further impact mental health in relatives. Most studies have dealt with the mere survival rate after cardiac arrest and not with long-term consequences to mental health in cardiac arrest survivors. Importantly, we face a gap in our knowledge about suitable screening tools in the early post-arrest phase for long-term risk prediction of mental health problems. This study aims to evaluate the efficacy of a novel screening procedure to predict risk of disabling cognitive impairment and psychopathology 3-months after cardiac arrest. Furthermore, the study aims to evaluate long-term prevalence of psychopathology in relatives.

METHODS AND ANALYSES: In this multicenter prospective cohort study, out-of-hospital cardiac arrest survivors and their relatives will be recruited. The post-arrest screening includes the Montreal Cognitive Assessment (MoCA), the Hospital Anxiety and Depression Scale (HADS), the Impact of Event Scale-Revised (IES-R) and the Acute Stress Disorder Interview (ASDI) and is conducted during hospitalisation. In a sub-sample of the patients, functional magnetic resonance imaging is done, and cortisol determination collected. At 3-months follow-up, the primary study outcomes for 200 survivors include the Danish Affective Verbal Learning Test-26 (VAMT-26), Delis-Kaplan Executive Function System tests (trail-making, colour-word interference, word and design fluency), Rey's Complex Figure and Letter-number sequencing sub-test of Wechsler Adult Intelligence Scale-IV, HADS and IES-R. For the relatives they include HADS and IES-R.

ETHICS AND DISSEMINATION: The study is approved by the local regional Research Ethics Committee (H-18046155) and the Danish Data Protection Agency (RH-2017-325, j.no.05961) and follows the latest version of the Declaration of Helsinki. The results will be published in peer-reviewed journals and may impact the follow-up of cardiac arrest survivors.

Article summary

Strength and limitations of this study

- A strength of the study is the prospective design and consistent follow-up with the use of standardised and validated measurement tools.
- A limitation of the study is the differential loss to follow-up which can introduce bias and challenge the internal validity of the study.
- A strength of the study is the multicenter approach. This will improve statistical power and generalisability of the results.
- A strength of the study is its potential to contribute to a better referral from cardiac care to targeted rehabilitation services.

INTRODUCTION

The global incidence of cardiac arrest with assumed primary cardiac cause is 55/100,000 inhabitants (1). In Europe approximately 275,000 people with all-rhythm cardiac arrests are treated by the Emergency Medical Systems (EMS) each year (2). Out-of-hospital cardiac arrest (OHCA) is a significant cause of global mortality (3). However, in recent years the survival rates have improved especially in developing countries due to advances in the chain of survival (1). At present the majority of published OHCA studies focus on the acute prehospital and intensive care treatment of OHCA sufferers. Far fewer studies have investigated the period from early recovery to long term return to everyday life. The existing literature on this period highlights two critical challenges for cardiac arrest survivors in the post-arrest recovery process, firstly diminished neurocognitive functions and secondly disabling emotional difficulties (4–7). In these survivors, long-term cognitive impairment and psychopathology constitute both a major personal and family burden, as well as a public health and economic concern (8–15).

Mild to moderate cognitive sequelae are reported in up to 50% of survivors (6,16). Transient or permanent memory loss, reduced visual–motor skills, attention deficit and executive impairment are the most dominant cognitive impairment found in this population (5,6,17,18). Importantly, impaired cognitive functioning at 3-months post-arrest has been found to correlate with worse physical and mental Health-related Quality of Life (HRQoL), and not being able to return to work around the first year after OHCA (19). Cardiac-induced cerebral hypoxia cause a diffuse injury that may damage the functional integrity of the brain (20) and cause cognitive impairment (21,22). Resting state functional magnetic resonance imaging (fMRI) is an informative imaging method that assays functional integrity and level of communication within the brain (23). In a recent study, patients with increased within-network and decreased between-network functional connectivity in the acute phase after cardiac arrest survival had a favorable outcome (FO) one year later compared to patients with a non-favorable outcome (nFO) (13), suggesting higher functional integrity in patients with a FO. This increased within-network functional connectivity was also observed in a smaller study of cardiac arrest patients with good outcome at hospital discharge (14). To date, no reliable cognitive screening or imaging method for use during the in-patient hospitalisation that can detect risk of long-term cognitive impairment in

cardiac arrest patients exist. A post-arrest screening model may contribute to prompt initiation of relevant follow-up and targeted cognitive rehabilitation.

A cardiac arrest is a severe and traumatising life event and long-term post-arrest psychopathology is prevalent (5,24–26). Processing near-death experiences, coping with prolonged preoccupation with somatic symptoms and fear of a second cardiac arrest is a burden to many cardiac arrest patients (5,24). Up to 61% of cardiac arrest patients experience anxiety, up to 45% depression and up to 27% post-traumatic stress disorder (PTSD) (5). In particular, anxiety and depression have been found to negatively impact Health-related Quality of Life (HRQoL) and physical health in patients up to several years after survival (27). Furthermore, a cardiac arrest yields the highest prevalence of PTSD among cardiac disease categories (24), and PTSD is reported to double the overall risk of mortality, recurrence of a new cardiac event, and causing long-term diminished mental health and quality of life (28,29). Little is currently known about the role of acute emotional reactions for developing long-term psychopathology in cardiac arrest survivors, but high acute stress reactions in other patient populations appear to be associated with worse long-term outcomes (30–32). Elucidating the role of acute emotional reactions may serve to support and advice the patients about future challenges, and to initiate targeted psychological interventions.

Being the close relative of a cardiac arrest survivor can cause enduring psychological strains (33–35). Research indicates that these psychological strains are caused by a burden of witnessing the cardiac arrest, having to care for the patient and from the emotional stress of living with someone who is at risk of another cardiac arrest (36). At 1-year post-arrest, 40% of the close relatives of patients with brain injury are still experiencing a high impact of the cardiac event and display a more severe traumatic stress level than the patient (Armand S. The acute traumatic stress response is associated with long-term post-traumatic stress in cardiac arrest survivors and their close relatives, Unpublished, March, 2020) , and after 2 years these caregivers show a higher level of trauma-related stress than that observed in the general population (37). As a growing number of patients are surviving cardiac arrest it is crucial to focus more attention on psychological challenges in relatives in the aftermath after surviving cardiac arrest.

The overall aim of the current study is therefore to evaluate and test a novel screening procedure during hospitalisation for its ability to predict at-risk patients for disabling cognitive impairment and psychopathology at 3-months. The incidence of psychopathology in close relatives 3-months post-arrest will also be explored. Overall, we expect that the screening procedure will be able to identify at-risk patients for disabling cognitive impairment and psychopathology at 3-months follow-up. In particular that:

Hypothesis 1: Lower level of cognitive impairment during hospitalisation (screening) is positively associated with cognitive outcome at 3-month follow-up.

Hypothesis 2: The strength of discrete resting-state networks in the brain assessed with fMRI during hospitalisation (screening) is positively associated with cognitive outcome at 3-months follow-up.

Hypothesis 3: Higher level of acute emotional reactions during hospitalisation (screening) is positively associated with psychopathology outcome at 3-months follow-up.

Hypothesis 4: Higher level of cognitive impairment and emotional reactions during hospitalisation in patients is positively associated with psychopathology outcomes in relatives at 3-months follow-up.

METHODS AND ANALYSIS

Study design, setting and population

The REVIVAL (REcovery after cardiac arrest surVIVAL) study is designed as a multicenter, prospective cohort study in which first-time out-of-hospital cardiac arrest (OHCA) survivors are followed for up to 1 year after the event (flowchart presented in figure 1). The study settings are three highly specialized heart centers at university hospitals in Denmark: Rigshospitalet and Herlev-Gentofte Hospital in the Capital Region of Denmark and Odense University Hospital, in the Southern Region of Denmark. All cardiac arrest patients will be approached for study participation and approximately 250 in-hospital patients (≥18 years of age) with a first-time OHCA admission diagnosis will be recruited, starting January 1, 2018 and ending December 31, 2021 Only patients with a presumed cardiac cause for their cardiac arrest, as defined by Utstein template will be included (38). Both cardiac arrests as primary and secondary diagnosis will be

included. Furthermore, the closest relatives will be identified and included during hospitalisation for a 3-months follow-up. Patients are excluded if they have a serious not treatable other somatic or psychiatric illness or previous cerebrovascular events or traumatic brain injury and those unable to speak and understand Danish. The cognitive screening and neuropsychological testing require the patients to follow verbal instructions and to see the tasks presented. Therefore, patients with solid hearing or visual impairments are excluded. In a sub-study exploring resting state fMRI and stress reactivity, respectively 40 patients without contraindications to MR will be included from Rigshospitalet. The REVIVAL study is described in accordance with the current Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Guidelines for reporting observational studies) (39).

Patient selection and recruitment

All the patients and relatives are selected and recruited in the three Danish cardiology wards. OHCA survivors transferred from the Intensive Care Units (ICU) to the ward will be included four to nine days after termination of analgo-sedatives to ensure no residual sedation used during therapeutic hypothermia. The survivors from the Coronary Care Units (CCU) who undergo percutaneous coronary intervention after a brief cardiac arrest without ICU admission will be included after intervention in the cardiac catheterisation laboratory (figure 1). This subgroup of cardiac arrest survivors will be included although they are awake or only had a brief period of coma after admission to the hospital and presumably recover earlier to their premorbid cognitive functioning than the critically ill patients. The patients and relatives at the included sites follow the same protocol.

A trained cardiac nurse will collect most of the clinical data from the patients' charts. The same nurse will approach eligible patients during hospital admission on the cardiology ward and invite them to participate in the study. The patients will be assessed clinically and provided with oral as well as written information about the study. The patients are given the opportunity to read and consider the study information leaflet carefully. If the patients agree to participate, they will be asked to provide written informed consent in consultation with their closest relative prior to inclusion. This is justified in ethical issues as some patients with cognitive

impairment may not feel empowered to refuse participation.

Collection of data and measures

Screening model during hospitalisation

A team of certified nurses with a background in cardiology will screen the patients. Administration and interpretation of data will take place under supervision by a trained psychologist (40).

Cognition: The cognitive screening is conducted using the Danish version of the *Montreal Cognitive Assessment tool* (MoCA), version 7.0 (41). The MoCA is a brief cognitive screening test designed to identify mild cognitive impairment. The MoCA covers six cognitive domains: Attention, visuospatial construction, executive functioning, memory, language and orientation (table 1), and is rated from 0-30. A cut-off ≥26 is considered as normal cognitive function level. In the summary score a level of education ≤12 years is given an extra point as education level has shown to decrease the overall score (41). The MoCA is suggested for use in the post cardiac arrest settings (21,42), however, it remains to be evaluated in a Danish patient population with possible hypoxic-ischaemic brain injury. The MoCA has shown high level of internal reliability with Cronbach's $\alpha = 0.83$ in detection of mild cognitive impairment (41).

-Insert Table 1: **The cognitive assessment** about here-

Mood and delirium: As symptoms of delirium often are subtle but still can have an impact on cognition, the cognitive screening is initiated with a rapid clinical assessment of delirium, using 4AT scale (43). Furthermore, the mood state and functional independence of the patients is collected (table 2). If the study nurse is in doubt regarding patients functioning, an informed nurse or relative is asked (44).

Resting state fMRI: Patients who meet inclusion criteria for MRI will undergo structural and functional brain imaging on a 3 Tesla Siemens Prisma MRI scanner at Rigshospitalet. Trained personnel will perform MRI scans; during transport and scanning, a trained nurse will monitor the patients. We will obtain high-

resolution structural T1- and T2-weighted images and T2*-weighted BOLD fMRI resting state scans (~10 minutes of resting state fMRI). During resting state fMRI, patients are asked to lie still with eyes closed and let their mind wander freely. Resting state fMRI data will be processed using canonical brain imaging tools, e.g. SPM (45) and Conn (23) to establish region-to-region connectivity estimates while accounting for motion, physiological and other noise sources. Resting state networks will be defined based on *a priori* connectivity networks descriptions (46).

Psychopathology: Self-rated symptoms of depression and anxiety and trauma reactions will be collected using the Hospital Anxiety and Depression Scale (HADS-D and HADS-A) (47), and the Impact of event Scale-revised (IES-R) (48). The Hospital Anxiety and Depression Scale (HADS) is a valid and internally consistent 14 items instrument to measure anxiety and depression. Each item is scored from 0-3 with a summary score between 0 and 21 for either anxiety or depression. Scores of 11 and above indicate the probable presence of a mood disorder. HADS has shown a mean α of 0.83 and 0.82 for the HADS-A and HADS-D, respectively (49). Impact of Event Scale - revised (IES-R) measures distress caused by a traumatic event is a widely used measures to assess traumatic stress symptoms with a maximum score of 88. The IES-R consist of 22-items measuring subjective distress caused by a traumatic event scored on a Likert scale from 0 (not at all) to 4 (extremely) and includes subscales for avoidance, intrusions and hyperarousal. The IES-R has shown high internal consistency with coefficient alphas ranging from 0.84 to 0.85 for avoidance, 0.87 to 0.92 for intrusion, and 0.79 to 0.90 for hyperarousal (48).

Acute Stress disorder: The Acute Stress Disorder Structured interview (ASDI) is a 19-item clinical interview which investigates the incidence and severity of acute stress responses operated as acute stress disorder (ASD) in DSM-5 in the month following trauma exposure (50,51). Acute stress disorder is divided into five symptom clusters: intrusive memories or revival, negative mood, dissociation, avoidance and arousal. To meet the criteria for acute stress disorder, the patient must have experienced a traumatic event (in this case a cardiac arrest) during the past month (criteria A) as well as the presence or deterioration of at least nine symptoms independent of the associated category after the onset of episode (Criterion B), which should occur within three days to one month (Criterion C) (52).

Cortisol Awakening Response: At the same day as the structured clinical interview (i.e. ASDI) is performed, saliva samples for determination of the Cortisol Awakening Response (CAR) will be obtained from eligible patients. Five samples are collected during awakening and three saliva samples will also be collected during the day at 12 at 18 and at 23 o´clock. The total amount of saliva per patient is 16 ml. After collecting the saliva, the samples will be stored and analysed at the Department of Clinical Biochemistry, Rigshospitalet, Glostrup.

Sociodemographic variables and several clinical pre- and inhospital data were obtained from electronic medical records (see table 2).

-Insert Table 2**: Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors** about here-

<u>At 3-months follow-up</u>

The patients included at Rigshospitalet and Herlev-Gentofte Hospital will undergo a detailed and individual neuropsychological assessment at the Neurobiology Research Unit at Rigshospitalet, and patients included at Odense University Hospital will be assessed with a similar test battery at the University of Southern Denmark. The cognitive assessment of the patient's cognitive functions will be given, administered and interpreted by a clinical and trained psychologist or psychology student under supervision. The patients and their relatives will furthermore complete a package of self-reported questionnaires.

The neuropsychological assessment: The tests used are a carefully selected neuropsychological test battery comprising the same subcomponents as for the MoCA; *attention, visuospatial construction, executive functioning, memory, language and orientation*. The tests used are all validated in clinical settings for a variety of populations and have shown good test-retest reliability. To address a source of bias, all tests are conducted by a psychologist, who is kept blind of the clinical data as well as the results of the previous brief

cognitive screening. A detailed outline of the neuropsychological tasks includes: Danish Affective Verbal Learning Test-26 (VAMT-26) (53) and Delis-Kaplan Executive Function System tests (D-KEFS) comprising trail-making, colour-word interference, design fluency and word fluency (54) together with the Rey's complex figure test (55) and Letter-number sequencing test from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (56) (table 1).

Psychopathology in patients: Furthermore, the patients will repeat the self-reported questionnaires identical to the questionnaires completed during hospitalisation: HADS-D, HADS-A and IES-R.

Psychopathology in relatives: The relatives are also asked to complete the HADS-D, HADS-A and IES-R. The questionnaires for both patients and their relatives are sent via e-mail two weeks before the 3-months follow-up.

<u>At 1-year follow-up</u>

The 1-year follow-up is designed as register-based (table 2). To investigate whether baseline data are associated with morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure and with mortality and health care utilisation, the collected data will be linked with data from national administrative registers; the Danish National Patient Register (57), the Danish Civil Registration System (58), the Danish National Prescription Registry (59), the Danish education registers (60), and the Danish registers on personal income and transfer payments (61).

Primary and secondary study outcome measures

Primary outcome measures for patients

The primary outcome is whether the patients present a favourable outcome (FO) or a non-favourable outcome (nFO) at 3-month follow-up. To elucidate cognition and psychopathology separately, primary outcomes will be established for each of these domains.

Cognition: As primary cognitive outcome the patients will be divided into two groups, FO and nFO, based on their performance in the neuropsychological tasks. The subset with an nFO is defined as minimum 1.5

standard deviation (SD) under the norm or reference data (53–55,62) on minimum one test or 1 standard deviation on two or more tests. The rest of the patients fall into the FO group.

Psychopathology: As primary psychopathology outcome the patients will be divided into two groups, FO and nFO, based on their scores on the HADS and IES-R. The subset with an nFO is defined one or more scores above cut-off for psychopathology on the HADS and IES-R: HADS-D and HADS-A >8 and IES-R >24. The rest of the patients fall into the FO group.

Secondary outcome measures for patients

As secondary outcomes for patients are self-reported measures of sleep quality, fatigue, executive functioning, and health-related quality of life at 3-months of follow-up (table 2). A detailed description of the secondary outcomes is described in the supplementary material 1. Secondary outcomes for patients also include register-based information of morbidity: depression, anxiety, dementia, chronical fatigue syndrome or heart failure, mortality and healthcare utilisation at 1-year post-arrest (table 2).

Primary outcome measures for relatives

The primary outcomes for the relatives include HADS-D, HADS-A and IES-R (47,63) (table 3).

-Insert Table 3**: Outcome domains, measurement instruments and measurement time for the relatives** about here-

Secondary outcome measures for relatives

Secondary outcome measures for relatives include self-reported health-related quality of life, experience of cognitive changes in the patient after the cardiac arrest, social support, major depression, the quality in the relationship with the cardiac arrest survivor, and the extent to which the cardiac arrest is viewed as being central to one´s identity (table 3).

Several exploratory outcomes will also be collected (figure 1).

Data analysis plan

The collected socio-demographic data will be presented as means ± standard deviation (SD) or percentages, respectively and group differences will be calculated by t-tests (continuous data) or χ^2 (categorical data). Appropriate regression models will be used to examine the associations between screening performance during hospitalisation and the primary and secondary study outcomes. In all model's relevant covariates e.g. sex, age, comorbidity, time to return of spontaneous circulation, coma duration time, time at intensive care unit, time of hospitalization, etc. will be included (table 2). A formal power calculation of sample size has not been performed due to the several aims and potential analyses of this study. With no comparative patient groups and only few small existing studies, we aim for a sample size of 200 cardiac arrest survivors at three months follow-up for the primary outcome to be statistically and clinically significant.

Patient and Public Involvement

As a patient involvement method, two theme-based sessions involving *direct patient feedback* have been carried out in the early pilot and design phase of the study. The aim of these sessions was to 1) identify patient preferences regarding the cognitive screening procedure (figure 2), and 2) develop the research priorities including implementation of possible changes based on the patient's feedback. Data derived from the theme-based patient feed-back sessions provides the basis for the cognitive screening procedure in the REVIVAL study. To ensure further patient involvement, we plan to engage the patients in the planning phase of disseminating the results.

DISCUSSION

To the best of our knowledge, the present study will be the largest study evaluating and testing a novel screening procedure for cognitive impairment and emotional reactions during hospitalisation in a population of OHCA survivors. As the incidence of cardiac arrest survival is increasing, establishing a standardized approach to screening in OHCA survivors will be critical in the future. Following the aims of the study and

to strengthen the standardization of the results, only patients with a presumed cardiac cause for their cardiac arrest as defined by Utstein template will be included. Since a common single etiology of cardiac arrest is respiratory failure, it could be considered to include this population in a future study. Although cognitive and mental health outcomes in OHCA survivors may be comparable to other medical populations (7,64,65), the study does not contain a comparative arm as it does not aim to investigate a specific intervention. Instead the study seeks to investigate OHCA survivors after standard treatment in a naturalistic setting. Due to the nature of the study and the vulnerable state of the patients, differential loss to follow-up is expected in the study. To elucidate data missing not at random, we plan to conduct phone calls to non-responders at 3-months follow-up regarding their withdrawal from the study. We expect that results from the REVIVAL study will inform an early screening procedure of OHCA survivors in clinical settings as well as inform future targeted rehabiliation in survivors who are likely to develop protracted cognitive impairment and psychopathology.

ETHICS AND DISSEMINATION

There is little to no discomfort for the patients and their relatives in this study. Due to the weakened constitution of the patients, the neuropsychological test at 3-months post-arrest could be experienced as taxing and can be divided into two days. The study complies with the Declaration of Helsinki and has been approved by the Danish national committee on health research ethics (H-18046155) and the Danish Data Protection Agency (RH-2017-325, I-Suite no: 05961). Patients and their relatives will receive oral and written information about the study and inclusion will require obtained written consent for all participants before enrolment. Results from this study will be disseminated at regional, national and international conferences and in peer-reviewed journals.

Authors' contributions

Department of Cardiology, Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Copenhagen University Hospital Rigshospitalet (MKW, SKB, and CH) and Neurobiology Research Unit, Rigshospitalet (DSS, PMF and GMK) has full access to all the data in the study and takes responsibility for the integrity of data. MKW, SKB, CH and DSS contributed to the study concept and design. MKW, SKB, CH, SA, JEM,

PMF, GMK and DSS contribute to the data acquisition. Analysis will be performed by MKW, SKB, CH, OE and DSS, MKW and DSS drafted the manuscript with critical input from SKB, CH, SA, JEM, OE, TBR, PMF and GMK. All authors approved the final version of the manuscript.

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Competing interest statement

On behalf of all authors, the corresponding author states that there are no conflicts of interest related to this study. The funding sources have no role in the design and conduct of the study.

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Table 1: The cognitive assessment

The cognitive assessment		
	During hospitalisation	**3-months follow up**
Target cognitive domain	**MoCA**	**Neuropsychological tests**
Attention	Number sequence Letter list	D2 (visual attention) (Trail-making + stroop)
Visuospatial construction	Cube copying	Rey's figure
Episodic memory	Verbal memory test	VAMT-26
Working memory	Serial subtraction	Letter-number sequence
Executive functioning	Trail making B Clock drawing Abstraction	Trailmaking B D-KEFS colour-word interference
Psychomotor Processing speed	Trail making B	Trail making A and B
Language	Naming Repeating Word mobilization	
Orientation	Orientation	

Table 2: Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors

Outcome domains, measurement instruments, time of measurement and quantity for the cardiac arrest survivors		
Outcome domains and measurement instruments	**Time of measure**	**Type of quantity**
Sociodemographic variables		
Age	T0	Continuous
Sex	T0	Binary
Marital status, type of occupation, employment status, living situation	T0	Categorical
Medical variables		
Known IHD, hypertension, previous MI, PCI or CABG, chronic heart failure, diabetes mellitus, COPD and chronic kidney disease	T0	Binary
Clinical variables related to the cardiac arrest		
Place of OHCA, aetiology of cardiac arrest, initial rhythm, TTM, medication during ICU stay, LVEF	T0	Categorical
Bystander witnessed cardiac arrest, bystander performed CPR, Use of AED, shockable rhythm, awake at arrival to hospital, TTM, intubated, medication during ICU, delirium at ICU	T0	Binary
Time to ROSC, intubation time, length of stay at ICU	T0	Continuous
Consious state GCS	T0	Categorical
Neurological outcome CPC	T1	Categorical
Length of stay at hospital	T1	Continuous
Performance based variables		
Delirium score 4AT	T1	Categorical
Functional independence Barthel Index- 20	T1	Categorical
Cognitive status MoCA	T1	Binary
Brain activity while resting rsfMRI	T1	Continuous
Neuropsychological outcome VAMT-26, D- KEFS trail-taking, D-KEFS colour-word interference, D-KEFS design fluency, Rey's complex figure and Letter-number sequencing**:** sub-test of WAIS-IV	T2	Binary
Cortisol Awakening response	T1	Continuous
Patient-reported outcome measures		
POMS	T1	
HADS, IES-R, CSS	T1, T2	Continuous
B-IPQ, FSS, HeartQoL, SF-12, PSQI, CISS, BRIEF-A, ECR-R, AMCQ, CES-S, MTEQ, PTGQ, ACQ, NDEQ	T2	Continuous
Lifestyle changes, Health profile	T2	Categorical
Register based		
Depression, anxiety, dementia, chronical fatigue syndrome and heart failure, mortality and health care utilisation	T3	Continuous

T0: Pre-arrest, medical and clinical data, T1: During hospitalisation, T2: 3 months follow-up, T3: 1 year follow-up

ICU: Intensive Care Unit, **LVEF**: Left Ventricular Ejection Fraction, **OHCA**: Out-of-hospital Cardiac Arrest, **CPR**: Cardiopulmonary resuscitation, **AED**: Automated External Defibrillator, **ROSC**: Return of spontaneous circulation, **TTM**: Targeted Temperature Management, **IHD**: Ischemic Heart Disease, **MI**: Myocardial infarction, **PCI**: Percutaneous coronary Intervention, **CABG**: Coronary Artery Bypass Surgery, **COPD**: Chronic Obstructive Pulmonary Disease, **GCS**: Glasgow Coma Scale, **CPC**: Cerebral Performance Category, **MoCA**: Montreal Cognitive Assessment, **rsfMRI**: resting state functional magnetic resonance imaging, **VAMT-26**: Danish Affective Verbal Learning Test-26, **D- KEFS**: Delis–Kaplan Executive Function System,_ **POMS:** Profile of Mood States, **HADS**: Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event- Revised, **CSS**: Crisis Support Scale, **B-IPQ**: Brief Illness Perception Scale, **FSS**: Fatigue Severity Scale, **SF-12**: 12-item short Form Survey, **PSQI**: Pittsburgh Sleep Quality Inventory, **CISS**: Coping Inventory for Stressful Situations, **BRIEF-A**: Behavior Rating Inventory of Executive Functions, adult version, **ECS-R**: Experience in close relationships, **AMCQ**: Autobiographical Memory Characteristics Questionnaire, **CES-S:** Centrality of Events – Short, **MTEQ**: Memory of Event Scale, **PTGQ:** Post Traumatic Growth Questionnaire, **ACQ**: Attribution, **NDEQ:** Near-death Experience Questionnaire,

Table 3: Outcome domains, measurement instruments and measurement time for the relatives

Outcome domains, measurement instruments and measurement time for the relatives		
Outcome domain	**Measurement instruments**	**Time**
Demographic variables and psychiatric medical history		T2
Health-related quality of life	**SF-12**	
Anxiety and Depression	**HADS**	
Distress caused by a traumatic event	**IES-R**	
Experience in close relationships	**ECR-R**	
Social support after a crisis	**CSS**	
Major depression	**MDI**	
The extent to which an **event** is viewed as being central to one's identity	**CES-S**	
Cognitive decline reported by informants (relatives or close friends)	**IQ-CODE**	

T2: 3 months follow-up

SF-12: 12-item Short Form Survey, **HADS**: Hospital Anxiety and Depression Scale, **IES-R**: Impact of Event- Revised, **ECR-R**: Experience in close relationships, **CSS**: The Crisis Support Scale, **MDI:** Major Depression Inventory, **CES-S**: Centrality of Event short, **IQ-CODE**: The Informant Questionnaire on Cognitive Decline in the Elderly.

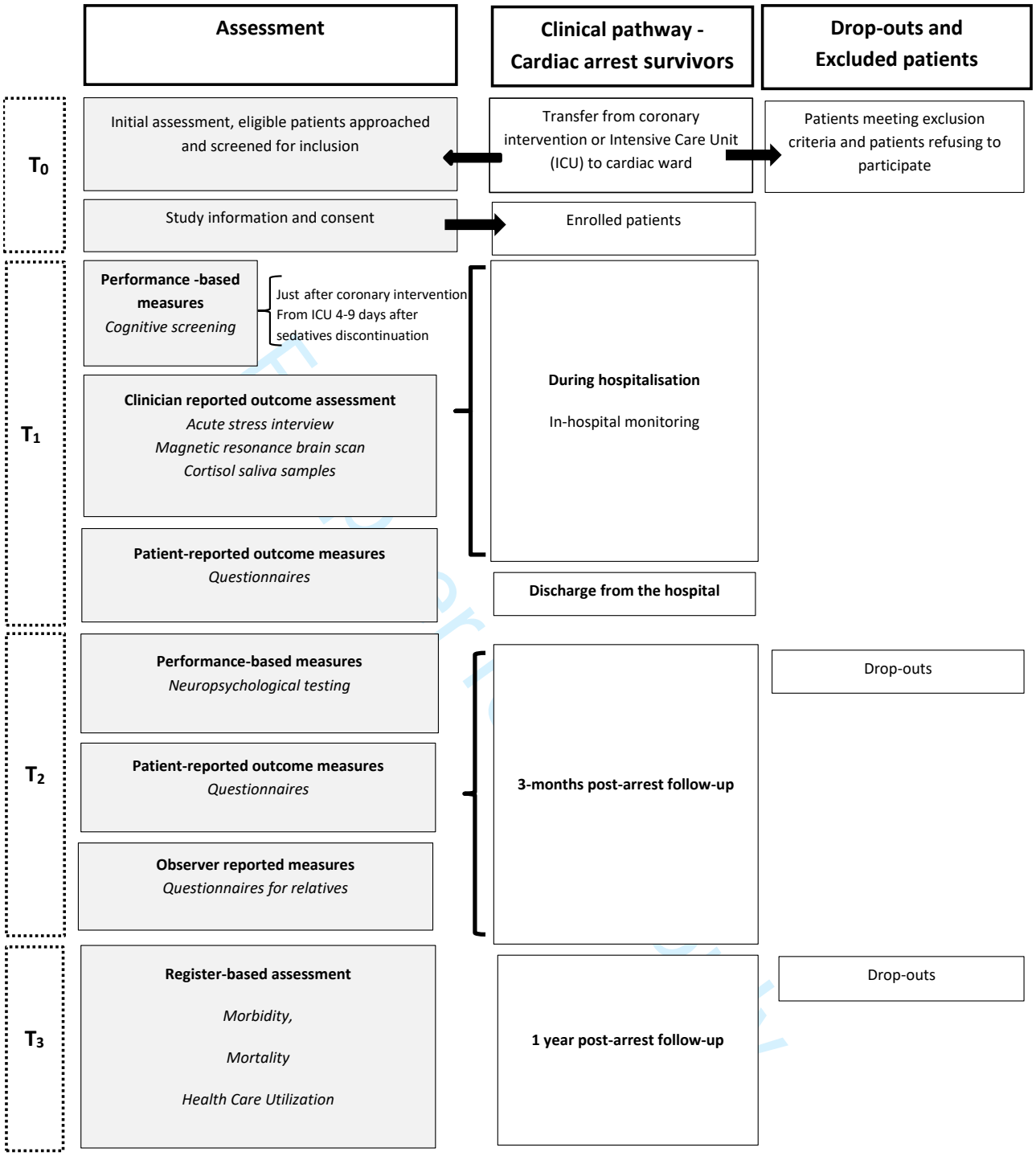

Figure 1: Flowchart of study assessment

T0: Study inclusion, **T1**: During hospitalisation, **T2**: 3 months follow-up, **T3**: 1-year follow-up

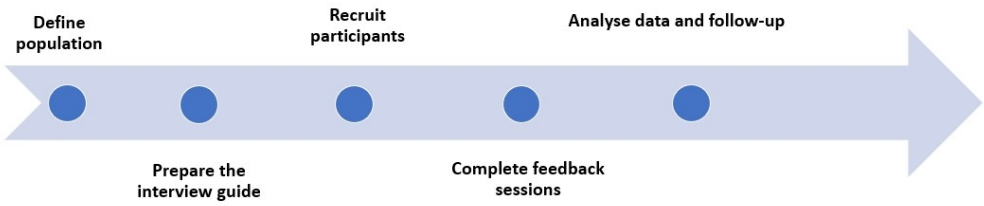

Figure 2
Direct patient-feed back

279x82mm (96 x 96 DPI)

Supplementary material 1: Description of secondary outcomes

Sleep quality

The Pittsburgh Sleep Quality Inventory (**PSQI**) is a 19-item measure which assesses sleep quality and disturbances over the last months. The items generate a seven-component score each weighted equally on a 0-3 scale. The sum of these scores provides a global score. Higher scores indicate worse sleep quality. A cut-off score of >5 indicates poor sleep quality (64). The PSQI has demonstrated internal consistency reliability with Cronbach's α 0.83 (65).

Fatigue

Fatigue Severity Scale **(FSS)** is a nine-item questionnaire that measures experienced severity of fatigue symptoms in daily activities on a seven-point scale. A mean score is calculated (range 1–7) with higher scores reflecting greater fatigue. The FSS has shown construct validity with correlation coefficient of 0.68 with the visual analogue scale as external criterion and a Cronbach´s α of 0.90 in stroke patients (66).

Executive functioning

Behaviour Rating Inventory of Executive Function **(BRIEF-A)** is a nine-item measure suitable for assessing adults executive functioning in everyday life. BRIEF-A measures different aspects of the executive functioning which are part of three overall clinical indices; *behavioral regulation*, *metacognition* and *general executive function*. Among others the BRIEF-A has been shown sensitive to assess executive function deficiencies in adults with a traumatic brain injury (67). The instrument has shown high internal consistency in clinical populations with a Cronbach´s α ranging from 0.93 to 0.96 (68).

Health-related quality of life

The Medical Outcomes Study 12-item Short Form Health Survey **(SF-12)** is an abbreviated version of the SF-36 and a generic health-related quality of life measure. SF-12 measures eight domains of health on 2 domains, respectively physical health and mental health. The scores ranges from 0-10 with higher scores indicating a higher level of health-related quality of life (69). The instrument has been extensively validated in several populations and has shown good reliability when used in a stable coronary population (70).

Quality of life

The **Heart-QoL** is a 14-item heart disease-specific questionnaire that measures the Quality of life in cardiac patients. The scale is divided into a global, physical (10 items) and emotional (four items) component. Items are answered on a four-point Likert scale (range 0–3) with higher scores indicating better HRQoL. Heart-QoL has shown satisfactory internal consistency Cronbach's α > 0.90 in Danish implantable cardioverter defibrillator recipients (71).

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page and abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page 3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 5-7	
Objectives	3	State specific objectives, including any prespecified hypotheses	page 6-7	
Methods				
Study design	4	Present key elements of study design early in the paper	page 7-8	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	page 7-12	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	page 11-13	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	page 9-13	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	page 8-13	
Bias	9	Describe any efforts to address potential sources of bias	page 7-8	
Study size	10	Explain how the study size was arrived at	page 13	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	page 13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	page 13
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			N/A
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

page 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.