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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

Aims: The overarching aim of the thesis was to explore aspects of physical function and activity in out-of-hospital cardiac arrest (OHCA) survivors and to explore risk factors associated with limitations in physical function and low levels of physical activity. The specific aims per papers included in the thesis were: **I)** To describe physical function in survivors 6 months after OHCA, and compare it with a group of ST-elevation myocardial infarction (STEMI) controls. To explore variables potentially associated with self-reported limitations in physical function in OHCA survivors. **II)** To investigate whether OHCA survivors had lower levels of self-reported physical activity compared to a non-cardiac arrest control group who had acute myocardial infarction (MI). To explore potential predictors of physical inactivity. To investigate the relationship between self-reported and objectively measured physical activity among OHCA-survivors. **III)** To investigate the agreement between self-reported and objectively assessed physical activity among OHCA survivors. **IV)** To describe the level of physical activity 6 months after an OHCA and to explore potential risk factors of a low level of physical activity. **V)** To investigate whether OHCA survivors had lower levels of self-reported physical activity compared to a non-cardiac arrest control group who had MI, and to explore if symptoms of anxiety, depression, kinesiophobia and fatigue were associated with low levels of physical activity.

Methods: I) A post-hoc analysis of a case-control cognitive sub-study of the international multicentre Targeted temperature management at 33℃ versus 36℃ after cardiac arrest (TTM) trial with a follow-up 6 months post cardiac event. **III)** A cross-sectional sub-study of the international multicentre Targeted hypothermia versus targeted normothermia after OHCA (TTM2) trial 7 months post OHCA. **IV)** A post-hoc analysis of survivors in the main TTM2 trial 6 months post OHCA. **V)** A cross-sectional case-control sub-study of the TTM2 trial 7 months post cardiac event.

Results: I) Self-reported limitations in physical function were more common in OHCA survivors than in MI controls and were associated with older age, female sex, cognitive impairment, and symptoms of anxiety and depression. **III)** The OHCA survivors self-reported more physically active days compared to the results of the objective assessments. **IV)** One third of the OHCA survivors self-reported low levels of physical activity and risk factors of low levels of physical activity were obesity, mobility problems and cognitive impairment. **V)** One quarter of the OHCA survivors and one fifth of the MI controls self-reported low levels of physical activity with no significant difference. Kinesiophobia (fear of movement) and fatigue were associated with low levels of physical activity.

Conclusions: Self-reported limitations in physical function and low levels of physical activity were common following OHCA. By screening physical function, level of physical activity and potential risk factors identified in the thesis, the survivors may be provided support and rehabilitation.

Key words cardiac arrest; physical function; physical activity; self-reports; accelerometery; outcome

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"Those who think they have no time for exercise will sooner or later have to find time for illness."

Edward Stanley 1826-1893

Table of Contents

List of publications

The thesis is based on the following papers which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. **Heimburg K**, Cronberg T, Tornberg ÅB, Ullén S, Friberg H, Nielsen N, Hassager C, Horn J, Kjærgaard J, Kuiper M, Rylander C, Wise MP, Lilja G. Self-reported limitations in physical function are common 6 months after out-of-hospital cardiac arrest. *Resuscitation Plus*, 11, 2022, 100275.

II. **Heimburg K**, Lilja G, Tornberg ÅB, Ullén S, Blennow Nordström E, Friberg H, Nielsen N, Gregersen Østergaard L, Grejs AM, Hill H, Keeble TR, Kirkegaard H, Mion M, Rylander C, Segerström M, Undén J, Wise MP, Cronberg T. Physical activity after cardiac arrest; protocol of a sub-study in the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest trial (TTM2). *Resuscitation Plus*, 5, 2021, 100076.

III. **Heimburg K**, Lilja G, Blennow Nordström E, Friberg H, Gregersen Østergaard L, Grejs AM, Keeble TR, Mion M, Nielsen N, Rylander C, Segerström M, Thomsen IK, Ullén S, Undén J, Wise MP, Cronberg T, Tornberg ÅB. Agreement between self-reported and objectively assessed physical activity among out-of-hospital cardiac arrest survivors. *Clinical Physiology and Functional Imaging*, 2023:1-10.

IV. **Heimburg K**, Blennow Nordström E, Dankiewicz J, Friberg H, Grejs AM, Haenggi M, Keeble TR, Kirkegaard H, Nielsen N, Rylander C, Tornberg ÅB, Ullén S, Wise MP, Cronberg T and Lilja G. Out-of-hospital cardiac arrest survivors with obesity, mobility problems and cognitive impairment report a low level of physical activity: Results from the TTM2 trial. *Unpublished manuscript.*

V. **Heimburg K**, Blennow Nordström E, Friberg H, Gregersen Østergaard L, Grejs AM, Keeble TR, Kirkegaard H, Mion M, Nielsen N, Rylander C, Segerström M, Tornberg ÅB, Ullén S, Undén J, Wise MP, Cronberg T and Lilja G. Comparison between self-reported physical activity after out-of-hospital cardiac arrest and myocardial infarction: a TTM2 sub-study. *Unpublished manuscript.*

Paper I, II and III are published open access.

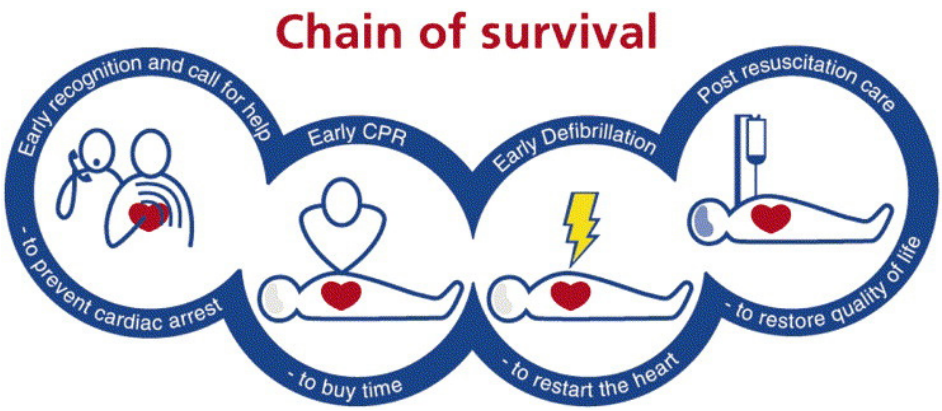
Abbreviations

ACS	acute coronary syndrome
AHA	American Heart Association
BMI	body mass index
CA	cardiac arrest
CAD	coronary artery disease
CPR	cardiopulmonary resuscitation
CR	cardiac rehabilitation
EQ-5D-5L	EuroQol group health survey 5 dimensions 5 levels response version
FITT	frequency, intensity, time, type
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS Anxiety subscale
HADS-D	HADS Depression subscale
HRQoL	health-related quality of life
ICU	intensive care unit
MET	metabolic equivalent of task
MFI-20	Multidimensional Fatigue Inventory 20 items
MI	myocardial infarction
MoCA	Montreal Cognitive Assessment
MPA	moderate intensity physical activity
mRS	modified Rankin Scale
Non-STEMI	non-ST-elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
PF-10	Physical Functioning 10 items
RPE	rating of perceived exertion
ROSC	return of spontaneous circulation
SDMT	Symbol Digit Modalities Test
SF-36	Short-Form Health Survey 36 items
STEMI	ST-elevation myocardial infarction
TSK Heart	Tampa Scale for Kinesiophobia Heart
TTM	targeted temperature management
TTM trial	Targeted temperature management at 33 °C versus 36 °C after cardiac arrest trial
TTM2 trial	Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial
VO_2 max	maximal oxygen consumption
VO_2 peak	peak oxygen consumption
VPA	vigorous intensity physical activity

Sammanfattning på svenska

Introduktion

Hjärtstopp inträffar när hjärtat plötsligt slutar att slå och är ett livshotande tillstånd. Vid hjärtstopp upphör hjärtat att pumpa blod och den drabbade personen blir efter några sekunder medvetslös till följd av syrebrist.[1] Kedjan som räddar liv är en serie åtgärder som påverkar överlevnaden vid ett plötsligt hjärtstopp (Figur 1). För att återställa en normal hjärtrytm krävs vanligtvis 1) upptäckt av hjärtstoppet och larm, 2) hjärt-lungräddning, 3) behandling med en hjärtstartare och 4) medicinsk vård.[2]



Figur 1: Kedjan som räddar liv.[3] © Elsevier, tryckt med tillstånd.

Endast en av tio som drabbas av plötsligt hjärtstopp utanför sjukhus överlever fram till utskrivning från sjukhus.[4] Hjärtstopp orsakas oftast av hjärtsjukdom.[5-7] Personer som har överlevt ett hjärtstopp utanför sjukhus kan uppleva olika svårigheter.[8]

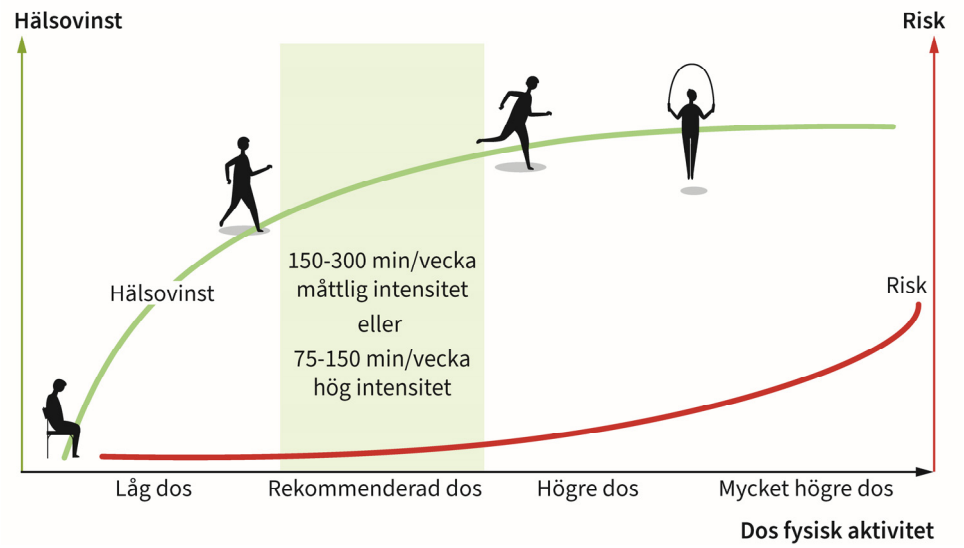
Människan är byggd för rörelse och fysisk aktivitet. Fysisk aktivitet kan definieras som ”*all kroppsrörelse som ökar energiförbrukningen utöver den energiförbrukning vi har i vila*”.[9] Fysisk aktivitet kan ske i hemmet, på arbetet, under transport eller som organiserad träning eller idrott på fritiden.[10] Dosen av fysisk aktivitet kan beskrivas med FITT-konceptet; Frekvens, Intensitet, Tid (duration) och Typ av aktivitet.[11] Fysisk

aktivitet kan minska risken för att drabbas av olika sjukdomar som t ex högt blodtryck, kranskärlssjukdom och stroke.[10] En vuxen person bör vara fysisk aktiv 150-300 minuter med måttlig intensitet eller 75-150 minuter med ansträngande intensitet varje vecka (Tabell 1).[12]

Tabell 1: Rekommenderad dos av fysisk aktivitet för hälsa och välmående enligt Världshälsoorganisationen (WHO)[12] och Yrkesföreningar för fysisk aktivitet.[10]

Tid och intensitet per vecka
150–300 minuter fysisk aktivitet med måttlig intensitet
eller
75–150 minuter fysisk aktivitet med ansträngande intensitet
eller
en kombination av måttlig och ansträngande aktivitet

Dosen av fysisk aktivitet påverkar graden av effekt på hälsan (Figur 2). Man bör undvika långvarigt sittande. Hälsovinsten börjar vid lägre nivåer än den rekommenderade dosen.[10, 12]



Figur 2: Dos-responskurva mellan fysisk aktivitet och hälsovinst enligt Yrkesföreningar för fysisk aktivitet. Illustration: FYSS 2021 (YFA/Typoform AB).[10] © Tryckt med tillstånd.

Fysisk aktivitet kan också vara behandling vid sjukdom. Rekommenderad dos av fysisk aktivitet vid t ex kranskärlssjukdom är 3-5 ggr per vecka med måttlig och/eller hög intensitet i minst 90 minuter per vecka (Tabell 2).[10]

Tabell 2: Rekommenderad dos av fysisk aktivitet vid kranskärlssjukdom.[10]

Frekvens	Intensitet	Tid	Typ
3–5 ggr/vecka	Måttlig och hög kombinerat	≥ 90/ minuter/vecka	Kontinuerligt eller i intervaller

Initialt bör träningen vara övervakad av sjukvårdspersonal. En person med kranskärlssjukdom behöver ofta stöd för att våga påbörja, öka och till sist vidmakthålla sin fysiska aktivitetsnivå och därmed sin fysiska kapacitet.[10]

Syftet med avhandlingen

Det övergripande syftet med denna avhandling var att utforska aspekter på fysisk funktion och aktivitet hos personer som har överlevt efter hjärtstopp utanför sjukhus. Det fanns en kunskapslucka om hjärtstoppsöverlevarnas begräsningar vad gällde fysisk funktion, hur fysiskt aktiva de var och om möjliga riskfaktorer för en nedsatt fysisk funktion och en låg fysisk aktivitetsnivå.

Metod

Avhandlingen består av 5 delarbeten, benämnda med de romerska siffrorna I till V. Aspekter på fysisk funktion och fysisk aktivitet hos personer som har överlevt ett hjärtstopp utanför sjukhus undersöktes samt riskfaktorer för en nedsatt fysisk funktion och en låg fysisk aktivitetsnivå. Information har samlats in om hjärtstoppet, om sjukhusvistelsen och om variablerna vid uppföljningen 6–7 månader efter hjärtstoppet. Delarbetena är baserade på två stora internationella hjärtstoppsstudier:

Targeted temperature management at 33 °C versus 36 °C after cardiac arrest (TTM) trial

Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM2) trial

TTM studien

Delarbete I[13] är baserat på den kognitiv substudien[14, 15] som ingick i den större hjärtstoppsstudien TTM.[16, 17] TTM studien jämförde två temperaturinterventioner, 33°C mot 36°C, i det akuta skedet med syftet att undersöka om patients hjärna skyddades från skada. I substudien ingick 282 hjärtstoppsöverlevare och 119 matchade hjärtinfarktskontroller i 5 länder i Europa.[13] Samtliga besvarade ett frågeformulär med 10 frågor om självrapporterad fysisk funktion.[18]

TTM2 studien

Delarbete II[19] beskriver bakgrunden till delarbete III[20] och V. Delarbete III och V är baserade på en substudie med fokus på fysisk aktivitet inom den stora hjärtstoppstudien TTM2. Substudien genomfördes på 8 olika sjukhus i 3 länder i Europa.[19] 106 hjärtstoppsöverlevare inkluderades varav 49 ingick i jämförelsen i delarbete III. Överenstämmelsen mellan självskattad fysisk aktivitet och objektivt mätt fysisk aktivitet den senaste veckan 7 månader efter hjärtstoppet undersöktes.[20] I delarbete V blev de 106 hjärtstoppsöverlevarna matchade med 91 hjärtinfarktskontroller. Den fysiska aktivitetsnivån samt riskfaktorer för en låg fysisk aktivitetsnivå 6–7 månader efter hjärtstoppet undersöktes.

Delarbete IV är baserat på den stora hjärtstoppstudien TTM2 som jämförde kylbehandling vid 33 grader °C med normal kroppstemperatur i det akuta skedet med syftet att undersöka om patients hjärna skyddades från skada.[21, 22] 807 hjärtstoppsöverlevare på 61 olika sjukhus i 14 länder besvarade frågorna om fysisk aktivitet 6 månader efter hjärtstoppet. Den fysiska aktivitetsnivån och möjliga riskfaktorer för en låg fysisk aktivitetsnivå undersöktes.

Hjärtinfarktskontroller delarbete I och V

För att undersöka hur stor påverkan hjärtstoppet hade matchades överlevarna med personer som drabbats av en hjärtinfarkt utan hjärtstopp i delarbete I[13] och V. Båda grupperna antogs ha samma riskfaktorer före hjärthändelsen och båda grupperna hade upplevt en akut hjärthändelse.

Resultat

Delarbete I visade att självskattade begränsningar i fysisk funktion var mer vanligt hos personerna som har överlevt ett hjärtstopp än hos hjärtinfarktskontrollerna. Högre ålder, kvinnligt kön, kognitiva svårigheter samt ångest- och depressionssymptom hade ett samband med fysiska begränsningar.[13] Delarbete III visade att överlevarna rapporterade fler fysiskt aktiva dagar jämfört med resultaten av den objektiva mätningen av fysisk aktivitet. I delarbete V fann vi endast små och inga signifikanta skillnader i fysisk aktivitetsnivå mellan hjärtstoppsöverlevarna och hjärtinfarktskontrollerna. Rörelserädsla och fatigue (trötthet) var riskfaktorer för en låg fysisk aktivitetsnivå hos både grupperna. [20] I delarbete IV redovisas att en tredjedel av hjärtstoppsöverlevarna hade en låg självskattad fysisk aktivitetsnivå. Kraftig övervikt, förflyttningssvårigheter och kognitiva svårigheter var riskfaktorer för en låg fysisk aktivitetsnivå.

Tillämpning av resultaten

Här följer kliniska förslag baserade på avhandlingen:

- Bedöm den fysiska funktionen hos hjärtstoppsöverlevarna genom att använda frågeformuläret PF-10 och uppresningstestet TST.
- Bedöm den fysiska aktivitetsnivån hos hjärtstoppsöverlevarna genom att använda de två frågorna om fysisk aktivitet eller objektivt genom accelerometermätning.
- Var uppmärksam på att hjärtstoppsöverlevarna rapporterade fler fysiskt aktiva dagar jämfört med den objektiva mätningen av fysisk aktivitet.
- Fråga om och var uppmärksam på möjliga riskfaktorer för självskattade begränsningar i fysisk funktion; högre ålder, kvinnligt kön, kognitiva svårigheter, ångest- och depressionssymptom.
- Fråga om och var uppmärksam på möjliga riskfaktorer för en låg fysisk aktivitetsnivå; kraftig övervikt, förflyttningssvårigheter, kognitiva svårigheter, rörelserädsla och fatigue.
- Erbjud hjärtstoppsöverlevarna med begränsningar i fysisk funktion hjälp med att förbättra sin fysiska funktion.

- Erbjud hjärtstoppsöverlevarna med låg fysisk aktivitetsnivå hjälp med att bli mer fysiskt aktiva.
- De identifierade riskfaktorerna, utom ålder och kön, går troligen att påverka och behandla med en ökad dos av fysisk aktivitet och/eller fysisk träning inom hjärtrehabilitering.

Det övergripande och viktigaste budskapet i denna avhandling är att:

Delarbete I: Av de personer som har överlevt ett hjärtstopp utanför sjukhus rapporterade 38 % begränsningar i fysisk funktion och detta hade ett samband med högre ålder, kvinnligt kön, kognitiva besvär, ångest- och depressionssymptom.

Delarbete III: De överlevande rapporterade fler fysiskt aktiva dagar jämfört med resultaten av den objektiva mätningen av fysisk aktivitet.

Delarbete IV-V: Av de personer som har överlevt ett hjärtstopp utanför sjukhus rapporterade 25-34% en låg fysisk aktivitetsnivå och detta hade ett samband med kraftig övervikt, förflyttningsproblem, kognitiva svårigheter, rörelserädsla och fatigue.

Introduction

Cardiac arrest

Cardiac arrest (CA) is defined as "*cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation*".[1] The CA causes a period of cerebral hypo perfusion resulting in varying degree of anoxic brain injury.[2,3] The CA may be reversible or lead to death. If the CA is occurring outside of a hospital setting it is defined as out-of-hospital cardiac arrest (OHCA).[5] The number of survivors of OHCA are increasing due to successful improvements in prehospital and acute medical care,[5] but are still few. Most CA survivors return home and live independently,[8] but a CA can cause cognitive, emotional and physical problems.[6]

In the thesis, all participants were out-of-hospital cardiac arrest (OHCA) survivors.

Causes of cardiac arrest

The causes of CA can be categorised into cardiac and non-cardiac causes. Cardiac causes can be divided into ischemic (coronary artery disease), non-ischemic (e.g. genetic cardiomyopathies, congenital heart disease) and electrical disorders (e.g. inherited arrhythmic diseases).[2,3]

Paper I: OHCA of a presumed cardiac cause.

Paper II-V: OHCA of a presumed cardiac or of an unknown cause.

Coronary artery decease (CAD) is the predominant cause of CA.[5, 7, 24] CAD is a pathological process characterized by atherosclerotic plaque accumulation in the endothelium of coronary arteries.[25] Physical activity delays the development of atherosclerosis and reduces the incidence of CAD events.[26] Acute coronary syndrome (ACS) includes myocardial infarction (MI) and unstable angina.[27] Acute MI occurs when one of the arteries that supplies the heart muscle becomes blocked. Diagnosis is made by electrocardiography and presence or absence of serology markers (Table 3).[27]

Table 3: Description of acute coronary syndrome.[27]

Diagnosis	Abbreviation	Description
Acute coronary syndrome:	ACS	STEMI, non-STEMI and unstable angina
ST-elevation myocardial infarction	STEMI	Myocardial ischemia results in myocardial injury or necrosis
Non-ST-elevation myocardial infarction	Non-STEMI	Myocardial ischemia results in myocardial injury or necrosis
Unstable angina	UA	Chest discomfort or pain caused by insufficient blood flow and oxygen to the heart

In paper I, 46 % of the OHCA survivors had STEMI as CA cause and the OHCA survivors were matched to STEMI controls.

In paper III and V, 58% of the OHCA survivors had MI as CA cause.

In paper V, the OHCA survivors were matched to MI controls.

In paper IV, 55% of the OHCA survivors had MI as CA cause.

The ACS spectrum ranges from asymptomatic to CA illustrated in Figure 3.

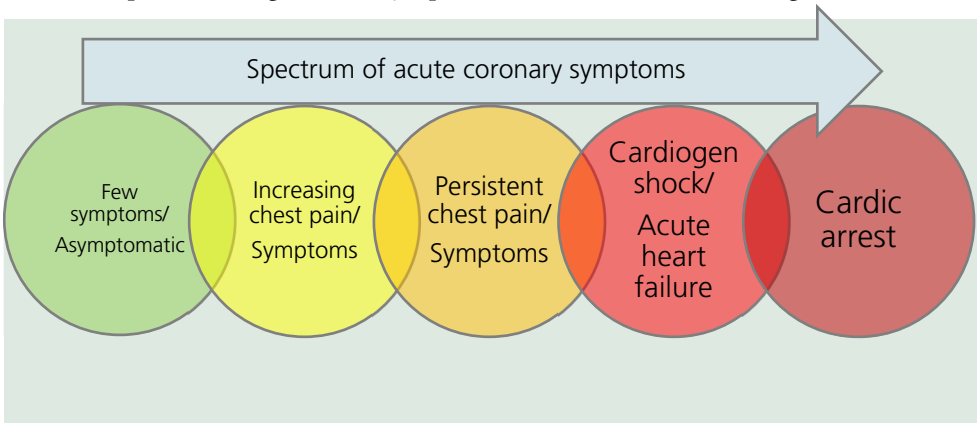


Figure 3: Spectrum of acute coronary syndrome from asymptomatic to cardiac arrest.[27]

Incidence, survival and prevention of OHCA

Worldwide, there are 4-5 million sudden cardiac deaths every year.[23] The annual incidence of OHCA in Europe is between 67 and 170 per 100 000 inhabitants.[28] In Europe, 8% of the patients suffering a CA are discharged from hospital alive.[4] In Sweden, just below 6000 OHCA were reported in 2022 and 12% survived until 30 days after the OHCA.[29] In Denmark, the survival rate was 13%.[30] In England, less than 8% survived to 30 days after an OHCA.[31] There are differences in survival rates between countries and regional differences within a country. The definition of OHCA may also differ.[23]

To reduce the number of OHCA, we need to focus on prevention of OHCA.[23] Most OHCA occur in the general population in individuals without known heart disease. First, we could screen for underlying cardiac diseases and risk factors which may cause CA. A low level of physical activity, hypertension, increased body mass index (BMI) and smoking are potential risk factors for both MI and CA.[23] According to the SWEDEHEART annual report 2023, 60% of the MI patients had hypertension, almost 30% were obese and 20% were smokers.[32] Second, we may try to prevent CA in those with established cardiac disease. A combination of risk markers and/or tests are suggested.[23]

Predictors of survival in the acute phase

Predictors of survival after OHCA can be categorized into patient factors, event factors, system factors and therapeutic factors. Patient factors include age, sex, and obesity.

Event related factors may include the location of the CA, the availability of cardiopulmonary resuscitation (CPR), and the cause of the CA. System factors could be time to CPR, quality of CPR and time to defibrillation. Therapeutic factors could be pharmacotherapy, quality of in-hospital care and distance to invasive heart centre.[5]

The chain of survival

The chain of survival refers to a series of actions that are associated with the survival rate of CA. Originally, the chain consisted of 4 steps; 1) activation of emergency response, 2) CPR, 3) defibrillation, and 4) resuscitation (Figure 4).[2]

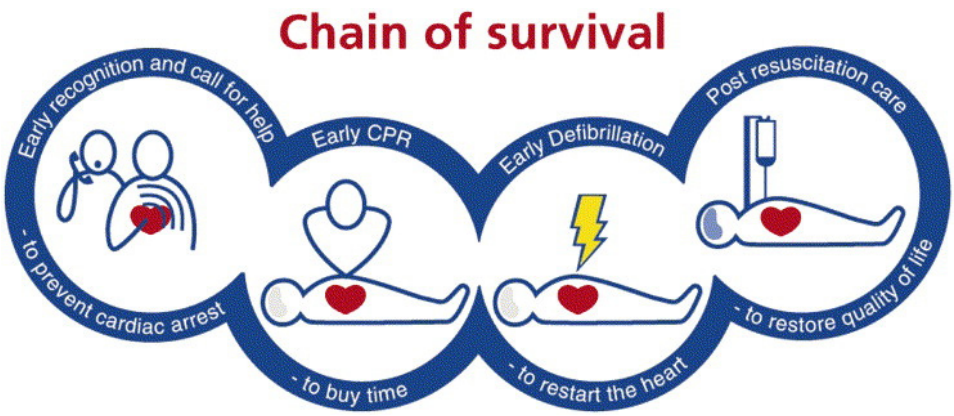


Figure 4: Chain of survival.[3] ©Elsevier, reprinted with permission.

The American Heart Association (AHA) added the 5th link post CA care in 2010 and the 6th link recovery in 2020 to the chain. The 6th link of recovery consists of CA survivors receiving support and rehabilitation (Figure 5).[33]

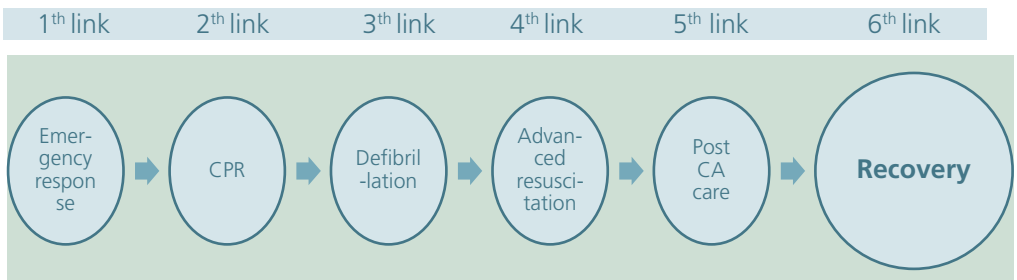


Figure 5: The updated chain of survival.[33] Abbreviations: CPR = cardiopulmonary resuscitation, CA = cardiac arrest.

In the thesis, focus is on the 6th link "Recovery" of the chain of survival.

Cardiac arrest and physical activity

The majority of persons suffering CA are performing light intensity physical activities. Vigorous intensity physical activity is a potential trigger of CA in a minority,[34] especially in untrained individuals with underlying heart disease.[23] In young individuals (≤40 years old), CA during physical activity is primarily due to genetic cardiomyopathies and congenital heart disease. In athletes >35 years of age, more than 80% of all CA deaths are due to atherosclerosis and CAD.[35, 36] Too vigorous physical activity can cause electrical disorders and CA.[37]

Outcome after OHCA

Outcome after OHCA are commonly reported by Cerebral Performance Category[38] or modified Rankin Scale (mRS)[39], often dichotomised into good or poor functional outcome categories.[40] Health-related quality of life (HRQoL) is another common way to report outcome after OHCA. HRQoL includes domains related to physical, mental, emotional, and social functioning and focuses on the impact that health status has on quality of life.[41] HRQoL is generally good after OHCA,[42] although physical impairment, cognitive impairment, emotional problems and fatigue are common.[8] Physical function seems to be more affected compared to other health domains after OHCA,[42] but have received little attention.[43, 44]

There are many possible explanations for limitations in physical function and a low level of physical activity in OHCA survivors. The survivors may have limitations in physical function and low levels of physical activity already before the CA. The lack of circulation during the CA may affect the heart and the exercise capacity.[45] OHCA survivors admitted to an intensive care unit (ICU) also have an increased risk of post intensive care syndrome (PICS). PICS includes new, or worsening, physical, cognitive and/or mental health problems.[8, 46]

Cognitive impairment and emotional problems may also affect the physical function and level of physical activity. Cognitive function includes the domains of perception, memory, learning, attention, decision making, and language abilities.[47] Most cognitive recovery occurs during the first 3 months with minor improvements up to 12 months

after the CA.[48, 49] One quarter of the OHCA survivors reported anxiety symptoms and one fifth reported depression symptoms.[50]

The prevalence of kinesiophobia and the association with level of physical activity in OHCA survivors was unexplored. Kinesiophobia is defined by Kori *et al* as *"an excessive, irrational, and debilitating fear of movement and activity resulting from a feeling of vulnerability to painful injury or re-injury".*[51] Many OHCA survivors experience fatigue but the association with physical activity level have only been examined in small groups of OHCA survivors.[44] Fatigue is defined by Dittner *et al* as "*an extreme and persistent tiredness, weakness or exhaustion mental, physical or both".*[52]

Screening and follow-up after OHCA

Through screening during follow-ups, problems can be identified and OHCA survivors can be provided with adequate information, support, and rehabilitation.[8] Guidelines and clinical pathways may differ, and some examples are listed below.

In 2015, the European Resuscitation Council and the European Society of Intensive Care Medicine collaborated to produce their first combined post-resuscitation care guidelines.[53] The guidelines were updated 2020 and rehabilitation and long-term outcome were added (Figure 6).[43]

1. Recommendation: Before hospital discharge, perform functional assessments of physical and non-physical impairment to identify early rehabilitation needs and refer to rehabilitation if necessary.
2. Suggestion: After hospital discharge within 3 months, screen for cognitive and emotional problems and fatigue. Provide information and support for the survivors and family members.[43]

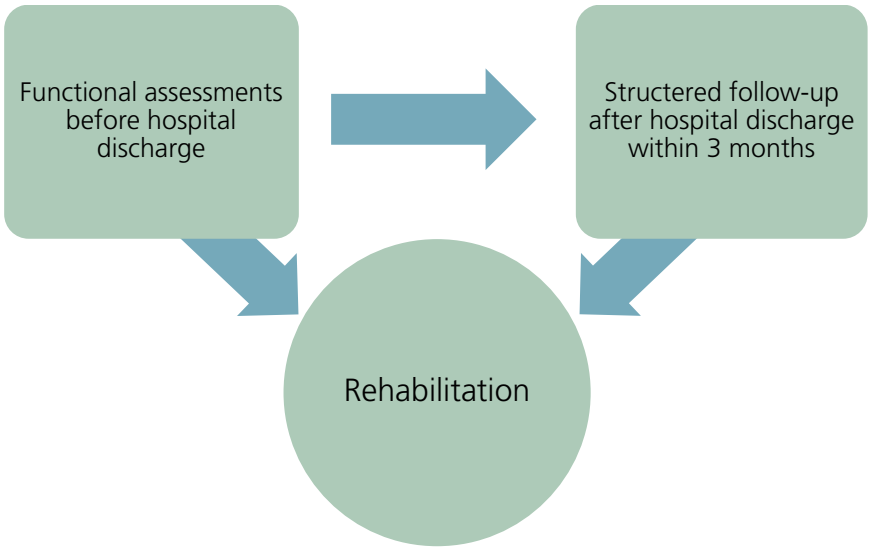


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Figure 6: The updated European Resuscitation Council and European Society of Intensive Care Medicine Guidelines including rehabilitation and long-term outcome.[43]

In Sweden, the guidelines recommend a follow-up within 1-3 months after the cardiac arrest[54]:

1. Investigate whether the survivor have been provided follow-up and information.
2. Screen for cognitive and physical impairment, emotional problems and fatigue.[54]

In Denmark, the guideline-based approach after cardiac arrest recommends[30]:

1. Establish the cause of CA to facilitate the right treatment.
2. Screen for cognitive impairment and symptoms of anxiety and depression.

In the UK, the British Cardiovascular Intervention Society published the following guidance around pre-discharge and follow-up care for OHCA survivors (Figure 7)[55]:

1. Prehospital discharge: assessment, information and support, cardiac rehabilitation.
2. Follow-up appointment after 1-3 months: multidisciplinary assessment.

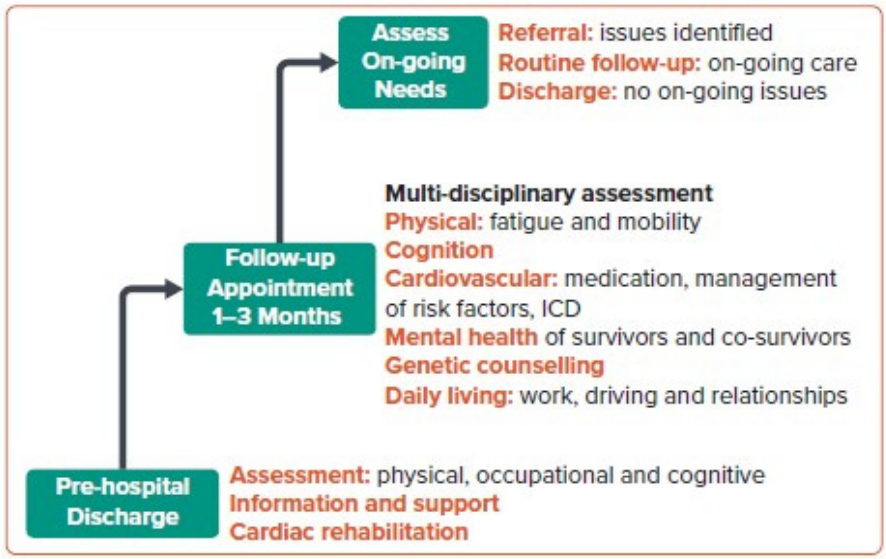

Figure 7: Time-points and key domains that need to be addressed after OHCA suggested by British Cardiovascular Intervention Society.[55] Licensed under CC BY-NC 4.0.

In the Netherlands, the clinical pathway after resuscitation recommends (Figure 8)[56]:

Screen for cognitive impairment and emotional problems:

1. Cardiac rehabilitation for all survivors with cardiac cause of the CA.
2. Combined cardiac and neurological rehabilitation when needed.
3. Neurological rehabilitation when needed.

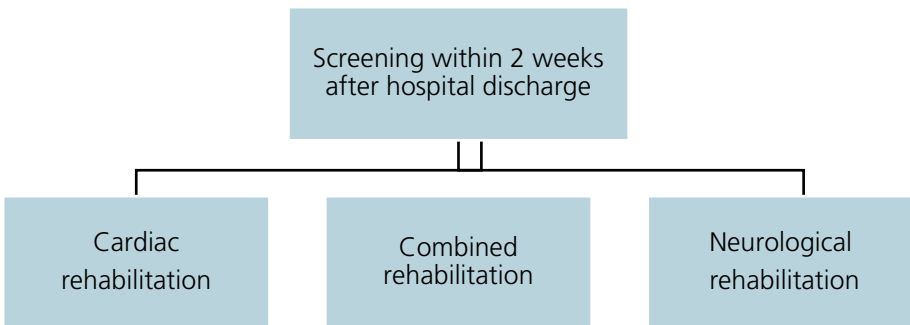

Figure 8: In Leiden in the Netherlands, the clinical pathway after resuscitation includes screening and rehabilitation.[56, 57]

OHCA survivors' perspective on screening and follow-up

A study by Mion *et al*[58] explored the OHCA survivors' perspective on screening and follow-up. More than half of the OHCA survivors reported that a follow-up meeting should be offered within the first month after hospital discharge. Fatigue, issues with memory/thinking, anxiety symptoms, physical limitations, and general physical deconditioning were frequently reported problems among the OHCA survivors.[58]

Physical functioning

One definition of physical functioning is "*the capacity of an individual to carry out the physical activities of daily living*".[59] There are several terms referring to physical functioning presented in Table 4.[60]

Table 4: Different terms referring to physical functioning.[60]

Physical functioning:
Exercise capacity
Functional ability / capacity / status
Health status
Physical ability / capacity / disability / fitness / functional status / limitation / performance

Physical functioning can be assessed by patient-reports and by performance-based measures.[61]

Physical function was assessed by patient-reports in paper I.

Physical function was assessed by a performance-based measure in paper IV.

Physical activity

Physical activity is defined as "*any bodily movement produced by skeletal muscles that results in energy expenditure*."[9] Physical exercise is defined as "*a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness*."[9] Physical activity can be described by the FITT principle; Frequency, Intensity, Time (duration) and Type of activity (Table 5).[11]

Table 5: The FITT principle of physical activity.[11]

Factor	Description
Frequency of performing an activity	Usually expressed as the number of sessions per week
Intensity	Can be monitored and expressed as absolute and relative intensity
Time or duration of performing an activity	Describes duration of physical activities in minutes
Type of activity	For exampel walking, running and cycling

Absolute intensity refers to the energy required to perform an activity. MET stands for the metabolic equivalent of task. One MET is the amount of energy used while sitting quietly (3.5 ml of oxygen consumed/kg of body weight/minute). Physical activities may be rated using METs to indicate their intensity.[62-64]

Relative intensity refers to how hard an individual is working relative to his/her maximum capacity,[65] and could be measured by percentage of maximal heart rate or percentage of maximal oxygen uptake (VO_2 max).[10] Rating of perceived exertion (RPE) on the Borg scale is a common way to assess physical relative intensity. 6 on the Borg RPE scale means perceiving no exertion at all and 20 means maximal exertion of effort.[66] In the thesis, moderate and vigorous intensity physical activity have been explored (Table 6).

Table 6: The Borg RPE scale[66] and level of physical activity.[10]

	Borg RPE scale	Level of physical activity
6	No exertion at all	
7	Extremely light	
8		
9	Very light	
10		
11	Light	
12		MPA
13	Somewhat hard	MPA
14		VPA
15	Hard	VPA
16		VPA
17	Very hard	VPA
18		
19	Extremely hard	
20	Maximal exertion	

Abbreviations: RPE = rating of perceived exertion, MPA = moderate intensity physical activity, VPA = vigorous intensity physical activity.

Type of physical activity refers to the type of exercise performed and what you need to do to achieve the intensity e.g. running, walking, cycling and swimming. The type of activities can be divided into 4 domains; 1) activities in the household, 2) occupational, 3) transportation and 4) leisure time.[9, 10, 12]

Physical activity and health

Physical activity is essential to preserve health, to prevent diseases and for well-being.[67] Being regularly physically active reduces the risk of coronary heart disease and other diseases.[68] Moderate and vigorous intensity physical activities are associated with health and fitness benefits. The more physical activity, the more health and fitness benefits up to a certain level as shown in Figure 9. The dose is related to the intensity and the duration.

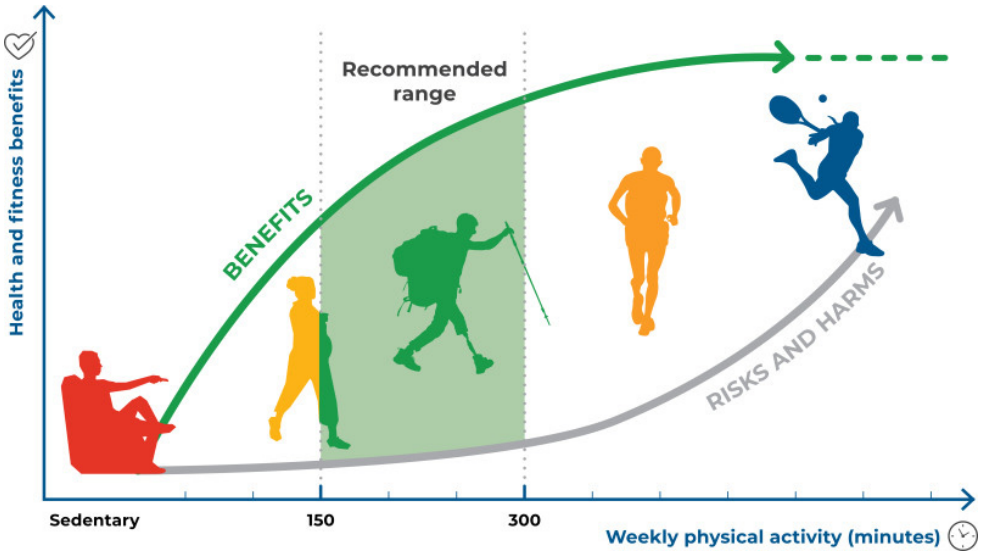

Figure 9: World Health Organization guidelines on physical activity and sedentary behaviour and the dose response curve. © Reprinted with permission: [WHO Guidelines on Physical Activity and Sedentary Behaviour]. [https://www.ncbi.nlm.nih.gov/books/NBK566045/pdf/Bookshelf_NBK566045.pdf]: World Health Organization; [2024]. Licence: CC BY-NC-SA 3.0 IGO

History of physical activity recommendations

In the 1950s, the epidemiologist professor Morris *et al* compared the physical activity levels of London double-decker workers to postal workers. Morris *et al* found that bus conductors, who spent the day standing and walking, and postmen, who delivered mail on foot, experienced less than half the number of myocardial infarctions compared to bus drivers or post office workers who spent most of their workday sitting.[69, 70]

Early physical activity guidelines and recommendations from American Heart Association (AHA) were released 1972 and later 1975, 1992[71] and 1995.[72, 73] In the 1992, the AHA included physical inactivity as a major risk factor for CAD.[71]

Physical activity recommendations for Americans 2007

In 2007, the updated recommendations on physical activity and public health for adults from the American College of Sports Medicine (ACSM) and the AHA were released. The primary recommendation to promote and maintain health in healthy adults, aged 18-65 years, was moderate intensity physical activity for a minimum of 30 minutes at least 5 days each week and/or vigorous intensity physical activity for a minimum of 20 minutes a week on 3 days each week. Combinations of moderate and vigorous intensity

physical activity could be performed to meet the recommendation (Table 7).[74] Individuals who wish to further improve their health and fitness may benefit by exceeding the minimum recommended amount of physical activity illustrated by the dose-response curve[74] (Figure 9).

Table 7: The physical activity recommendations for adults from the American College of Sports Medicine and the American Heart Association published in 2007.[74]

Frequency, Intensity, Time	Type, Examples
MPA for a minimum of 30 minutes at least 5 days each week	Equivalent to a brisk walk and noticeably accelerates the heart rate. Can be added up towards 30 minutes minimum by performing bouts each lasting 10 or more minutes.
or	
VPA for a minimum of 20 minutes a week on 3 days each week	Exemplified by jogging and causes rapid breathing and a substantial increase in heart rate.
or	
A combination of MPA and VPA	

Abbreviations: MPA = moderate intensity physical activity, VPA = vigorous intensity physical activity.

The two questions on moderate and vigorous physical activity, used in paper II-V, were based on this recommendation.

In addition to the recommendation for physical activity, adults aged 18-64 were encourage to perform activities that maintain or increase muscle strength and endurance for at least 2 days a week. Adults ≥65 years were recommended to include flexibility and balance exercises.[75]

Physical activity recommendations for Americans 2018

In 2018, the physical activity guidelines advisory committee in the United States summarized the scientific evidence on physical activity and health. Physical activity reduces the risk of excessive weight gain, improve cognitive function and mental health. One of the news was that all bouts of moderate and vigorous intensity physical activity of any duration may be included in the daily accumulated total volume of physical activity[76] and not only ≥10 minutes bouts.

Physical activity recommendations globally

The current physical activity recommendations for primary prevention are based on the 2020 World Health Organization (WHO) guidelines on physical activity and sedentary behaviour.[12] For adults, the WHO recommends the same minimum dose as before. A novelty in the updated guidelines was the introduction of 150 to 300 minutes per week of physical activity (Table 8).[12] If you are physically active for more than 150 minutes up to 300 minutes, you could achieve more health benefits (Figure 9).

Table 8: The 2020 World Health Organization guidelines on physical activity and sedentary behaviour.[12]

Intensity, Time per week
150–300 minutes of moderate intensity physical activity
or
75–150 minutes of vigorous intensity physical activity
or
A combination of moderate and vigorous intensity physical activity
Adults should limit the amount of time spent being sedentary.

Physical activity recommendations for Swedes

In Sweden, the professional associations for physical activity have released guidelines and recommendations for physical activity in prevention and treatment of disease (FYSS) in 2003, 2008, 2017[77] and 2021[10]. Both FYSS and the Public Health Agency of Sweden recommend the same dose of physical activity as WHO for primary prevention.[12] FYSS also describes disease-specific guidelines for physical activity and physical exercise training.[10]

Rehabilitation after OHCA

The WHO has defined rehabilitation as "*a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment*".[78] Early rehabilitation could start when the OHCA survivor is still in the ICU and includes mobilisation.[6] An OHCA survivor may be provided cardiac rehabilitation and/or neurological rehabilitation. Cardiac and neurological rehabilitation are often located within different groups, departments, or institutions.[30] Most rehabilitation teams specialised in neurological rehabilitation have limited knowledge of cardiac rehabilitation and vice versa.[57] OHCA survivors should be

screened for cognitive impairment and emotional problems after hospital discharge and before starting cardiac rehabilitation.[30, 56, 57]

Boyce *et al* have described an integration of cardiac and neurological rehabilitation in clinical practice for OHCA survivors including 3 different clinical pathways (Figure 8).[56] Those with cognitive impairment should be provided a combination of neurological and cardiac rehabilitation or start with only neurological rehabilitation.[56, 57] Adjustments for the exercised-based cardiac rehabilitation could include creating small groups, using the same staff every time and play music with low volume or not play any music at all.[56]

In paper IV, 28% of the 807 OHCA survivors were provided cardiac rehabilitation and 18% neurological rehabilitation.

Cardiac rehabilitation phase 1-3

Most OHCA survivors have a cardiac cause of the CA and are eligible for cardiac rehabilitation. Cardiac rehabilitation includes physical exercise training to optimize the physical condition,[79] management of risk factors, lifestyle advice, education and psychological support.[80] Cardiac rehabilitation programmes are cost effective, decrease cardiovascular mortality, reduce hospital admission and improve HRQoL.[81, 82] Cardiac rehabilitation typically consists of 3 phases and should ideally begin during in-hospital stay (phase 1) and continue after hospital discharge (phase 2). Cardiac rehabilitation should be maintained for life (phase 3).[83] Cognitive screening and neurological rehabilitation are not a part of standardized cardiac rehabilitation but are recommended after OHCA.[79] In Europe, only half of eligible CAD patients were referred to cardiac rehabilitation and only a minority attended cardiac rehabilitation programme.[80]

Exercised-based cardiac rehabilitation during phase 2

The cardiac rehabilitation programme during phase 2 includes supervised physical exercise training. A training session should include warm-up and cool down and is described according to the FITT principle (Frequency, Intensity, Time, Type)[11] in Table 9.[80, 84] The supervision should include physical examination, monitoring of heart

rate, blood pressure and heart rhythm before, during and after the sessions of physical exercise training.[80]

Table 9: Exercise-based cardiac rehabilitation recommendations during phase 2.

Reference	Frequency	Intensity	Time
Europe 2010[85]	3-4 days/week	50-70% of VO_2 max*	≥150 minutes/week
Europe 2020[80]	≥3 days/week preferably 6-7 day/week	MPA-VPA	≥20-30 minutes/session
Sweden 2017[77] and 2021[10]	3-5 days/week	MPA-VPA	≥90 minutes/week

Abbreviations: VO_2 max = maximal oxygen consumption, MPA = moderate intensity physical activity, VPA = vigorous intensity physical activity. *Moderate intensity 40-59% of VO_2 max, vigorous intensity 60-89% of VO_2 max.[10]

Physical activity counselling during cardiac rehabilitation phase 3

During the cardiac rehabilitation phase 3, the recommendation was a minimum of 30-60 minutes/session of moderate intensity physical activity at least 3-4 days/week according to the guidelines from 2010.[85] The updated guidelines recommend 150 activity minutes a week distributed on 5 days a week[80] (Table 10).

Table 10: Physical activity recommendations within cardiac rehabilitation phase 3.

Reference	Frequency	Intensity	Time
Europe 2010[85]	3-4 days/week, preferable daily	MPA	30-60 minutes/session
Europe 2020[80]	5 days/week	MPA	30 minutes/session
	or		
	5 days/week	VPA	15 minutes/session
	or		
	A combination of	MPA and VPA	

Abbreviations: MPA = moderate intensity physical activity, VPA = vigorous intensity physical activity.

Assessments of physical function and activity

Assessing physical function and physical activity in clinical practice and research can include both patient-reports and performance-based measures.

"Measurement is the first step that leads to control and eventually to improvement. If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it."

H. James Harrington (1929-2002)

In paper I, patient-reports were used to assess physical function.

In paper III-V, patient-reports were used to assess physical activity.

In paper III, a performance-based measure was used to assess physical activity.

In paper IV, a performance-based measure was used to assess physical function.

Patient-reports

Physical activity questionnaires are cost-effective and easy to administer, but patient-reports are subjective. Older adults are more likely to engage in light to moderate intensity physical activity which is the most difficult type of activity to assess by questionnaires.[68] Different questionnaires about physical activity are used in different studies and make it difficult to compare the results. Patient-reports create varying amounts of assessments error. One example is recall bias whereby individuals have difficulty in recalling past activities. Another example is response bias describing situations where participants do not answer questions truthfully for some reasons.[67]

Performance-based measures

Objective assessments from wearable sensors are sensitive in collecting physical activity data and are performance-based measures. The use of accelerometers to assess movement-based behavior is called accelerometery.[67] Administration of accelerometers is logistically more complex than questionnaires and more expensive.[68] An accelerometer assesses the body's movement acceleration in different directions. The higher the acceleration, the higher the intensity. By converting movement acceleration, the total movement activity of a person during a certain time period can be assessed.[86, 87] Another performance-based measure is the Timed Stands Test (Figure 11).[88]

Agreement between patient-reports and performance-based measures

Studies that use both questionnaires (patient-reports) and accelerometers (performance-based measures) gain the most comprehensive information about physical activity.[68] Evaluating physical activity levels using both questionnaires and objective accelerometer assessments ("gold standard") is a way to investigate the validity and reliability of questionnaires.[89] Few questionnaires have been validated against a "gold standard" assessments e.g. accelerometer.[67] In a Swedish study, two thirds of the participants attained the physical activity recommendation according to self-reports and only one third attained the recommendation when the physical activity level were assessed by accelerometers.[90]

Knowledge gap in evidence

Many OHCA survivors report physical problems, including rib fractures, muscle weakness and mobility problems. Almost half of the survivors reported limitations because of physical difficulties at 6 months and up to 40% described mobility problems and limitations in usual activities at 12 months.[43] Despite this knowledge in OHCA survivors, aspects of physical function and activity and the association with potential risk factors for limitations in physical function and low levels of physical activity have received little attention.

My first goal was to write a review about aspects of physical function and activity in OHCA survivors. Unfortunately, there were too few papers published on this topic. To improve our knowledge, we must start by assessing and exploring physical function and activity in OHCA survivors. The Lancet Commission *to reduce the global burden of sudden cardiac death: a call for multidisciplinary action*[23] describes a knowledge gap about screening, support, and rehabilitation in OHCA survivors (Table 11).

Table 11: Knowledge gap about screening, support, and rehabilitation in OHCA survivors.

Knowledge gap:
How and when to intervene?
Duration of support?
How the outcomes should be assessed?

The focus of the thesis was aspects of physical function and activity following OHCA including how to assess physical function and activity.

Aims of the thesis

General aim

To explore aspects of physical function and activity in out-of-hospital cardiac arrest survivors 6-7 months after the cardiac arrest.

Study specific aims

I. The primary aim was to describe physical function in survivors 6 months after OHCA and compare it with a group of STEMI controls. A second aim was to explore variables potentially associated with self-reported limitations in physical function in OHCA survivors, including sociodemographic characteristics (age, sex, and education), pre-event comorbidities (diabetes and hypertension), pre-hospital resuscitation variables (reflected by time to return of spontaneous circulation), hospital length of stay, and the 6 months outcomes of cognitive impairment and symptoms of anxiety and depression.

II. The primary aim was to investigate whether OHCA survivors had lower levels of self-reported physical activity compared to a non-CA control group who had acute MI. Additional aims were to explore potential predictors of physical inactivity (older age, female gender, problems with general physical function, global cognition, mental processing speed/attention, anxiety symptoms, depression symptoms, kinesiophobia and fatigue) and to investigate the relationship between self-reported and objectively measured physical activity among OHCA survivors.

III. This study aimed to investigate the agreement between self-reported and objectively assessed physical activity among OHCA survivors.

IV. The aims were to describe the level of physical activity 6 months after an OHCA and to explore potential risk factors of a low level of physical activity.

V. The primary aim was to investigate whether OHCA survivors had lower levels of self-reported physical activity compared to a non-cardiac arrest control group who had MI, and to explore if symptoms of anxiety, depression, kinesiophobia and fatigue were associated with low level of physical activity.

Study specific hypotheses

The alternative hypotheses (H_α) described in the study protocol[19] were:

1. OHCA survivors will have lower levels of self-reported physical activity compared to MI-controls.

2. Older age, female gender, problems with general physical function, global cognition and mental processing speed/attention, anxiety symptoms, depression symptoms, kinesiophobia and fatigue will be predictors of lower levels of self-reported physical activity amongst OHCA survivors.

3. Self-reported levels of physical activity among OHCA survivors will show at least moderate agreement with objectively measured levels of physical activity.

Methods

Overview

A brief overview of the methods used in the papers of the thesis can be found in Table 12.

Table 12: An overview of the methods used in the papers of the thesis.

Paper	I	II	III	IV	V
Design	Post-hoc analysis on a cross-sectional case control sub-study of an international multicentre trial	Study protocol	Cross-sectional sub-study of an international multicentre trial	Post-hoc analysis on a cross-sectional study of an international multicentre trial	Cross-sectional case control sub-study of an international multicentre trial
Study context, ClinicalTrials.gov identifier	The TTM trial cognitive sub-study, NCT 01946932	The TTM2 trial physical activity sub-study, NCT 03543332	The TTM2 trial physical activity sub-study, NCT 03543332	The TTM2 trial, NCT 02908308	The TTM2 trial physical activity sub-study, NCT 03543332
Participants	282 OHCA survivors, 119 STEMI controls	n/a	49 OHCA survivors	807 OHCA survivors	106 OHCA survivors, 91 MI controls
Time-point	6 months post cardiac event	6-7 months post cardiac event	7 months post OHCA	6 months post OHCA	7 months post cardiac event
Main instruments	PF-10	n/a	Two questions on physical activity, accelerometery	Two questions on physical activity	Two questions on physical activity
Main statistical analyses	Chi-square test, Mann-Whitney U-test, logistic regression, mean difference	n/a	Wilcoxon signed-rank test, Spearman's rho, Cohen's weighted kappa	Logistic regression	Mann-Whitney U-test, logistic regression

Abbreviations: TTM trial = Targeted temperature management at 33°C versus 36°C after cardiac arrest (TTM) trial, TTM2 = Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial, OHCA =out-of-hospital cardiac arrest, STEMI = ST-elevation myocardial infarction, MI = myocardial infarction, PF-10 = Physical Functioning 10.

The TTM trial paper I

The Targeted temperature management (TTM) trial was a prospective international multicentre randomized clinical trial. The trial included patients at 36 hospitals in Europe and Australia. 950 comatose OHCA patients were randomized to targeted temperature management at either 33 °C or 36 °C at hospital admission. The TTM trial included participants from 2010 to 2013.[16, 17]

In the main TTM trial, 491 OHCA survivors were invited to a face-to-face follow-up 6 months after the CA, and 455 survivors consented. The trial found no differences in all-cause mortality, neurological function or HRQoL at 6 months between the two temperature groups.[17, 91]

Within the cognitive sub-study, 287 OHCA survivors at 20 of 36 hospitals underwent cognitive tests. The cognitive sub-study was performed in Sweden, Denmark, the Netherlands, Italy and the United Kingdom. A cohort of participants with STEMI but no CA were recruited as a control group with an intended 2:1 ratio. The controls were matched for country, age, sex and time-point of hospitalization.[14] The cognitive tests showed no differences between the two temperature groups in the sub-study.[15] Therefore, OHCA survivors were considered as one group in Paper I.

Inclusion criteria were OHCA of a presumed cardiac cause, age ≥18 years, unconsciousness at hospital arrival, >20 minutes consecutive minutes of sustained return of spontaneous circulation (ROSC). Exclusion criteria were unwitnessed CA, asystole as the initial rhythm, >240 minutes between ROSC and screening, suspected or known stroke or intracranial haemorrhage, body temperature <30 °C, pregnancy, persistent cardiogenic chock despite medical interventions, and pre-existing neurological disability.[16]

Paper I was a post-hoc analysis on a cross-sectional case-control study investigating differences in self-reported physical function between OHCA survivors and matched MI controls. Descriptive statistics are presented in the paper. The Chi-square test and the Mann-Whitney U-test were used to detect differences between the OHCA survivors and the MI controls. Univariable and multivariable logistic regressions were calculated to investigate the associations between self-reported physical function and different variables. Mean differences were used to investigate if there were clinically relevant differences between various sub-groups of OHCA survivors (Table 12).

The TTM2 trial

The Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM2) trial was a prospective international multicentre randomized clinical trial that included patients at 61 hospitals in Europe, Australia and New Zealand. 1861 comatose OHCA patients were randomized to temperature control with targeted hypothermia at 33 °C or targeted normothermia and early treatment of fever (37.8 °C or higher). The TTM2 trial included participants from 2017 to 2020.[21, 22]

In the main TTM trial, 939 OHCA survivors were invited to a face-to-face follow-up 6 months after the CA and 836 survivors consented. An interpreter was used when participants were unable to speak the local language. There was no difference in mortality or functional outcome at 6 months after the OHCA between the two temperature groups.[22, 92] Therefore, the OHCA survivors were regarded as one group in paper III-V.

OHCA patients of a presumed cardiac cause or of an unknown cause to the CA age ≥18 years were included. Other inclusion criteria were unconsciousness at hospital arrival, 20 minutes of sustained ROSC, ≤180 minutes between ROSC and screening, eligibility for intensive care without restrictions. Exclusion criteria were unwitnessed CA, with asystole as the initial rhythm, intracranial haemorrhage, a body temperature <30 °C, pregnancy, extracorporeal membrane oxygenation, and chronic obstructive pulmonary disease with home oxygen therapy prior to ROSC.[21]

Paper II, III and V

Paper II is a study protocol describing the design and rationale of the TTM2 sub-study focusing on physical activity (Table 12). Paper III and V are sub-studies performed in conjunction with the main TTM2 trial. At the 6-month TTM2 trial follow-ups, survivors at 8 selected sites in Sweden, Denmark and the United Kingdom were invited to the sub-study, with a detailed focus on physical activity including an additional face-to-face visit. The sub-study was coordinated with another TTM2 sub-study investigating neuropsychological function.[93, 94] The participants could choose to participate in only one of the studies or both.

Additional exclusion criteria for the sub-study were >80 years of age, a Clinical Frailty Scale[95] score >7 before the CA, a pre-arrest dementia diagnosis, inability to speak the local language well enough to answer the questions and to complete the assessments without assistance from an interpreter, active drug abuse, and wheel-chair user.[19]

Paper III is a cross-sectional study investigating the agreement between two questions on self-reported physical activity and objectively assessed physical activity. Descriptive statistics are presented. The Wilcoxon signed-rank test was used to compare the number of days. Spearman's rho correlation coefficients (r_s) were calculated, and agreements were examined by Cohen's weighted kappa (k) (Table 12). To further examine the agreements between the two assessments of physical activity, cross-tabulations were used.

Paper V is a cross-sectional case-control study investigating the difference between OHCA survivors and matched MI controls regarding physical activity level. The aim was to compare OHCA survivors, who were at risk of hypoxic brain injury, to MI controls who did not suffer CA (or the risk of brain injury) with a 1:1 ratio. Descriptive statistics are presented. Logistic regressions were used to identify risk factors of a low level of physical activity (Table 12).

Paper IV

Paper IV is a post-hoc analysis and a cross-sectional study of the main TTM2 trial. All included OHCA survivors were invited to a follow-up 6 months after OHCA. The paper investigated the differences between OHCA survivors with low versus a moderate/high level of self-reported physical activity. Descriptive statistics are presented. Logistic regressions were used to identify risk factors associated with low levels of physical activity (Table 12).

Outcome assessments

An overview of the outcomes, questionnaires and assessments used in paper I-V are found in Table 13.

Table 13: Overview of the outcomes, questionnaires and assessments used in the papers.

Outcome	Questionnaire and assessment (abbrevitation)	Used in paper	Source for outcome
Physical functioning: self-care, mobility, movements	Physical Functioning 10 items (PF-10)	I	Patient-reports
Physical activity	Two questions on physical activity	III, IV, V	Patient-reports
Cognitive function: memory	Rivermead Behavioral Memory Test (RBMT)	I	Performance-based
Cognitive function: executive function	Frontal Assessment Battery (FAB)	I	Performance-based
Cognitive function: mental processing speed/attention	Symbol Digit Modalities Test (SDMT)	I, IV	Performance-based
Anxiety and depression symptoms	Hospital Anxiety and Depression Scale (HADS)	I, V	Patient-reports
Objectively assessed physical activity	Accelerometer Actigraph GT3X-BT	III	Performance-based
Physical exercise training	Training log of physical exercise training	III	Patient-reports
Global cognitive function: memory, executive functioning, attention, language, visuospatial, orientation	Montreal Cognitive Assessment (MoCA)	III, IV	Performance-based
Kinesiophobia: perceived danger for the heart, avoidance of exercise, fear of injury, dysfunctional self	Tampa Scale for Kinesiophobia heart (TSK heart)	III, V	Patient-reports
Functional outcome	modified Rankin Scale (mRS)	IV	Clincian-reported
General physical function: lower extremity strength	Timed Stands Test (TST)	IV	Performance-based
Health-related quality of life: mobility, self-care, usual activities, pain/discomfort, anxiety/depression	EuroQol 5 dimensions 5 levels (EQ-5D-5L)	IV	Patient-reports
General, physical and mental fatigue, reduced activity, reduced motivation	Multidimensional Fatigue Inventory (MFI-20)	V	Patient-reports

Self-reported physical functioning

The Short-Form Health Survey 36 items version 2.0 (SF-36v2®) includes the domain Physical Functioning (PF) as a part of physical aspects of health. The SF-36 PF domain can be used on its own known as the Physical Functioning-10 items scale (PF-10).[96] PF-10 samples three main attributes of perceived limitations in physical function: self-care, mobility and other physical activities, and movements such as lifting and bending.[97] The 10 items are rated on a hierarchical ordinal scale ranging from 1=not limited to 3=limited a lot.

The sum of the 10 items is transformed into a 2009 US general population norm-based T-score. A T-score of 50 represents the norm mean. A normal score is ±3 T-scores of the mean at a group level, and ±5 T-scores of the mean at an individual level.[96] A minimal important difference of 3 T-scores is recommended to differentiate between groups[96] (Table 13).

Two questions on physical activity

The first question addresses the frequency of moderate intensity physical activity totaling 30 minutes or more per day during the previous week. The second question addresses the frequency of vigorous intensity physical activity for at least 20 minutes per day during the previous week. The two questions were based on the physical activity recommendations to promote and maintain health by Haskell *et al.*[74] The range of answers is from 0 to 7 days for moderate and vigorous intensity physical activity respectively. The questions were followed by examples (Table 13, 14).

We categorized the level of physical activity to low, moderate or high level of physical activity based on the two questions. A low level of physical activity corresponded to a level below recommended for primary prevention.[12, 98] A moderate level attained the physical activity level of primary prevention.[12] To attain a high level of physical activity, the frequency should be a least 5 days a week and at least 3 days of vigorous intensity physical activity (Table 15).[10]

Table 14: The two questions on moderate and vigorous intensity physical activity.

	Questions on physical activity	Examples given to the participants
Question 1: MPA	In the last week, how many days have you engaged in moderate physical activity for at least 30 minutes a day? (Could be performed in blocks that last for at least 10 minutes adding up to a total of 30 minutes or more) RPE 12-13 on the Borg scale[66]	MPA performed for at least 10 minutes that leads to a moderate level of effort and a noticeable acceleration of the heart rate. Examples of activities on this level include a brisk walk, heavy cleaning, washing windows, cleaning the car, carpentry, bicycling with light effort, golf, swimming leisurely or similar.
Question 2: VPA	In the last week, how many days have you engaged in vigorous (intense) intensity aerobic physical activities for at least 20 minutes (in one block)? RPE 14-17 on the Borg scale[66]	VPA is an activity that leads to a substantial increase in heart rate and causes rapid breathing. Examples of activities at this level include jogging, running, walking very brisk, shoveling/digging, bicycling with a moderate effort/fast, swimming moderate/hard, tennis or similar.

Abbreviations: MPA = moderate intensity physical activity, VPA = vigorous intensity physical activity.

Table 15: Categorization in three ordered groups based on number of days of self-reported moderate and vigorous intensity physical activity during the last week.

Physical activity level	Self-reported MPA and VPA in days last week
Low level of physical activity: frequency <3 days	<5 days of MPA ≥ 30 minutes in total per day or <3 days of VPA ≥20 minutes per day
Moderate level of physical activity: frequency ≥3 days	≥ 5 days of MPA ≥30 minutes in total per day or ≥3 days VPA ≥20 minutes per day,
High level of physical activity: frequency ≥5 days	≥2 days of MPA ≥30 minutes in total per day and ≥3 days VPA ≥20 minutes per day

Abbreviations: MPA = moderate intensity physical activity, VPA = vigorous intensity physical activity.

Cognitive function

Three cognitive domains are commonly affected after CA; memory, executive function and processing speed/attention and were represented by the tests:

1. The Rivermead Behavioural Memory Test (RBMT) evaluates memory function needed in everyday life. The profile score has presented cut-off levels to grade the memory performance as normal, mild, moderate or severe impairment[99] (Table 13).
2. The Frontal Assessment Battery (FAB) is a screening test for executive impairment. Score ranges from 0 to 18 and lower scores indicate poorer performance[100] (Table 13).

3. Processing speed/attention was assessed with the Symbol Digit Modalities Test (SDMT).[101] The total amount of correct answers within 90 seconds are calculated and transformed into age and education adjusted z-scores. Z-scores ≤1.5 SD below the mean was used to indicate impaired function[102] (Table 13).

A dichotomized score of no cognitive impairment versus cognitive impairment was based on a combination of the three performance-based instruments and used in the analysis: no/mild cognitive impairment versus moderate/severe cognitive impairment.[103]

Anxiety and depression symptoms

Information on emotional problems were collected by using the Hospital Anxiety and Depression Scale (HADS). It consists of 14 questions, 7 related to anxiety symptoms (HADS-A), and 7 related to depression symptoms (HADS-D). Each item is scored from 0-3 and a total sum score for each subscale is calculated with a cut-off of >7 indicating clinically significant difficulties (Table 13).[104]

Accelerometer

The accelerometer ActiGraph GT3X-BT (ActiGraph, Pensacola, Florida, USA) was used to assess minutes in moderate and vigorous intensity physical activity per day (Table 13). The participants were instructed to wear the accelerometer for 7 consecutive days. The accelerometer was attached to the right hip with a rubber strap (Figure 10). For extraction and analysis of raw data collected by the ActiGraph, we used the ActiLife software version 6.16.3. A valid day was defined as a minimum of 10 hours wear time.[105, 106] The counts per minute cut-off values for vector magnitude (VM), chosen for this study, were 2690-6166 counts per minute for moderate and ≥6167 counts per minute for vigorous intensity physical activity by Sasaki *et al.*[107]

Figure 10: The accelerometer ActiGraph GT3X-BT.

Training log

To add information on activities that could not be assessed by the accelerometer during the week, the participants were asked to fill in a training log according to the FITT principle (Table 5, 13).[11]

Global cognitive screening

The Montreal Cognitive Assessment (MoCA) was used and is recommended for cognitive screening after OHCA.[53] The MoCA contains 11 sub-tasks of 6 cognitive domains combined into a total maximum score of 30. We used the full version 7.1-7.3 and added 1 point for participants who had ≤12 years of formal education according to the manual.[108] A score ≥26 points was considered to be within the average range (Table 13).

Kinesiophobia

The Tampa Scale for Kinesiophobia Heart (TSK Heart) was used to evaluate self-reported kinesiophobia. TSK Heart is a modified version of the original Tampa Scale[109] aimed to detect kinesiophobia in patients with coronary artery disease. The questionnaire includes 17 statements/questions added into a total score ranging from 17 to 68. Values >37 represent a high level of self-reported kinesiophobia (Table 13).[110]

Modified Rankin Scale

The clinician-reported modified Rankin Scale (mRS) assesses functional outcome.[39] The mRS-9Q, including 9 questions, and the mRS calculator (modifiedrankin.com) were used.[111] The scale includes 7 levels that range from no symptoms (0) to dead (6). (Table 13).

General physical function

The Timed Stands Test (TST) is an objective assessment of lower extremity strength. We used it as a rapid assessment of general physical function.[88, 112] The participant was asked to rise 10 times to straight upright position from sitting as quickly as possible (Table 13, Figure 11). A shorter time indicates a better functioning of the lower extremity muscles. Age and sex adjusted norm values are available.[88] We categorized the outcome into three groups (Table 16).

Table 16: Categorization of the outcome of the Timed Stands Test into three groups according to the performance.

1	Normal
2	Slower than expected given the age- and sex cut-offs but within 60 seconds
3	Does not manage within 60 seconds or at all

Figure 11: The Timed Stands Test from sitting to straight upright position 10 times.

EQ-5D-5L

Health-related quality of life (HRQoL) is an individual's perception of the impact of illness on domains of daily life and functioning.[6] The EuroQol health survey includes 5 dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 levels response version EQ-5D-5L[113, 114] was used (Table 13).

Fatigue

The Multidimensional Fatigue Inventory (MFI-20) is a 20-item questionnaire that assesses fatigue over the last few days in 5 dimensions (Table 13). Sum-scores are calculated for each dimension separately and range from 4 to 20. Higher scores indicates a higher level of fatigue.[115]

Strategies used to prevent missing data

Strategies to minimize missing data in paper I-V:

1. Providing education for the outcome assessors before starting the follow-ups at each site.
2. Offering a study team available for questions.
3. Having written manuals for the TTM cognitive sub-study, the TTM2 main trial and the physical activity sub-study.
4. Publishing study protocols for the TTM cognitive sub-study,[14] the TTM2 main trial[116] and the physical activity sub-study.[19]
5. Providing a homepage for TTM2 https://ttm2trial.org/ with contact information and manuals.
6. Utilizing an electronic case report form (eCRF) for all participating sites in the TTM2 trial.
7. Monitoring the data during the trials.

Covid-19

The Covid-19 pandemic affected the follow-ups in paper III, IV and V. There were rules and restrictions at different hospitals during the years 2020-2022 during different time periods. The follow-ups were delayed or cancelled in some cases due to the restrictions and due to the participants' fear to visit hospitals. We performed telephone follow-ups in some cases and then SDMT and TST were missing (paper IV). SDMT and TST required a face-to-face follow-up.

Ethical considerations

Mild to moderate difficulties are common after CA and may improve with time but may cause problems in daily life. In order to support the survivors in the best possible way, we need better knowledge of aspects of physical function and activity and use appropriate assessments.

The trial research protocol was approved by ethical review boards in all participating countries. Patients admitted to hospitals for treatment after OHCA were unconscious, unable to consent to treatment or to participate in the clinical trials. Prior to participating in the follow-ups in TTM cognitive sub-study, TTM2 main trial and TTM2 sub-study, all OHCA survivors and MI controls gave their written informed consent. The participants were allowed to withdraw from the studies at any time, without stating a reason.

If any problems were discovered during the screening procedure, the outcome assessor should ask the participant if he/she has received support for this. Such interventions were not part of the trial, but in line with good clinical practice. The organisation that the outcome assessor works for should have an agreed local policy and strategy of referral in case it is deemed necessary for a participant. The participants did not receive any economic compensation except for an optional travel reimbursement.

Author's contribution

In 1999, I graduated as a physiotherapist. Physiotherapy is a clinical practice and can be described as the science of movement. The aim of physiotherapy is to promote health by reducing illness and minimise suffering. Physiotherapy also aims to enable people who have suffered illness or injury to maintain or regain optimal mobility, functional ability and participation in social life.[117]

My first encounter with OHCA survivors was when I started to work at the cardiac rehabilitation centre at the Skane University hospital in Lund in 2009. A couple of weeks after hospital discharge, the OHCA survivors came to an individual meeting including a pre-exercise screening test. My experience was that many of the OHCA survivors had impaired physical function and low levels of physical activity. Most seemed positive about starting physical exercise training within cardiac rehabilitation at the hospital, but several did not come to the agreed training session.

On the other hand, the OHCA survivors who participated in exercise-based cardiac rehabilitation improved their physical function and increased their physical activity level. Sometimes they needed additional support. At that time-point, I knew very little about hypoxic brain injuries, cognitive impairment and emotional problems. I identified the following clinical problems:

OHCA survivors with cognitive impairment and emotional problems may need additional support. Cognitive impairment and emotional problems can negatively affect participation in exercise-based cardiac rehabilitation.

In 2017, I became a PhD student at the Faculty of Medicine, Lund University. The TTM2 trial was registered at Clinical Trials (NCT02908308) in November the same year and I initiated for the two questions on physical activity and for the TST to be included.[116] My first goal was to write a review about aspects of physical function and activity in OHCA survivors, but unfortunately there were too few papers published for this topic. Therefore, I started with paper I with the data from the TTM trial.[13]

The year after, paper III and V were designed. We registered the sub-study of the TTM2 trial with focus on physical activity at Clinical trials in June 2018 (NCT 03543332) and wrote paper II the study protocol[19] (Figure 12). For the TTM2 main trial, with the support of colleagues, I carried out the 30 day, 6 month and 24 month follow-ups at site Malmö. I coordinated the physical activity sub-study at 8 hospitals in Sweden, Denmark, and the in the United Kingdom. The sub-study of physical activity was coordinated alongside another TTM2 sub-study investigating neuropsychological function.[93, 94] After including an OHCA survivor to the sub-study/studies, we had to find a MI control matched for age, sex and time of the cardiac event.

Paper IV was designed after the half-time review and seminar (Figure 12). I got the opportunity to analyse the two variables that I had initiated for the main TTM2 study follow-up (the two questions on physical activity and the TST).

To gain a greater understanding at different time-points of the sub-study, I paid visits to the sub-study sites (Gothenburg, Aarhus in Denmark, and Basildon in the United Kingdom) before, during and after the sub-study was ongoing.

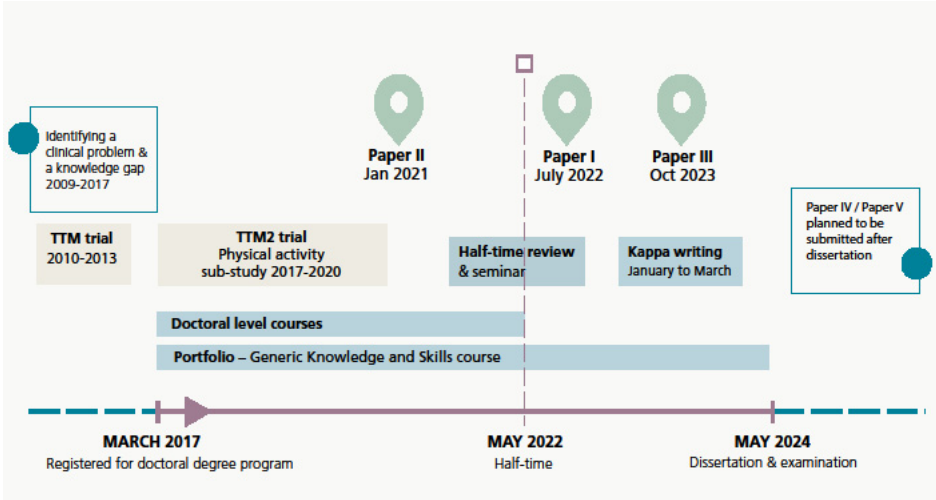

Figure 12: Timeline of the author's contribution.

Results

In the TTM cognitive sub-study, the TTM2 main trial and the TTM2 physical activity sub-study, most participants were men with a median age of just above 60 years. The MI controls were slightly older (Table 17).

Table 17: OHCA survivors and MI controls included in paper I, III, IV and V.

Paper	Number of particiants	Male sex n (%)	Age median [Q1:Q3]
I	287 OHCA survivors 119 STEMI controls	247 (86) 102 (86)	62 [54:69] 64 [57:71]
III	49 OHCA survivors	43 (88)	64 [59:70]
IV	807 OHCA survivors	676 (84)	61 [52:70]
V	106 OHCA survivors 91 MI controls	94 (89) 81 (89)	63 [57:70] 65 [57:71]

Abbreviations: OHCA = out-of-hospital cardiac arrest, STEMI = ST-elevation myocardial infarction, MI = myocardial infarction.

Paper I

The nationality of OHCA survivors and matched STEMI control in the sub-study of the TTM trial are presented in Table 18.

Table 18: OHCA survivors and matched STEMI controls in the sub-study of the TTM trial.

Country	OHCA survivors	STEMI controls
	n=287	n=119
Denmark n (%)	103 (36)	35 (29)
Sweden n (%)	66 (23)	34 (28)
Netherlands n (%)	49 (17)	14 (12)
United Kingdom n (%)	36 (13)	15 (13)
Italy n (%)	33 (11)	21 (18)

Abbreviations: OHCA =out-of-hospital cardiac arrest, STEMI = ST-elevation myocardial infarction.

282 of 287 (98%) OHCA survivors and 119 STEMI controls completed the questionnaire PF-10[96] on self-reported physical function. The OHCA survivors indicated limitations with physical function at a group level (mean 46.0, SD 11.2). The STEMI controls were within the norm at a group level (mean 48.8, SD 9.0). There was a statistically significant difference between the OHCA survivors and STEMI controls (p=0.025). The mean difference (2.8 T-scores, 95% CI 0.7-4.8) did not reach the threshold of minimal important difference of 3 T-scores.

Self-reported limitations in physical function were present in 38% of the OHCA survivors and 26% of the STEMI controls (p=0.022) at an individual level. There were no statistically significant differences in any of the individual PF-10 items between the OHCA survivors and the STEMI controls. In the OHCA survivors, older age, female sex, cognitive impairment, and anxiety and depression symptoms were associated with self-reported physical limitations.

Paper III

Paper III and V are based on the same TTM2 sub-study cohort. We excluded 19 OHCA survivors due to language difficulties, 13 OHCA survivors due to older age (>80 years old) and one OHCA survivor who was a wheelchair user. 55 OHCA survivors declined to participate in the additional follow-up.[20]

Of the 106 included OHCA survivors, 85 participants had ≥4 valid days of accelerometer assessments. 49 of 106 OHCA survivors answered the two questions on physical activity[74] and had 7 valid days of accelerometer assessment, and were thus included in the analysis. For moderate intensity physical activity, more physically active days were registered by self-reports compared to accelerometery (median 5 [3:7] versus 3 [0:5] days, p<0.001). For vigorous intensity physical activity, more physically active days were registered by self-reports compared to accelerometery (1 [0:3] versus 0 [0:0] days, p<0.001).

The correlations between self-reported and accelerometer assessed physical activity were sufficient (MPA r_s=0.34, VPA r_s=0.38). The agreements were fair (MPA k=0.27) and none to slight (VPA k=0.15). The categorization of self-reported versus objectively assessed physical activity showed that 26% versus 65% had a low level of physical activity.

3. Self-reported levels of physical activity in OHCA survivors showed fair and none to slight agreements to the levels of physical activity obtained by an objective assessment. Therefore, the null hypothesis (H_0) was accepted, and we failed to meet our criteria for accepting the alternative hypothesis H_α.

Paper V

108 OHCA survivors and 92 MI controls were included in paper V (Table 19). Two OHCA survivors and one MI control did not answer the two questions on physical activity[74] and were therefore excluded from the analysis. The two excluded OHCA survivors had severe cognitive impairment and had problems answering the two questions on physical activity and the questionnaires TSK heart, HADS and MFI-20.

Table 19: Number of OHCA survivors and MI controls included in paper V.

Country	Sites/country	OHCA survivors/country	MI controls/country
In total	8	108	92
Sweden	5	57	53
Denmark	1	19	12
United Kingdom	2	32	27

Abbreviations: OHCA =out-of-hospital cardiac arrest, MI = myocardial infarction.

There was no significant difference in levels of physical activity between OHCA survivors and MI controls (p=0.13). Of the OHCA survivors, 25% reported a low level of physical activity compared to 20% of the MI controls. 49% of the OHCA survivors compared to 44% of the MI controls reported a moderate level and 26% versus 36% a high level of physical activity.

1. OHCA survivors did not have lower levels of self-reported physical activity compared to MI controls. The H_0 was accepted but we acknowledge the risk of a type II error because of fewer included MI controls than the power calculation indicated.

Symptoms of kinesiophobia (Table 20) and fatigue (Table 21) were significantly associated with a low level of physical activity in both OHCA survivors and MI controls. OHCA survivors had significantly more problems with kinesiophobia compared to MI controls (p=0.04). Levels of anxiety and depression symptoms and fatigue were similar (HADS-A p=0.18, HADS-D p=0.18).

Table 20: Kinesiophobia by TSK heart (scale 17-68) in OHCA survivors and MI controls was a risk factor of a low level of physical activity.

Risk factor	OR, 95% CI	p-value
OHCA: Kinesiophobia	1.09 (1.02, 1.16)	0.01
MI: Kinesiophobia	1.09 (1.02, 1.18)	0.01

Abbreviations: OR = odds ratio, CI = confidence interval, OHCA =out-of-hospital cardiac arrest, MI = myocardial infarction.

Table 21: Fatigue by MFI-20 (scale 4-20) in OHCA survivors and MI controls was a risk factor of a low level of physical activity.

Risk factor	OR, 95% CI	p-value
OHCA: General fatigue	1.17 (1.04, 1.31)	0.007
MI: General fatigue	1.16 (1.02, 1.33)	0.03
OHCA: Physical fatigue	1.15 (1.03, 1.28)	0.01
MI: Physical fatigue	1.18 (1.04, 1.33)	0.01
OHCA: Mental fatigue	1.12 (1.00, 1.25)	0.04
MI: Mental fatigue	1.18 (1.03, 1.35)	0.02
OHCA: Reduced activity	1.18 (1.06, 1.31)	0.003
MI: Reduced activity	1.14 (1.01, 1.30)	0.04
OHCA: Reduced motivation	1.14 (1.01, 1.29)	0.03
MI: Reduced motivation	1.10 (0.95, 1.27)	0.22

Abbreviations: OR = odds ratio, CI = confidence interval, OHCA =out-of-hospital cardiac arrest, MI = myocardial infarction.

2b. Low levels of self-reported physical activity in OHCA survivors were associated with kinesiophobia and fatigue but not with anxiety and depression symptoms. Therefore, the H_0 was partly rejected.

Paper IV

807 of 939 (86%) OHCA survivors answered the two questions on physical activity at the 6-month follow-ups in the main TTM2 trial (Table 22).

Table 22: Participating countries, number of sites/country and number of OHCA survivors/site who answered the two questions on physical activity.

Country	Number of sites/ country n (%)	Number of participants/ site n (%)
	In total 56	In total 807
Austria	1 (2)	2 (0)
Australia	8 (14)	35 (4)
Belgium	2 (4)	2 (0)
Chez Republic	3 (5)	69 (9)
Denmark	1 (2)	39 (5)
France	5 (9)	69 (9)
Germany	1 (2)	23 (3)
Ireland	1 (2)	7 (1)
Italy	2 (4)	23 (3)
New Zeeland	2 (4)	35 (4)
Norway	4 (7)	68 (8)
Sweden	13 (23)	166 (20)
Switzerland	5 (9)	125 (15)
United Kingdom	8 (14)	144 (18)

ACS, including STEMI (42%) and non-STEMI (13%), was the most common cause of CA followed by arrhythmia (23%) (Table 23). Among the included OHCA survivors, 34% reported a low, 44% a moderate and 22% a high level of physical activity. Obesity, mobility problems reported by EQ-5D-5L, and cognitive impairment assessed by SDMT were significantly associated with a low level of physical activity (Table 24).

Table 24: Risk factors significantly associated with a low level of self-reported physical activity in the multivariable final model including all potential risk factors.

Risk factor	OR, 95% CI	p-value
Obesity (normal weight/overweight - obesity)	1.75, 1.10–2.77	0.018
Mobility problems by EQ-5D-5L (no problems - problems)	1.73, 1.06–2.84	0.029
Cognitive impairment by SDMT (no problems - problems)	1.78, 1.13–2.82	0.013

Abbreviations: OR = odd ratio, CI = confidence interval, SDMT = Symbol Digit Modalities Test.

Table 23: Cause of the cardiac arrest in the main TTM2 trial in 807 OHCA survivor who participated in the 6-month follow-up and answered the two questions on physical activity.

Cardiac arrest cause	Number of participants n (%)
ACS non-STEMI	107 (13)
ACS STEMI	338 (42)
Anaphylaxis	2 (0)
Arrhythmia	186 (23)
Congenital heart disease	5 (0)
Electrolyte disorders	5 (0)
Heart failure	18 (2)
Hypertrophic obstructive cardiomyopathy	9 (1)
Hypoxia	12 (1)
Idiopathic ventricular fibrillation	33 (4)
Idiopathic ventricular tachycardia	5 (0)
Myocarditis	8 (1)
Non-cardiac or non-medical	5 (0)
Other cardiac causes	58 (7)
Other medical causes	6 (1)
Overdose	6 (1)
Pulmonary embolism	3 (0)
Sepsis	1 (0)

Abbreviation: ACS = Acute coronary syndrome, STEMI = ST-elevation myocardial infarction, MI = myocardial infarction.

2a. A low level of self-reported physical activity in OHCA survivors was not associated with age, female sex, impaired general physical function or with impaired global cognition but with impaired mental processing speed/attention. Therefore, the H_0 was accepted except for the variable impaired mental processing speed/attention.

Discussion

The overall aim of the current thesis was to explore aspects of physical function and activity in OHCA survivors 6-7 months after the CA. The thesis has added knowledge about how we may assess aspects of physical function and activity following OHCA by patient-reports and by performance-based measures. Additionally, potential risk factors associated with limitations in physical function and low levels of physical activity were explored. The results of the thesis are discussed followed by discussion on generalizability and methodological considerations.

Results discussion

Limitations in physical function and low levels of physical activity were common 6-7 months after OHCA. In the TTM sub-study, 38% of the OHCA survivors reported limitations in physical function.[13] In the main TTM2 trial, 34% of the OHCA survivors reported low levels of physical activity compared to 25% of the OHCA survivors in the TTM2 physical activity sub-study. According to accelerometery, 65% of the OHCA survivors had low levels of physical activity.[20] Survivors with limitations in physical function and low levels of physical activity may run an increased risk of suffering new cardiac events and may therefore need support to become more physically active.

Moderate and vigorous intensity physical activity

We queried for both moderate and vigorous intensity physical activity in paper I-V. According to the questionnaire PF-10[18], only 18% of the OHCA survivors and 17% of the MI controls reported that they were able to perform vigorous intensity physical activity without limitations. Many more, 56% of the OHCA survivors and 61% of the MI controls, reported that they were able to perform moderate intensity physical activity without limitations.[13] Among the OHCA survivors in the main TTM2 trial, the median of number of days in moderate intensity physical activity was 5 days per week and the median of number of days in vigorous intensity physical activity was 0

days per week. This means that many of the OHCA survivors attained the physical activity recommendation only through moderate intensity physical activity.

At the main study follow-up, 22% reported high levels of physical activity including vigorous intensity physical activity 3 times previous week. At the additional follow-up in the sub-study, 26% of the OHCA survivors versus 36% of the MI controls reported high levels of physical activity. One year after the cardiac event, only 16% of the European patients with coronary artery disease attained vigorous intensity physical activity for 20 minutes or longer at least 3 times a week.[118] If the goal is to decrease the risk of new cardiac events, a regular regimen of moderate intensity physical activity seems adequate in the long run (cardiac rehabilitation phase 3).[74, 119]

Cognitive function

Two-thirds of OHCA survivors with self-reported limitations in physical functioning (PF-10 <45) had cognitive impairment compared to one-third of OHCA survivors without limitations in physical function (PF-10 ≥45).[13] Nearly half of the OHCA survivors with cognitive impairment shown thorough the SDMT had low levels of physical activity compared to one third among those with moderate/high levels of physical activity. This suggests that limitations in physical function and/or low levels of physical activity and cognitive impairment often coexist. Physical activity positively influences cognition but little is known about the dose of physical activity needed to improve the cognitive function.[120] A limitation was that we do not know if the cognitive impairment were present in the OHCA survivors already prior to the CA.[121]

Anxiety and depression symptoms

In paper I, there were differences in physical function between OHCA survivors with and without anxiety and depression symptoms reported with HADS.[13] In paper IV, there were also significant differences in physical activity level between OHCA survivors with and without anxiety and depression symptoms reported with EQ-5D-5L. Surprisingly in paper V, there were no significant differences in physical activity levels between OHCA survivors with or without anxiety or depression symptoms reported with HADS. One explanation could be that fewer OHCA survivors with anxiety and depression symptoms chose to participate in the physical sub-study because of the additional follow-up.

Obesity

Obesity had a significant association with low levels of physical activity. 21% of the OHCA survivors were obese compare to 30% of the Swedish MI patients[32] and 16% of adults worldwide.[122] Lifestyle interventions are important in prevention of CA and MI and low physical activity level and obesity are modifiable risk factors.[123]

Mobility and TST

If you have difficulty walking or getting up from a chair, you may also have difficulty being physically active to some extent. No mobility problems, reported by EQ-5D-5L, and values within the age- and sex cut-offs of the performance-based Timed Stands Test were probably a prerequisite to attain the physical activity recommendation.[12] The OHCA survivors who reported mobility problems and/or were slower than expected by the TST may need support to become more physically active. The reference values for the TST need to be updated for a cardiac population.

Kinesiophobia and fatigue

Kinesiophobia and fatigue were associated with low levels of physical activity in both OHCA survivors and MI controls. Kinesiophobia was significantly more common in OHCA survivors compared to MI controls, but no significant differences were found between the groups regarding fatigue. Physical fatigue was the domain with highest median score in the OHCA survivors and general fatigue in the MI controls. An exploratory approach through a qualitative study may increase the knowledge of aspects of physical activity in OHCA survivors and the impact of risk factors such as kinesiophobia and fatigue.

Generalizability

The TTM cognitive sub-study included OHCA patients in 5 countries in Europe (Table 18), the TTM2 physical activity sub-study in 3 countries in Europe (Table 19) and the TTM2 main trial in 14 countries in Europe, Australia and New Zeeland (Table 22). There are differences both between and within the countries. The results of the thesis are of ascertained applicability in the countries that participated in the studies.

Only patients with CA of a presumed cardiac origin or unknown cause were included in the thesis (Table 23). Further, we have not included patients suffering from CA in

hospitals. In-hospital CA offers rapid access to medical service and the patients suffering the CA in-hospital are often critically ill. Therefore, the results of the thesis may not be applicable to survivors with CA of other causes than cardiac or to in-hospital CA survivors.

Patients with a short, witnessed CA with immediate awakening were excluded from the TTM trial and the TTM2 trial. The results of the thesis are not applicable for OHCA survivors who were conscious at time of arrival to hospital. We have included OHCA survivors ≥18 years old in paper I-V and the results are only applicable for adults. In paper III and V, we excluded OHCA survivors who were ≥80 years old and the results are therefore not applicable for those.

Methodological considerations

When we designed the thesis in 2017, the screening and the follow-up according to the European guidelines after OHCA focused on cognitive impairment and emotional problems.[53] Aspects of physical function and activity were not included. In 2020, the European guidelines included functional assessments of physical impairment before hospital discharge (Figure 6)[43] and in 2021, the Swedish guidelines included screening for physical impairment in the follow-ups.[54]

The thesis was based on current physical activity guidelines and were inspired by the Swedish quality register post MI SWEDEHEART - SEPHIA.[32, 124] The physical activity guidelines have been updated after 2017. We had to design the study, register the study at ClinicalTrials.gov, and apply for ethics approval in the participating countries before we could start the trial and the sub-study. Therefore, the 10 minutes rule is included in the question on moderate intensity physical activity but is excluded from the updated guidelines.[12] The two questions by Haskell *et al*[74] were added to the SWEDEHEART - SEPHIA registry in 2016, and are still used in the registry and in clinical practise at cardiac rehabilitation centres in Sweden.

We chose to ask about the last week of physical activities. Another option could have been to ask about a regular week (Table 25).[125] We wanted to assess the last week to make it possible to investigate the agreement between the two questions on physical activity[74] and objectively assessed physical activity in paper III. Therefore, these questions on a regular week were not an option in the thesis but could be of interest in forthcoming studies. A limitation in paper III-V was that we did not know if and how the assessed weeks differ from regular weeks.

Table 25: The Swedish National Board of Health and Welfare´s questions on physical activity during a regular week from 2011.

Physical activity/exercise	Question	Answers
Everyday physical activity RPE 12-13 on the Borg scale[66]	During a regular week, how much time are you physically active in ways that are not exercise, for example walks, bicycling, or gardening? Add together all activities lasting at least 10 minutes	Seven fixed answers were available from no time to 300 minutes
Physical exercise RPE ≥14 on the Borg scale[66]	During a regular week, how much time do you spend exercising on a level that makes you out of breath, for example running, fitness class, or ball games?	Six fixed answers from no time to 120 minutes

Abbreviation: RPE = rating of perceived exertion.

We have used the physical activity recommendations published 2007 and the two questions by Haskell *et al*.[74] A limitation was that we have not asked about the exact number of minutes in moderate or vigorous intensity physical activity respectively. According to Haskell *et al*, 3 sessions of 20 minutes of vigorous intensity physical activity per week were enough to attain the physical activity recommendation.[74] We do not know if they have been physically active for more than 20 minutes per session. According to the secondary prevention recommendation cardiac rehabilitation phase 2 (Table 9),[80] vigorous intensity physical activity should start with a minimum of 5 minutes warm up and end with a minimum of 5 minutes cool down in moderate intensity physical activity.

3 sessions x 20 minutes VPA x 2 = 120 activity minutes

3 sessions x 5 minutes warm up MPA + 5 minutes cool down MPA = 30 activity minutes

+_____

150 activity minutes

We decided that at least 3 sessions per week with at least 20 minutes per session in vigorous intensity physical activity were equivalent to a moderate level of physical activity (150 activity minutes). The updated recommendation for vigorous intensity physical activity in cardiac rehabilitation phase 3 from 2020[80] (Table 10) could be an

option in forthcoming studies (frequency: 5 days/week, intensity: vigorous, time: 15 minutes/session).[80]

We changed the term of the categories of physical activity (Table 26) because the recommendations for secondary prevention and physical exercise training within cardiac rehabilitation could be different according to the CA cause. More than 50% had MI as CA cause but the other half had other causes (Table 23).

Table 26: Physical activity levels in paper II-V.

Physical activity level paper II	Physical activity level paper III, IV and V
Physical activity below recommended levels for primary prevention	A low level of physical activity
Physical activity to a level recommended for primary prevention	A moderate level of physical activity
Physical activity to a level recommended for primary, and secondary prevention for CAD	A high level of physical activity

Abbreviation: CAD = coronary artery disease.

Methodological considerations paper I

In paper I, patient-reports reflected what the OHCA survivors and MI controls thought they could do and not what they had done. The PF-10 questionnaire asks: "*Does your health now limit you in these activities? If so, how much?*"[18] A limitation of paper I was that no performance-based measure was included. The most valid and reliable test of physical function is performance-based.[60] The performance-based measure TST was included in addition to patient-reports in the TTM2 trial follow-up.[116]

Methodological considerations paper III

Self-reported levels of physical activity showed fair agreement for moderate intensity physical activity to the levels of physical activity obtained by the accelerometers and none to slight for vigorous intensity physical activity. We failed to meet our criteria of moderate agreement. This could be due to several factors regarding accelerometery such as wear time, number of valid days and counts per minutes cut-offs. A limitation was that the data collection was very dependent on compliance by the participants to wear the accelerometers.[68] A valid day was defined as a minimum of 10 hours wear time.[105, 106] Less than 10 hours wear time per day could be an option in forthcoming studies.

Only 49 of 106 (46%) had 7 valid days and were included in the final analysis. 4 valid days is enough in clinical trials due to guidelines[105, 106] and 87 of 106 (82%) participants had ≤4 valid days of accelerometer assessments. We found no guidelines for analysing accelerometer data with missing data in clinical trials.[126] There is probably small differences within each individual but a large difference between individuals. If we had imputed data, it would no longer be objectively assessed physical activity.

In the sub-study protocol,[19] we stated that we plan to use uniaxial counts per minute cut-off values by Freedson.[87] We have used triaxial accelerometers Actigraph GT3X-BT and therefore changed to triaxial counts per minute cut-off values by Sasaki.[107] The counts per minute cut-off values by Freedson[87] and by Sasaki[107] are based on healthy adults. We identified one accelerometer study based on high functional patients with coronary artery disese.[127] A limitation was that age, sex, relative intensity by METs and VO_2 peak differ a lot between the participants (Table 27). Boyce *et al*[121] tested the relative intensity on an ergometer bicycle in OHCA survivors with MI as a CA cause (Table 27). No accelerometer assessments were used in their study.[121]

Another option may be individualized counts per minute cut-off values based on relative intensity of cardiopulmonary exercise tests.[128] Based on the person's maximum exercise capacity VO_2 max, the counts per minute cut-off values for moderate and vigorous intensity physical activity can be calculated.

There is a need for OHCA specific accelerometer counts per minute cut-off values, preferably age and sex matched.

Table 27: Summary of four studies of accelerometery and one study of exercise capactity.

Reference	**Freedson** (VA)[87]	**Sasaki** (VM)[107]	**Mark** (VM)[127]	**Boyce**[121]	**Heimburg** (VM)[20]
Accelerometer	Uniaxial GT1M	Triaxial GT3X	Triaxial GT3X	n/a	Triaxial GT3X
Position	Right hip	Right hip	Right hip	n/a	Right hip
Time-point of assessment	Healthy individuals	Healthy individuals	Post CR	6-8 weeks after OHCA before CR	7 months after OHCA
Participants	50 healthy adults	36 healthy adults	18 high functional CAD patients	53 OHCA caused by MI	49 OHCA survivors cardiac cause
Male sex n (%)	25 (50)	28 (78)	17 (94)	45 (85)	43 (88)
Age in years mean (SD)	24 (4)	28 (9)	58 (11)	60 (range 42-84)	61 (11)
BMI mean (SD/range)	N/A	24 (3.3)	N/A	26 (20-38)	27 (19-37)
METs: relative intensity, VPA	9.7	N/A	N/A	5.5	N/A
VO_2 peak (ml/kg/min) mean (SD)	33.9 (2.6) treadmill	N/A	29.5 (7.6)	19.3 (IQR 15.2-23.9) ergometer bicycle	N/A

Abbreviations: VA = vertical axis, VM = vector magnitude, CR = cardiac rehabilitation, CAD = coronary artery disease, BMI = body mass index, MET= metabolic equivalent of task, VPA = vigorous intensity physical activity, VO_2 peak = peak oxygen consumption, IQR = interquartile range.

The accelerometer Actigraph is not waterproof. The aim of the training log was to add information on activities that could not be assessed by the accelerometer e.g. swimming. Fortunately, swimming and other water activities were unusual among the OHCA survivors (Table 28). The participants specified their activities during the week according to the FITT principle (Table 5).[11] We focused on activities with perceived exertion ≥12 on the Borg scale (Table 6)[66] corresponding to moderate and vigorous intensity physical activity respectively.

Table 28: Swimming sessions registered in the training logs, frequency, duration in minutes and perceived exertion on the Borg scale[66].

ID	Frequency of swimming sessions	Minutes per session	RPE 12≥ on the Borg scale	Number of days
7 valid days*				
SWXXXX	2	30, 30	16, 16	2 VPA
SWXXXX	1	50	13	1 MPA
UKXXX	1	30	12	1 MPA
<7 valid days**				
SWXXXX	1	30	missing	
SWXXXX	2	30, 30	14, 14	2 VPA

Abbreviations: RPE= rating of perceived exertion, VPA = vigorous intensity physical activity, MPA = moderate intensity physical activity. * Included in the analysis, **excluded from the analysis.

One wheelchair user was excluded from the physical activity sub-study. We could not control for when the participant was physically active on his own or when the wheelchair was driven by someone else.

A limitation was that we did not assess the MI controls with accelerometers. 57 MI patients were assessed in another study by Bargholtz *et al.*[129] The same two questions by Haskell *et al*[74] and triaxial accelerometers (Actigraph GT3X) were used. The study accepted 9 hours wear time per day and showed higher correlation between the two questions[74] and the accelerometer assessments regarding moderate intensity physical activity but lower regarding vigorous intensity physical activity.[129]

Methodological considerations paper V

We found no significant difference between OHCA survivors and MI controls regarding physical activity level. We acknowledge the risk of a type II error[130] because of fewer included MI controls than the power calculation indicated.[19] A limitation in paper V was that we performed only univariable logistic regressions due to small groups of OHCA survivors and MI controls. In this paper, we chose to analyse the risk factors as continuous variables. To our knowledge, there were no cut-off values in the different domains of the questionnaire MFI-20. The cut-off value of the TSK heart questionnaire has not been specifically validated in OHCA survivors. Future studies are needed to get accurate cut-off values to use in clinical practice and research regarding MFI-20 and TSK heart in OHCA survivors.

Methodological considerations paper IV

In paper IV, multivariable logistic regressions were possible due to the large cohort of over 800 OHCA survivors. We chose to use the potential risk factors as dichotomized variables, except for the variable age, to facilitate the interpretation of the questionnaires in clinical practice. A dichotomous scale is often easier to comprehend and interpret, but a continuous scale is more sensitive.[131]

Conclusions

I. Self-reported limitations in physical function were more common in OHCA survivors than in STEMI controls. Risk factors for self-reported limitations in physical function amongst OHCA survivors were older age, female sex, cognitive impairment, symptoms of anxiety and depression at the 6-months follow-up.

III. The OHCA survivors reported more physically active days compared to the results of the accelerometer assessments. The self-reported and the objective assessed physical activity showed that 24% of the OHCA survivors were categorized in the group low level of physical activity by both assessments. The two questions on self-reported physical activity could be useful in clinical practice and research settings to screen for a low level of physical activity.

IV. One third of the OHCA survivors reported a low level of physical activity. Risk factors for a low level of physical activity were obesity, mobility problems and cognitive impairment.

V. One quarter of the OHCA survivors and one fifth of the MI controls reported a low level of physical activity with no significant difference. Kinesiophobia and fatigue were associated with a low level of physical activity in both groups.

Clinical implications

Here follows clinical suggestions based on the thesis:

- Assess physical function in OHCA survivors regardless of the CA cause, by using the questionnaire Physical Functioning 10 and the performance-based Timed Stands Test.
- Assess the physical activity level in OHCA survivors regardless of the CA cause, by using the two questions or objectively by accelerometery.

- Focus on the OHCA survivors identified with limitations in physical function and/or a low level of physical activity. Survivors who are physically active at a moderate/high level probably need no or little support.
- Based on factors identified as risk factors of limitations in physical function, screen for cognitive impairment, anxiety and depression symptoms.
- Based on factors identified as risk factors of a low level of physical activity, screen for obesity, mobility problems, cognitive impairment, kinesiophobia and fatigue.
- Collaboration between the Department of Cardiology and Neurology for better support of both OHCA survivors and MI patients.
- Provide OHCA survivors supervised physical exercise training within cardiac rehabilitation regardless of the CA cause.
- Provide physical activity counselling regardless of the CA cause.
- Screen MI patients for cognitive impairment, anxiety and depression symptoms, kinesiophobia and fatigue. The MI patients may suffer from cognitive impairment as an effect of cardiovascular burden.[121]

Knowledge gaps

- Explore aspects of physical function, physical activity and risk factors before and after rehabilitation in OHCA survivors.
- Investigate potential differences in physical function, physical activity and risk factors between conscious and unconscious patients suffering OHCA at hospital arrival.
- Calculate new counts per minute cut-off values for accelerometer data, based on cardiopulmonary exercise tests, in OHCA survivors.
- Update the reference values for the performance-based Timed Stands Test for a cardiac population.
- Perform a qualitative study to increase the depth of information on aspects of physical function and activity in OHCA survivors to identify problems and solutions.

Future perspectives

Completing the right assessment at the right time is crucial in promoting recovery. Our suggestion is to focus on the OHCA survivors having limitations in physical function and/or low levels of physical activity. The OHCA survivors having normal physical function and being physically active at a moderate/high level probably need little or no support regarding physical function and physical activity. If the OHCA survivor has limitations in physical function, screen for cognitive impairment, anxiety and depression symptoms. If the OHCA survivor has a low level of physical activity, screen for obesity, mobility problems, cognitive impairment, kinesiophobia and fatigue. If any impairment or symptoms are detected during the screening procedure, the outcome assessor and the medical staff should provide the OHCA survivor with guidance and support.

"Knowledge is of no value unless you put it into practice".

Anton Chekhov 1860-1904

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Aspects of physical function and activity in out-of-hospital cardiac arrest survivors

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