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SOCIOECONOMIC DIFFERENCES IN CARE AND OUTCOMES AFTER OUT-OF- HOSPITAL CARDIAC ARREST

EPIDEMIOLOGICAL STUDIES

BY
SIDSEL GAMBORG MØLLER

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AALBORG UNIVERSITY
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Socioeconomic differences in care and outcomes after out-of-hospital cardiac arrest

Epidemiological studies

By Sidsel Gamborg Møller

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Preface and acknowledgements

I was introduced to the fantastic research environment at the Department of Cardiology at Gentofte Hospital back in 2014, where I as a confused medical student met Gunnar Gislason for the first time. I owe him a lot for not only introducing me to research at the department, but to introducing me to the research field of out-of-hospital cardiac arrests and thereby to my amazing supervisors Christian Torp-Pedersen, Mads Wissenberg, Fredrik Folke, Carolina Malta Hansen and Freddy Lippert. Thank you!

Even though my work with research began back in 2014, the research of this thesis was first conducted from 2017-2021, mainly at the Department of Cardiology, Gentofte Hospital. My work in these four years has overall lead to four published papers (two of them included in this thesis) and four manuscripts currently under review or in final stage of submission. For these results to happen as well as this thesis being finalized I am very grateful for my outstanding group of supervisors.

To Christian, even though I know you are not a fan of a too emotional PhD preface, I still want to thank you. Thank you for your clear guidance, inspirational words, and encouragements. Thank you for teaching me to count before I think, and for your unlimited knowledge with answers to every asked question.

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I would also like to thank all my colleagues at the Department of Cardiology at Gentofte Hospital and Hillerød Hospital for making the offices fun and motivating places to work. I am also very thankful to be a part of the cardiac arrest research group from Gentofte, Ballerup and Aalborg. Also many thanks to Thomas Gerds and Liis Starkopf for the invaluable statistical guidance and challenging, but always enlightening discussions.

At last, I would like to thank my family and friends for their unconditional support, patience and encouragement, and especially thank you to Kasper and Alfred.

Sidsel Gamborg Møller, 2021

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1. Papers

This thesis is based on three papers:

1.1. Paper I

Socioeconomic disparities in pre-hospital factors and survival after out-of-hospital cardiac arrest.
Sidsel Møller, Mads Wissenberg, Liis Starkopf, Kristian Kragholm, Steen Møller-Hansen, Kristian B. Ringgren, Fredrik Folke, Julie Andersen, Carolina Malta Hansen, Freddy Lippert, Lars Køber, Gunnar Gislason, Christian Torp-Pedersen, Thomas Alexander Gerds.
Heart. 2021, Jan 8.

1.2. Paper II

Socioeconomic differences in coronary procedures and survival after out-of-hospital cardiac arrest: A nationwide Danish study.
Sidsel Møller, Mads Wissenberg, Kristian Kragholm, Fredrik Folke, Carolina Malta Hansen, Kristian Bundgaard Ringgren, Julie Andersen, Carlo Barcella, Freddy Lippert, Lars Køber, Gunnar Gislason, Thomas Alexander Gerds, Christian Torp-Pedersen.
Resuscitation. 2020 Aug; 153:10-19.

1.3. Paper III

Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status.
Sidsel Møller, Mads Wissenberg, Kathrine Søndergaard, Kristian Kragholm, Fredrik Folke, Carolina Malta Hansen, Kristian B. Ringgren, Julie Andersen, Freddy Lippert, Amalie Lykkemark Møller, Lars Køber, Thomas Alexander Gerds, Christian Torp-Pedersen.
Submitted.

2. Summary

Despite worldwide improvements in out-of-hospital cardiac arrest (OHCA) management and survival over time, OHCA remains a significant health problem associated with a poor prognosis. Large variations in survival outcome have been reported, and in relation to this, socioeconomic factors have been of increasing interest as a possible explanatory factor. Previous studies have mainly focused on area-level socioeconomic differences in pre-hospital factors and especially bystander interventions. The aim of this thesis was to examine the relationship between socioeconomic factors and OHCA further by looking at the association between patient socioeconomic factors and: (1) pre-hospital factors and 30-day survival (Paper I), (2) in-hospital performed coronary procedures and 30-day survival (Paper II), and (3) long-term outcomes as 1- and 5- year survival, onset of anoxic brain damage or nursing home admission and return to work (Paper III).

In all three papers we included patients with OHCA from the Danish Cardiac Arrest Registry (2001-2014) ≥30 years of age, of presumed cardiac cause and non-witnessed by the emergency medical services (EMS). Patients were divided in groups (quartiles/tertiles) according to income as primary exposure and education as supplementary exposure. The final study populations comprised 21,480 patients in Paper I; 6,105 patients in Paper II, since we only included OHCA patients admitted to the hospital; and 2,309 patients in Paper III since we only included 30-day survivors.

In all three papers we found that patients with higher income compared to patients with the lowest income were associated with more positive prognostic characteristics such as younger age, fewer comorbidities, a higher likelihood of having a public and witnessed OHCA, receiving bystander cardiopulmonary resuscitation (CPR) and having an initial shockable rhythm.

In Paper I, we found that patients with highest income compared to patients with lowest income had higher chance of bystander CPR (highest 57.6% vs. lowest 34.7%), and higher 30-day survival after OHCA (highest 19.4% vs. lowest 4.2%). The difference persisted in adjusted analyses where we observed the biggest survival difference in public located witnessed arrests where highest income patients had 26% higher 30-day survival compared to lowest income patients. When we included bystander CPR as a mediator in the analysis, by giving all patients the same chance of bystander CPR as the chance among highest income patients, only 0.79% of the observed socioeconomic difference in survival was eliminated. Similar, but smaller trends were overall observed in the other three subgroups (residential located witnessed arrests, public located non-witnessed arrests, and residential located non-witnessed arrests), and with education instead of income as exposure.

In Paper II, we observed that patients with highest income had a higher chance of receiving coronary angiography compared to patients with lowest income day 0-1 (age-standardized incidence rate [IRR] 1.79, 95% confidence interval [CI] 1.46-2.21), day 2-7 (IRR 2.14, 95%CI 1.26−3.83) and day 8-30 (IRR 1.78 95%CI 0.87−3.69) after OHCA. Comparable trends were observed in stratified analyses for sex, Charlson Comorbidity Index, witnessed arrest with bystander CPR and patients with initial shockable rhythm. Approximately half of the patients undergoing coronary angiography received either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), with overall no observed socioeconomic gradient. In

relation to 30-day survival, patients with highest income had higher odds of survival in adjusted analyses compared to patients with lowest income, both among patients with and without coronary angiography day 0-1 after OHCA (with: OR 1.61, 95%CI 1.12−2.32; and without OR 2.54, 95%CI 1.83−3.53). Similar trends were observed using education instead of income as exposure.
In Paper III we observed in adjusted analyses that patients with highest income had 8.2% higher probability of 1-year survival (highest 95.3% vs. lowest 87.1%) and 11.9% higher probability of 5-year survival (highest 83.0% vs. lowest 71.1%), compared to patients with lowest income. Patients with highest income were also observed having -4.5% lower risk of 1-year anoxic brain damage or nursing home admission (highest 7.3% vs. lowest 11.9%) and -5.0% lower 5-year risk (highest 8.8% vs. lowest 13.8%), compared to patient with lowest income. Among those who were employed right before their OHCA <66 years of age, patient with highest income had 18.0% higher probability of 1-year return to work (highest 75.0% vs. lowest 56.7%) and 14.1% higher probability of 5-year return to work (highest 83.9% vs. lowest 69.7%), compared to patients with lowest income. Similar trends were observed using education instead of income as exposure.

The results of this thesis demonstrate that even in a relatively homogenous country such as Denmark, socioeconomic differences exist in care and outcomes after OHCA, and that neither important patient- nor cardiac arrest-characteristics explained the observed associations. Socioeconomic differences are important to acknowledge, but can be difficult to determine and act upon, especially in an acute situation as an OHCA. The three papers and this thesis overall highlight a great potential to improve care further through greater understanding of socioeconomic differences as a first step towards minimizing these differences in the future.

3. Dansk resume

På trods af forbedret behandling og overlevelse efter hjertestop udenfor hospital (out-of-hospital cardiac arrest, OHCA) over tid over hele verden, er OHCA stadig et stort sundhedsproblem med en dårlig prognose. Der er set stor variation i overlevelsen og i forhold til dette har socioøkonomiske faktorer tiltrukket sig stadig større opmærksomhed som en forklarende faktor. Tidligere studier har primært fokuseret på område-relaterede socioøkonomiske forskelle i præ-hospitale faktorer og især lægmands interventioner. Formålet med denne afhandling var at undersøge forholdet mellem socioøkonomiske faktorer og OHCA videre ved at kigge på om patient-relaterede socioøkonomiske faktorer var associeret med: (1) præ-hospitale faktorer og 30-dages overlevelse (Studie I), (2) hospitalsbehandling med koronar procedurer og 30-dages overlevelse (Studie II), samt (3) langsigtede mål som 1- og 5-års overlevelse, anoksisk hjerneskade eller plejehjemsindlæggelse samt genoptagelse af arbejde (Studie III).

I alle tre studier inkluderede vi patienter med OHCA fra Dansk Hjertestop Register (2001-2014) ≥30 år, af formodet kardiel årsag og ikke bevidnet af ambulance personale. Patienterne blev opdelt i grupper ift. indkomst (kvartiler/tertiler) som primær eksponering og uddannelse som supplement. Den endelige studiepopulation udgjorde 21,480 patienter i Studie I; 6,105 patienter i Studie II da vi kun inkluderede patienter indlagt på hospital; og 2,309 patienter i Studie III, da vi kun inkluderede 30-dages overlevende.

I alle tre studier fandt vi at patienter med højere indkomst sammenlignet med patienter med laveste indkomst var associeret med flere positive prognostiske karakteristika som lavere alder, færre komorbiditeter, en større chance for at have et offentligt og bevidnet OHCA, at modtage lægsmands hjerte-lunge-redning (HLR) og at have en initial stødbar rytme.
I studie I fandt vi at patienter med højeste indkomst sammenlignet med patienter med laveste indkomst havde større chance for lægmands HLR (højeste 57.6% vs. laveste 34.7%) og højere 30-dages overlevelse efter OHCA (højeste 19.4% vs. laveste 4.2%). Forskellen vedblev i justerede analyser, hvor vi så den største forskel i overlevelsen i bevidnede hjertestop i offentligt rum hvor patienter med højeste indkomst havde 26% højere 30-dages overlevelse sammenlignet med patienter med laveste indkomst. Når vi inkluderede lægmands HLR som mediator i analysen ved at give alle patienter den samme chance for lægmands HLR som patienterne med højeste indkomst, blev kun 0.79% af den observerede socioøkonomiske forskel i overlevelsen elimineret. Overordnet lignende, men mindre forskelle så vi i de andre tre sub-grupper (bevidnede hjertestop i private hjem, ikke-bevidnede hjertestop i offentligt rum, ikke-bevidnede hjertestop i private hjem), samt med uddannelse i stedet for indkomst som eksponering.
I Studie II så vi at patienter med højeste indkomst i højere grad fik en koronar angiografi sammenlignet med patienter med laveste indkomst dag 0-1 (alders-standardiseret incidence rate [IRR] 1.79, 95% confidence interval [CI] 1.46-2.21), dag 2-7 (IRR 2.14, 95%CI 1.26−3.83), og dag 8-30 (IRR 1.78 95%CI 0.87−3.69) efter OHCA. Lignende sammenhænge så vi i stratificerede analyser for køn, Charlson Comorbidity Index, i bevidnede hjertestop med lægmands HLR og i patienter med initial stødbar rytme. Cirka halvdelen af de patienter der fik en koronar angiografi fik enten en perkutan koronar intervention (PCI) eller en koronar bypass (CABG), men her var

overordnet ingen socioøkonomisk gradient. I forhold til 30-dages overlevelse havde patienter med højeste indkomst højere odds for overlevelse i justerede analyser sammenlignet med patienter med laveste indkomst både blandt patienter med og uden koronar angiografi dag 0-1 efter OHCA (med: odds ratio [OR] 1.61, 95%CI 1.12−2.32; uden: OR 2.54, 95%CI 1.83−3.53). Lignende resultater sås med uddannelse i stedet for indkomst som eksponering.
I Studie III så vi i justerede analyser at patienter med højeste indkomst havde 8.2% større sandsynlighed for at overleve 1 år (højeste 95.3% vs. laveste 87.1%) og 11.9% større sandsynlighed for at overleve 5 år (højeste 83.0% vs. laveste 71.1%), sammenlignet med patienter med laveste indkomst. Patienterne med højeste indkomst havde også -4.5% lavere risiko for anoksisk hjerneskade eller plejehjemsindlæggelse inden for 1 år (højeste 7.3% vs. laveste 11.9%) og -5.0% lavere risiko inden for 5 år (højeste 8.8% vs. Laveste 13.8%) sammenlignet med patienter med laveste indkomst. Blandt de patienter der var i arbejde op til deres OHCA <66 år, havde patienter med højeste indkomst 18.0% større sandsynlighed for at genoptage arbejdet inden for 1 år (højeste 75.0% vs. laveste 56.7%) og 14.1% større sandsynlighed for at genoptage arbejdet inden for 5 år (højeste 83.9% vs. laveste 69.7%) sammenlignet med patienter med laveste indkomst. Lignende resultater sås med uddannelse i stedet for indkomst som eksponering.

Resultaterne i denne afhandling viser, at selv i et relativt homogent land som Danmark, eksisterer der socioøkonomiske forskelle i både behandling af og prognose efter hjertestop, og hverken vigtige patient- eller hjertestops-karakteristika kunne forklare de observerede sammenhænge. Socioøkonomiske forskelle er derfor vigtige at anerkende, men kan være svære at forstå og agere efter især i en akut situation som et hjertestop. Overordnet sætter de tre studier i denne afhandling fokus på et stort potentiale for at forbedre behandlingen yderligere igennem forståelse af de socioøkonomiske forskelle som et første skridt mod at minimere disse forskelle i fremtiden.

4. Background

4.1. Out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) is defined by the cessation of mechanical activity in the heart with absence of signs of circulation occurring outside of a hospital [1]. The most common cause of cardiac arrest is cardiovascular disease and especially coronary artery disease [2-4]. OHCA constitutes a significant health problem worldwide affecting approximately 625,000 people in the United States and Europe every year [5, 6] and on average around 10% survives though with large variation [6-11].

To improve prognosis after OHCA, several initiatives have been implemented worldwide in cardiac arrest management over time. Overall these initiatives have been summarized in the concept “Chain of Survival” [12, 13]. The Chain of Survival consists of five equally important links that require rapid, consistent, and coordinated actions: (1) Early recognition of cardiac arrest and early emergency call, (2) Early initiation of cardiopulmonary resuscitation (CPR), (3) Early and rapid defibrillation, (4) Advanced cardiovascular life support, followed by (5) Post-resuscitation care with targeted temperature management and early revascularization [12, 13]. The Chain of Survival was introduced in the early 1990’s [12], and extended with the fifth link in 2010 [13]. In 2020, the American Heart Association recommended adding a sixth link: (6) Recovery, which should include long-term physical, cognitive, and psychosocial support [14]. Focus on these factors in cardiac arrest management has likely resulted in the increased survival observed [15-17], where especially involvement of the public in the immediate resuscitative care until the emergency medical service (EMS) arrives has been found essential for an improved outcome [18-24]. Many factors including those in the Chain of Survival affect outcome after OHCA either directly or indirectly. For an overview, these factors can overall be divided into two groups depending on whether they are modifiable or non-modifiable.

4.2. Modifiable and non-modifiable factors in relation to OHCA

Modifiable factors are factors that can be modified by intervention. Examples could be the important factors in the Chain of Survival: Initiation of early CPR and defibrillation, where increased rates of both bystander CPR and defibrillation have been associated with improved survival chances after OHCA [15-24]. Studies have overall showed that without any intervention, the chance of survival decreases approximately 10% per minute from collapse to first defibrillation [25, 26]. This decrease in survival is more gradual when bystander CPR is provided; estimated to approximately 3-4% on average per minute from collapse to defibrillation [19, 21, 25]. Most often the time interval from the emergency call to EMS arrival is 8 minutes or longer [17, 22, 23, 27], hence the victim’s chance of survival greatly depends on bystanders or first responders during the first minutes after collapse. Rates of CPR and defibrillation can be modified in many ways. For example, the proportion of patients who receive bystander CPR may be modified by educating large groups of people, and for this reason mandatory resuscitation training has been implemented in elementary schools and when acquiring a driver’s license in Denmark [17]. Though the only randomized study that has assessed how to improve the proportion of patients receiving bystander CPR showed that dispatching registered citizen responders through text-messages or mobile phone

applications to nearby OHCA patients increased bystander CPR compared to no dispatch of citizen responders [28]. A similar program has been implemented in Denmark and the pilot study has also found an association between arrival of citizen responder prior to EMS and increased CPR [29]. The proportion of patients who receive bystander defibrillation may be modified by increasing the number of publicly available automated external defibrillators (AEDs), specifically in areas with high incidence of OHCA, as well as increasing AED accessibility, AED registration with linkage to EMS and training the population in AED use [22, 30]. Increased bystander defibrillation has also been observed in cases where dispatched citizen responders arrived prior to EMS [29].
Another example of a modifiable factor in relation to OHCA is EMS response time where a faster response has been found associated with improved survival [18, 19]. This can be modified through more ambulances or helicopters, as well as implementing professional first responder programs as part of the EMS response, as in Washington State in the United States [31]. In Washington State, first responders are professionally trained in basic life support with CPR and use of AED and act as a formal part of the EMS [31].

Opposite to modifiable factors, non-modifiable factors are for the most part not changeable by intervention. These include patient-related factors such as age, sex, race, and socioeconomic status. Studies have previously observed that OHCA patients of older age and black race have lower chance of survival after OHCA [32-34], whereas studies on patient sex have shown inconsistent results [35-37]. Other examples of non-modifiable factors are those related to the cardiac arrest such as location of arrest (public or residential) and witnessed status of arrest. Although not modifiable, these factors have found to be important for survival outcome, hence studies have found that having a public located arrest witnessed by a bystander is associated with a higher chance of bystander interventions and survival compared to a residential located non-witnessed OHCA [17, 18, 22, 23, 38].

An example of a factor that can be considered as both modifiable and non-modifiable is the first recorded heart rhythm of the patient: shockable or non-shockable rhythm, which is of great importance for the outcome after OHCA [16-18]. However, the extent to which this factor is modifiable is still unknown, but a Danish study has shown that approximately 10% of the OHCA population converted from initial non-shockable rhythm to shockable rhythm during the pre-hospital resuscitation attempt [39]. This suggests some modifiability in this very important factor during resuscitation.

4.3. Socioeconomic factors

Patient socioeconomic factors are overall categorized along with age, sex and race as non-modifiable factors. Socioeconomic factors describe the social and economic position of people or groups in the society. There are generally no accepted definitions for these factors, but the most commonly used measures are education, occupation and income [40]. Education is usually achieved early in life in the beginning of adulthood and provides the official qualifications for a person' future work and income. Education overall represent knowledge and can thereby affect a person's lifestyle in the future [40]. A person's work or occupation often links education to income and is more often related to material resources due to paid work, status and power in the society [40].

Income is often a result of education and occupation and provides the household with resources [40]. These measures are related and often used interchangeably in the terms social position, socioeconomic status and socioeconomic position etc. [41]. However, studies have suggested that they should not be used interchangeably, since they measure different things and act in different causal mechanisms [40, 42]. Socioeconomic effects are often challenging to interpret due to their multiple dimensions and complexities that are often affected by many different factors [40-46]. For this thesis, patient socioeconomic status will be used as overall description for socioeconomic factors.

4.3.1. Socioeconomic factors in OHCA research

In OHCA research, socioeconomic factors can be examined on both an area-level and individual-level. Most studies have used socioeconomic factors based on area-level data of the OHCA location and thereby illuminated potential areas for targeted interventions [47-58]. These studies have found socioeconomic differences in incidence of OHCA, bystander interventions and survival outcomes, with mainly observed associations between areas of higher socioeconomic status, lower incidence of OHCA and higher chance of bystander CPR, whereas an association with survival has been found more conflicting [47-58]. Studies using individual-level data are limited, and have primarily examined socioeconomic differences in survival outcomes with mainly an observed association between higher socioeconomic status and survival [57-62]. Even though studies on individual-level data are limited, they have been found with a higher predictive value for outcomes [45].

In 2015 the Institute of Medicine, United States, published a report on resuscitation research and cardiac arrest outcomes concluding that, due to missing or unreliable data on ethnicity and socioeconomic factors in most cardiac arrest registries, analyses on OHCA treatment and outcome according to socioeconomic status were almost impossible to conduct [63]. Further, the report stated that this gap in knowledge makes it difficult to identify especially vulnerable populations and to adequately measure and rectify potential disparities in cardiac arrest treatment and outcomes [63]. In Denmark, we have the unique opportunity to obtain individual-level data using the nationwide Danish registries, including information on socioeconomic factors on an individual-level for OHCA patients. The aim of this thesis was therefore to examine whether patient socioeconomic factors were associated with care and outcomes after OHCA. We therefore examined individual-level (patient) socioeconomic differences in:

- (1) Pre-hospital factors focusing on bystander CPR and survival (Paper I)
- (2) In-hospital care with performed coronary procedures and survival (Paper II)
- (3) Long-term outcomes as 1- and 5- year survival, onset of anoxic brain damage or nursing home admission, and return tor work (Paper III).

4.3.2. Pre-hospital factors and survival after OHCA

Although every link in the Chain of Survival needs to be improved to increase chance of a positive outcome after OHCA, early CPR and defibrillation have been of high interest in recent years, as these factors are modifiable and have been shown to significantly improve survival rates after OHCA [15-24, 27]. Neighborhood variations in bystander CPR have to some extent been explained by area-level socioeconomic factors; neighborhoods of lower socioeconomic status showed markedly lower rates of bystander CPR when compared with neighborhoods of higher socioeconomic status [49-52, 56, 58]. However, knowledge about whether individual-level socioeconomic factors affect bystander interventions remains unknown. Conversely, survival after OHCA has been found associated with individual-level socioeconomic factors, whereas studies on area-level socioeconomic factors have been more conflicting [49, 54, 57-62, 64]. To elaborate this further, Paper I examined whether patient socioeconomic factors were associated with the pre-hospital factors: location of arrest, witnessed status, and bystander intervention especially bystander CPR after OHCA. Paper I also examined the association between patient socioeconomic factors and survival after OHCA including bystander CPR as a mediator in the analysis, and thereby elaborating how much of a potential socioeconomic difference in survival that was mediated through bystander CPR.

4.3.3. Coronary procedures and survival after OHCA

The fifth link of the Chain of Survival focuses on the post-resuscitation care after OHCA including in-hospital care. Since ischemic heart disease and coronary artery disease are the most common underlying cause of OHCA [2-4], the in-hospital strategy has been increasingly focused on coronary angiography and revascularization procedures (percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]) [65, 66]. However, studies examining the association between socioeconomic factors and coronary procedures in OHCA patients are limited but have been performed in patients suffering from myocardial infarction [67-71]. These studies overall observed a higher proportion of coronary procedures among patients with higher socioeconomic status compared to patients with lower socioeconomic status. Paper II explores this context further in OHCA patients, and also examines survival in relation to this.

4.3.4. Long-term outcomes after OHCA in relation to patient socioeconomic factors

Studies examining long-term outcomes after OHCA have been of increasing interest, and have included survival, as well as onset of anoxic brain damage, nursing home admission and return to work as indicators of the functional status of the OHCA patient [72-76]. The latter outcome measures have previously been associated with quality of life and risk of depression [77, 78]. In relation to long-term outcomes after OHCA, it has been reported that only 10.5% of 30-day survivors had anoxic brain damage or were admitted to a nursing home after OHCA, 90.3% of patients were alive 1 year after OHCA, and 76.6% of patients in working age (18-65 years) returned to work after OHCA [73, 74]. Additionally, these studies have shown that bystander interventions had a positive impact on the aforementioned outcomes [73, 74]. In relation to socioeconomic differences in long-term outcomes after OHCA, knowledge is scarcer, and it remains unknown whether a socioeconomic gradient exists for long-term functional outcomes such as anoxic brain damage, nursing home admission and return to work. Paper III elaborates on this aspect.

4.4. Objectives

Using the nationwide registries in Denmark, we overall aimed to examine potential individual-level (patient) socioeconomic differences in care and outcomes after OHCA. We examined patient socioeconomic differences in (1) pre-hospital factors focusing primary on bystander CPR and 30-day survival (Paper I), (2) in-hospital care of performed coronary procedures and 30-day survival (Paper II), and (3) long-term outcomes as 1- and 5-year survival, onset of anoxic brain damage or nursing home admission as well as return to work (Paper III). To achieve these overall objectives, the following questions were pursued:

- Paper I: Are patient socioeconomic factors associated with pre-hospital factors and survival after OHCA? And if patient socioeconomic factors are found to be associated with pre-hospital factors, especially bystander CPR, how does that potentially affect survival?
- Paper II: Are patient socioeconomic factors associated with the likelihood of receiving coronary procedures as part of in-hospital care after OHCA in the universal free-of-charge Danish healthcare system?
- Paper III: Are patient socioeconomic factors associated with long-term outcomes after OHCA?

5. Methods

5.1. The Danish Cardiac Arrest Registry

The three papers in this thesis are all based on the Danish Cardiac Arrest Registry. The Danish Cardiac Arrest Registry has existed since June 2001 and is a nationwide registry that holds data on all OHCA patients in Denmark [8]. In the registry an OHCA patient is defined by a patient suffering from a cardiac arrest outside of a hospital resulting in resuscitation attempt either by a bystander or EMS personnel. Hence, patients with late signs of death who are not subjected to resuscitation attempt are not included in the registry. The data in the registry is obtained by the EMS personnel in Denmark that is activated for all medical emergencies and for every OHCA they fill out a mandatory standardized case-report form that fulfils the Utstein guidelines for reporting of OHCA [1, 79]. From the Danish Cardiac Arrest Registry, we obtained information on date of cardiac arrest, location of cardiac arrest (public or residential), whether the cardiac arrest was witnessed by bystander or EMS, bystander CPR status, bystander defibrillation status (use of AED), EMS response time (the estimated time interval from recognition of arrest, defined either by receipt of emergency call at the dispatch center or interviews of the bystanders on the scene, to first rhythm analysis by EMS), first recorded heart rhythm (shockable or non-shockable), and survival status upon arrival to the hospital.

5.2. Other Danish nationwide registries

For all three papers we used the unique Danish civil registration number that is assigned to all Danish inhabitants to link the patients from the Danish Cardiac Arrest Registry to data on a wide range of variables from other nationwide Danish administrative registries. The databases were accessed through secure servers at Statistics Denmark where the civil registration number is encrypted to ensure patient anonymity.

From the Danish Civil Registration System we obtained information on patient age, sex, and vital status [80]. From the National Causes of Death Registry we obtained information on causes of death from death certificates (end of registry December 31, 2016) [81]. From the Danish National Patient Registry we obtained information on hospital admissions including admission- and discharge dates, procedure codes, and discharge diagnosis codes (end of registry December 31, 2015) [82, 83]. Data from the Danish National Patient Registry is considered near complete since the hospital departments are reimbursed based on registered diagnoses and procedure codes [83]. Data from this registry was used to obtain information of patient comorbidities and calculate Charlson Comorbidity Index using discharge diagnosis codes up to ten years before OHCA for Paper II and Paper III [84]. We also obtained information on procedure codes for Paper II as well as information on anoxic brain damage for Paper III defined from the diagnosis code G93.1 as previously done [74]. A recent study has showed that >99% of patients with anoxic brain damage were diagnosed by hospital neurologists and >80% of the diagnoses were confirmed by highly specialized neuro-rehabilitation departments [74]. All included diagnosis codes, including diagnoses from death certificates, are in accordance with the International Classification of Diseases system (ICD-8/ICD-10). In addition to using discharge diagnosis codes we defined diabetes from redemption of antidiabetic medication up to 180 days before OHCA. This information was obtained from the National Prescription Registry. Data on medication use in the registry is also considered near complete since every pharmacy is required to register all dispensed medication prescriptions as the Danish healthcare system partially reimburses the medicine expenses [85, 86]. Each dispensed medication is registered according to the international Anatomical Therapeutical Chemical (ATC) classification system. From Statistics Denmark we obtained information on nursing home admissions for Paper III, which has been registered and validated since 1994 until December 31, 2015 [63, 77]. From a registry administered by the Danish National Labor Market Authority (DREAM) we obtained information on status of employment and social benefits on a weekly basis from 1991 until the end of June 2016 [87]. We considered that a patient was working if the patient was self-supporting and did not receive any government-financed social benefits (unemployment benefits, sick leave benefits, early retirement or disability pension), state education grant, parental leave pay or leave of absence in a 5-week period prior to OHCA with <3 weeks of sick leave during this 5-week period as previously defined [73, 87, 88].

5.3. Socioeconomic information

From the Statistics Denmark we obtained socioeconomic information of the individual patients [89-91]. We included income and education, and overall used income as primary exposure and education as supplemental in all three papers. Patient income was defined from an average household income over a five-year period from the year prior to OHCA in attempt to account for potential yearly variation due to acute illness. The income was weighted according to the number of people in the household using the Organization for Economic Co-operation and Development (OECD) modified scale (the first adult counts as 1 and additional adults count 0.5 per person [92]) and corrected for inflation to year 2015. The income status was divided in quartiles for Paper I and II and in tertiles for Paper III.

Patient education was defined by the highest completed educational level and classified in relation to the International Standard Classification of Education (ISCED) system that allows comparison internationally [93]. Patient education was divided in three groups in all three papers: 1) Basic education including elementary school, 2) High school and short secondary education, and 3) Bachelor degree (BA), Master (MA) or Doctoral degree or equivalent.

5.4. Study design and setting

All three papers in this thesis are nationwide registry-based studies conducted in Denmark. Denmark is a relatively small Scandinavian country covering 43,000 km2 mixed rural, suburban and urban areas with approximately 5,600,000 inhabitants in 2014 that all have equal access to the universal tax-financed healthcare system [94]. In Denmark the healthcare system is operated from three political and administrative levels: (1) the government that sets the overall legislation and guidelines for the healthcare system, (2) the five politically defined regions that manage the healthcare system including psychiatry, pre-hospital, hospital and primary care under the legislation and guidelines set by the government, and (3) the municipalities that are responsible for local parts of the healthcare system such as rehabilitation and nursing homes [95]. The EMS is managed on regional level and consists of a two-tier response-system with (1) basic life support ambulances staffed with emergency medical technicians (EMT) or paramedics; and (2) mobile emergency care units staffed with paramedics or specialized anesthesiologists in cars/helicopters [96]. The EMS transports the patients to the hospitals for further diagnostics, treatment and care. All patients were handled using the same treatment strategies throughout the study period and was based on the latest guidelines for resuscitation and post-resuscitation care.

5.5. Study populations

Using data from the Danish Cardiac Arrest Registry we identified all OHCA patients from June 1 2001 through December 31 2014. Patients <30 years of age with OHCA of presumed non-cardiac cause or witnessed by the EMS were excluded in all three papers. This selection process was done to obtain a more homogenous study population to study and compare following the definitions used in previous studies and the Utstein template from 2004 [1, 17]. The Utstein template has been modified in the most recent guidelines from 2015 where it was recommended that the cause of arrest should be reported in more detailed categories rather than only presumed cardiac or non-cardiac cause [79]. Presumed cardiac cause of arrest was defined as cases with diagnosis codes containing cardiac and unknown disease, and unexpected collapse. Presumed non-cardiac cause of arrest was defined as cases with diagnosis codes of other medical disorders (and absence of the before mentioned diagnoses), trauma, drug-overdose, suicide attempts and drowning. The study populations were further restricted for the individual papers:

5.5.1. Paper I:

In Paper I we identified 21,480 OHCA patients from 2001 to 2014. The included patients were ≥30 years of age with presumed cardiac cause to the OHCA and not witnessed by the EMS. We further excluded patients with missing data on location of arrest, witnessed status and bystander CPR. Following, the patients were divided according to quartiles of household income.

5.5.2. Paper II:

In Paper II we identified 6,105 OHCA patients with an in-patient hospital admission from 2001 to 2014. The included patients were ≥30 years of age with presumed cardiac cause to the OHCA and not witnessed by the EMS. Patients who died before hospital arrival or died in the emergency department were excluded [97]. Following, the patients were divided according to quartiles of household income.

5.5.3. Paper III:

In Paper III we identified 2,309 30-day survivors from OHCA from 2001 to 2014. The included patients were ≥30 years of age with presumed cardiac cause to the OHCA and not witnessed by the EMS. We further excluded patients with anoxic brain damage or nursing home admission prior to OHCA. Following, the patients were divided according to tertiles of household income.

5.6. Main outcome measures

The main outcome measures for the three papers were:

5.6.1. Paper I:

For Paper I the main outcomes were bystander CPR and 30-day survival. Bystander CPR was analyzed as primary outcome and as mediator in relation to survival.

5.6.2. Paper II:

For Paper II the main outcomes were divided in two:

- (1) Coronary procedures with (A) coronary angiography procedures in three pre-defined time periods: day 0-1 after OHCA; day 2-7 after OHCA; and day 8-30 after OHCA, and (B) among the patients undergoing a coronary angiography the composite outcome of revascularization procedures (PCI and CABG) day 0 to 30 after OHCA admission;
- (2) Thirty-day survival in 2-day survivors after OHCA in (A) patients that underwent a coronary angiography day 0-1 after OHCA, and (B) patients that did not undergo a coronary angiography day 0-1 after OHCA.

5.6.3. Paper III:

For Paper III the main outcomes were (1) survival within a 1- and 5- year follow-up period or until end of registry, (2) the composite outcome of anoxic brain damage or nursing home admission within a 1- and 5-year follow-up period or until end of registry, and (3) return to work within a 1- and 5-year follow-up period or until end of registry for patients who were employed prior to OHCA and younger than 66 years of age since 65 years is the normal age of retirement in Denmark.

5.7. Statistical analyses

In all three papers categorical variables were presented as frequencies with percentages and differences were tested with Chi-Square and Fisher Exact tests. Continuous variables were presented as medians with interquartile ranges (IQR, Q1-Q3, 25%-75%) and differences were tested with Kruskall-Wallis tests. To explore whether a socioeconomic gradient existed over time in the outcome measures (bystander CPR, coronary angiography and 30-day survival) we performed time trend analyses for these outcomes in Paper I and Paper II.

5.7.1. Causal inference

For all analyses of associations between patient socioeconomic factors and the outcomes of interest (Paper I-III), directed acyclic graphs (DAG) were performed to visualize the causal pathways between the exposures and outcomes including potential confounders and mediators (Figure 1) [98]. DAGs can be useful in showing causal pathways between an exposure and an outcome especially in OHCA research where the time aspect is an important element.

Figure 1: Directed Acyclic Graph (DAG) for the association between patient income and survival after OHCA (Paper I)

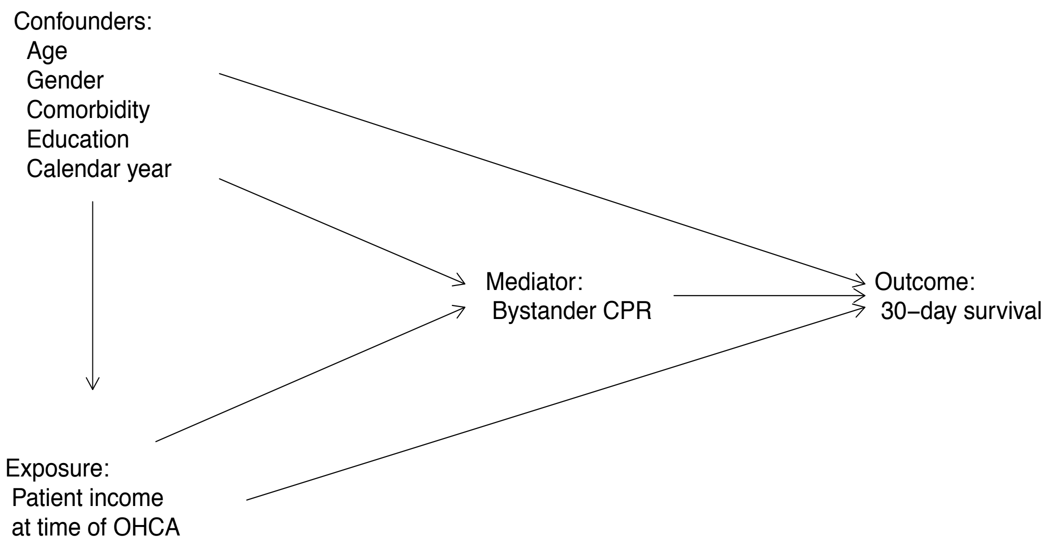

Figure 1 from Paper I: Socioeconomic disparities in pre-hospital factors and survival after out-of-hospital cardiac arrest, by S. Møller et al. Heart. 2021, Jan 8.

In Paper I and Paper III we used causal inference and specifically G-formula and average treatment effect analyses when examining the relationships between patient income and the outcome measures (30-day survival, 1- and 5-year survival, 1- and 5-year onset of anoxic brain damage or nursing home admission, and 1- and 5-year return to work) [99, 100]. Causal inference can overall be considered as a framework to derive average treatment effects from observational studies that in a perfect world, with no unmeasured confounders, can be interpreted as the causal effects we would have seen, if the studies had been randomized trials [101]. For results to be interpreted as causal effects, there are overall three assumptions that need to be fulfilled: positivity, consistency and exchangeability [99, 100, 102].

5.7.1.1. Positivity, Consistency and Exchangeability

Positivity is the assumption of that any included patient will have a positive probability to be assigned to one of the exposures. In our studies this means that there had to be OHCA patients in either one of the four (Paper I) or three (Paper III) income groups investigated.

Consistency is when the observed outcome for an individual patient, whether the patient is exposed or unexposed, is the exact outcome for that individual patient. This means that there had to be clearly defined and consistent exposure groups and outcomes. In our studies the exposure groups (income groups) and the outcomes (30-day survival, 1- and 5-year survival, 1- and 5-year onset of anoxic brain damage or nursing home admission, and 1- and 5-year return to work) were all clearly defined and consistent based on the Danish registries.

Exchangeability is the assumption of the exposed and the unexposed being exchangeable. This means that the exposed would have the same outcome as the unexposed if the exposed had been unexposed, as well as the unexposed would have the same outcome as the exposed if the unexposed had been exposed [99, 100, 102]. This is the case in randomized trials where the randomization causes potential confounders to be equally distributed between the investigated groups (exposed and unexposed patients). In relation to observational studies this can be a problem since we cannot adjust for all potential confounders, and the exposed and unexposed patient groups will therefore not be exchangeable, and the results will not necessarily lead to causal interpretation.

So since there were unmeasured confounders in both Paper I and Paper III it was not possible to interpret the results in these papers as the causal effects that we would have seen in a randomized trial. However, using G-formula and the average treatment effect analyses gave us the possibility to estimate standardized absolute probabilities and absolute probability differences for the outcomes, which may be more intuitive to understand than other risk measures [99-102]. We calculated the standardized absolute probabilities and probability differences for the outcomes: 30-day survival in Paper I, and 1- and 5-year survival, anoxic brain damage or nursing home admission and return to work in Paper III, using the same method. We performed logistic regression analyses for the outcome of interest based on standardized data where every patient in the study population first was assigned to one exposure for example highest income, but kept the original patient- and cardiac arrest-related characteristics. Then every patient was assigned to one of the other two (Paper III) or three (Paper I) exposures: high income, low income and lowest income, but in all analyses kept the original patient- and cardiac arrest-related characteristics. For Paper I we then had four calculated 30-day survival probabilities for each patient, and for Paper III we had three calculated probabilities for each of the outcomes for each patient. These probabilities were then summarized into averages of standardized absolute probabilities for each outcome as well as absolute probability differences between the income groups that were afterwards reported in the papers.

5.7.2. Paper I

For Paper I the association between patient income and bystander CPR was examined using logistic regression analysis with reported odds ratios (ORs) and corresponding 95% confidence intervals (CI). The association between patient income and 30-day survival was examined based on causal inference with G-formula and average treatment effect analyses as previously described, and by using mediation analysis including bystander CPR as an intermediate factor on the causal pathway from patient income to 30-day survival. Figure 1 shows the underlying structure of the analysis. All analyses were adjusted for the following confounders: age, sex, calendar year, education and comorbidities, and stratified in four subpopulations based on other mediators: location of arrest (public or residential) and witnessed status (non-witnessed or witnessed): (1) Private location + witnessed arrest, (2) Private location + non-witnessed arrest, (3) Public location + witnessed arrest, and (4) Public location + non-witnessed arrest.

5.7.2.1. Mediation analysis

As part of causal inference understanding causal mechanisms in health has been of increasing interest. One way to explore this is to break down the simple total effect of an exposure on an outcome to separate causal pathways. As stated DAGs can be beneficial in visualizing the potential causal pathways between an exposure and an outcome, including both confounders and mediators [98]. Figure 1 shows the DAG and underlying structure for our survival analysis for Paper I. In this paper we sought to explore the total effect of patient income on 30-day survival by using causal inference, as well as examine whether a potential socioeconomic difference in the intermediate factor (bystander CPR) between our exposure and outcome, affects 30-day survival. To estimate this possible effect, we used mediation analysis. Typical mediation analysis aims to determine the total effect of an association between an exposure and an outcome broken down to a direct effect of the exposure on the outcome and an indirect effect of the exposure on the outcome through a mediator [103, 104]. As Figure 1 shows we defined patient income as exposure, bystander CPR as mediator and 30-day survival as outcome in Paper I.

However when using social exposures as income and education, typical mediation analysis methods may not be justified, due to the assumption that the exposure should be available for a hypothetical intervention, in order to interpret the estimated effects from a mediation analysis [105, 106]. Interventions on social exposures pose some challenges. Therefore we developed a new method with inspiration from different methods in which it is possible to intervene on the mediator (in our case, bystander CPR) instead of the social exposure [104, 105, 107, 108]. Using this method, we were able to examine how income disparities in 30-day survival possibly would change if the chances of bystander CPR for all the patients would be equal to what they are among patients with the highest income. By this method we sought to estimate the following parameters:

- (1) Overall *observed* income disparity in 30-day survival (the difference in observed survival probabilities across income groups),
- (2) *Remaining* income disparity in 30-day survival under the intervention (the disparity in survival across income groups if the chances of bystander CPR for all patients was identical to the highest income group), and
- (3) *Eliminated* income disparity in 30-day survival under the intervention of changed chance of bystander CPR for all patients to be identical to the highest income group (the difference between the observed and the remaining income disparity in survival).

As previously described in section 5.7.1 about *Causal Inference*, we used G-formula and average treatment effect analyses based on logistic regression analyses to estimate both the observed and the remaining income disparities in 30-day survival. In the results for remaining income disparities in 30-day survival we included the mediator (bystander CPR) in the analysis by changing the probability for bystander CPR in the lower income groups to the probability of the highest income group. Corresponding 95% CIs were computed using bootstrap with 1,000 bootstrap samples for all results [99].

5.7.3. Paper II

In Paper II we examined the associations between patient income and coronary procedures by calculating age-standardized incidence rates (SIR) and relative incidence rate ratios (IRR) of performed coronary angiography and revascularization procedures. For calculation of risk time, the patients were followed from hospital admission to date of death, hospital discharge or 30-days from admission – whatever came first. For coronary angiography procedures, SIRs and IRRs were calculated separately for three time periods: day 0-1, day 2-7 and day 8-30 after OHCA, and the analysis was repeated in the following subgroups: (1) sex, (2) Charlson Comorbidity Index (CCI,

CCI=0 (low level), CCI=1 (medium level) and CCI>1 (high level)), (3) witnessed arrests with bystander CPR, (4) arrests with first recorded shockable heart rhythm, (5) in two calendar time periods (years 2001-2007 and years 2008-2014) and (6) using patient education instead of income.
We further examined the association between patient income, coronary angiography and revascularization procedures by Cox regression analyses where death was handled as competing risk. To avoid incorrect interpretation the analyses were adjusted for the following confounders: age, sex, Charlson Comorbidity Index, education and calendar year, and further analyzed in subgroups of the following mediators: (1) witnessed arrests with bystander CPR, and (2) arrests with first recorded shockable heart rhythm [109].

For 2-day survivors after OHCA, the probability of survival within the first 30 days according to patient income was estimated using the empirical distribution function and divided in subgroups of patients with and without coronary angiography day 0-1. To examine the association between patient income and 30-day survival in 2-day survivors after OHCA we used logistic regression analysis, adjusted for age, sex, Charlson Comorbidity Index, education and calendar year. The analyses were performed in stratified groups of mediators: (1) with and without coronary angiography performed during day 0-1, (2) based on patient education instead of income, and (3) in subgroups of witnessed arrests with bystander CPR and arrests with first recorded shockable heart rhythm opposed to confounders since they appear on the pathway between exposure and outcome. We reported ORs and corresponding 95% CI.

5.7.3. Paper III

For Paper III we summarized the frequencies for 1- and 5-year survival, onset of anoxic brain damage/nursing home admission and return to work according to the three income groups. For anoxic brain damage/nursing home admission and return to work death was handled as competing risk [110].
As described in the section 5.7.1 *Causal Inference* the association between patient income and the outcomes were assessed using G-formula and average treatment effect analyses based on logistic regression analyses. The results were reported as standardized absolute probabilities and absolute probability differences together with 95% CI based on 1,000 bootstrap samples [99]. All the analyses were adjusted for the following confounders: age, sex, calendar year, education and groups of Charlson Comorbidity Index: CCI=0 (low level), CCI=1 (medium level) and CCI>1 (high level). The analyses were performed for the overall population and in pre-defined subgroups of the following mediators: (1) witnessed arrests with bystander CPR, (2) arrests with first recorded shockable heart rhythm, and (3) using patient education instead of income [109].

All analyses were performed in collaboration with the statisticians Thomas Alexander Gerds and Liis Starkopf. For data management and statistical analyses SAS version 9.4 (“SAS Institute Inc., Cary, NC, USA”) and R version 3.4.1 (“R Development Core Team”) [111] were used.

5.8. Ethics

All the three papers in this thesis were approved by the Danish Data Protection Agency (Ref.no. 2007-58-0015, local ref.no. GEH-2014-017, I-Suite.no. 02735). Due to the encrypted civil registration number the included patients were anonymous. Ethical approval is not required in Denmark for retrospective registry-based studies.

6. Results

This section summarizes the main findings of the three papers in this thesis. The presentation is the same for all papers: (1) short summary of the background highlighting the importance of the objectives, followed by (2) the main results including main figures, and finally, (3) the conclusion. Detailed descriptions and additional results including tables and figures for each paper can be viewed in Paper I-III in the Appendix.

6.1. Paper I: Socioeconomic disparities in pre-hospital factors and survival after out-of-hospital cardiac arrest

6.1.1. Background and objectives:

Socioeconomic differences in pre-hospital factors and especially in bystander CPR, as well as survival after OHCA have previously been observed. Studies on pre-hospital factors have been based on area-level socioeconomic factors that have found varying results on survival, whereas studies on individual-level socioeconomic factors have been lacking on pre-hospital factors, but found survival to be higher in patients with higher socioeconomic status. Hence it remains unknown whether there is an association between patient socioeconomic factors and bystander CPR after OHCA, as well as whether a potential socioeconomic difference in bystander CPR might affect survival. Therefore this study examined patient socioeconomic disparities in pre-hospital factors and survival in a nationwide scale, including bystander CPR as a mediator in the analysis for survival.

6.1.2. Main results:

A total of 21,480 OHCA patients of ≥30 years of age of presumed cardiac cause and not witnessed by the EMS were included from 2001 to 2014. The patients were divided according to income quartiles with 5,370 patients in each income group (highest [Q4], high [Q3], low [Q2] and lowest [Q1] income). Patients with highest income (Q4) compared to lowest income (Q1) were overall younger (median age: highest 61 years vs. lowest 77 years), more often male (highest 79.3% vs. lowest 63.0%), had higher education, less comorbidities, higher chance of public located arrests (highest 33.6% vs. lowest 21.1%), bystander CPR (highest 57.6% vs. lowest 34.7%), initial shockable rhythm (highest 41.1% vs. lowest 21.2%), and 30-day survival (highest 19.4% vs. lowest 4.2%). From 2002 to 2014, we observed increases in bystander CPR and 30-day survival for all income groups. From 2002 to 2014, bystander CPR increased from 24% to 73% for highest income patients (Q4) and from 15% to 61% for lowest income patients (Q1); and 30-day survival increased from 5% to 20% in the highest income patients (Q4) and from 2% to 9% in lowest income patients (Q1).

Figure 2 shows the adjusted analysis for bystander CPR, where highest income patients (Q4) had higher odds for bystander CPR compared to patients with lowest income (Q1) in all combinations of location of arrest and witnessed status: private located witnessed arrests OR 1.54, 95%CI 1.30-1.82; private located unwitnessed arrests OR 1.74, 95%CI 1.47-2.05; public located witnessed arrests OR 1.31, 95%CI 1.05-1.65; and public located unwitnessed arrests OR 1.66 95%CI 1.18-2.34.

Figure 2: Association between patient income and bystander CPR

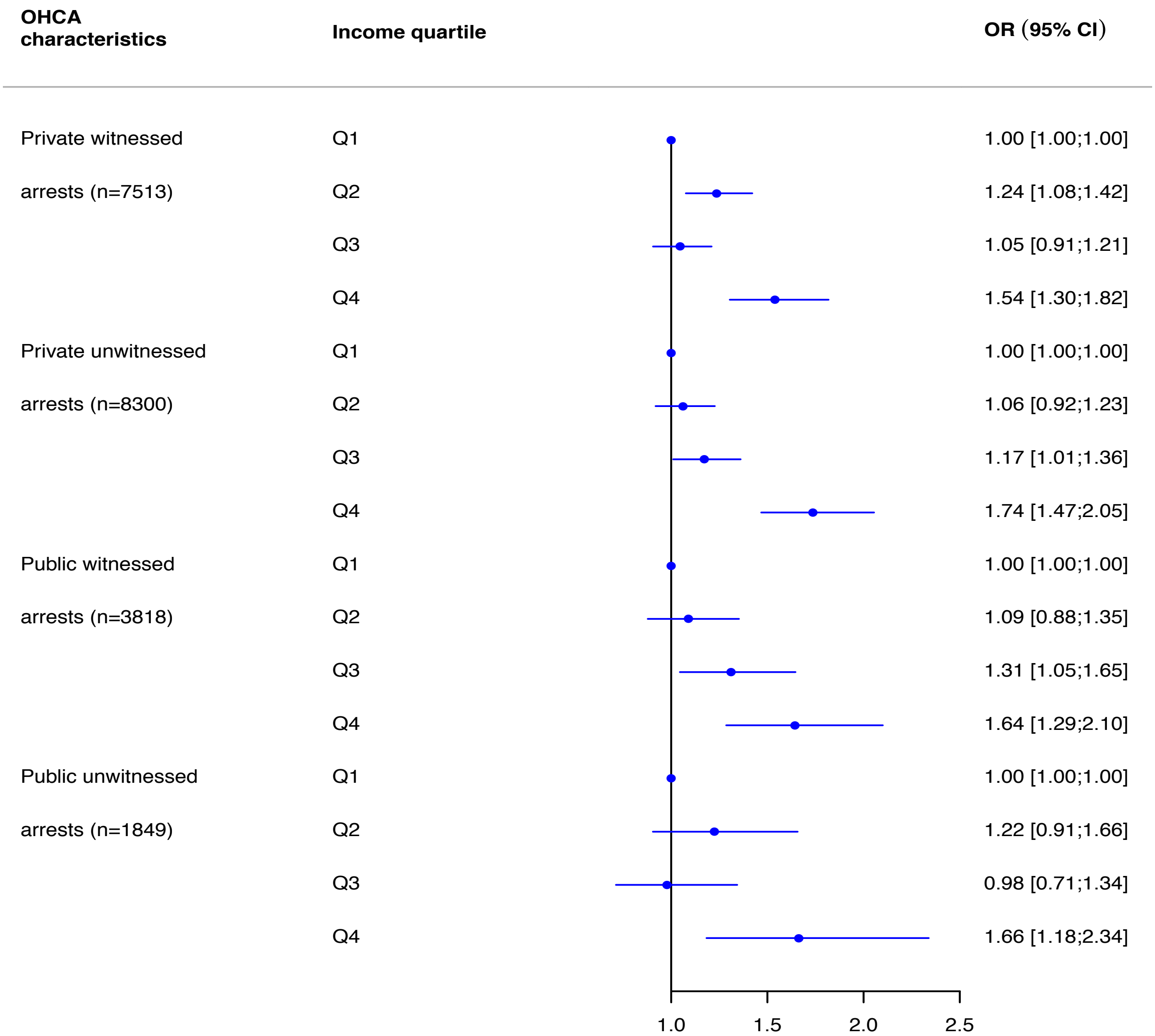

Figure 3 from Paper I: Socioeconomic disparities in pre-hospital factors and survival after out-of-hospital cardiac arrest, by S. Møller et al. Heart. 2021, Jan 8.

Similarly highest income patients (Q4) also had higher probability of 30-day survival in adjusted analyses across all combinations of location of arrest and witnessed status (Figure 3). The biggest difference between highest (Q4) and lowest income patients (Q1) was in public-witnessed arrests with 26.0% (95%CI 22.4%-29.7%) higher probability of survival in highest-income patients (Q4) compared to lowest (Q1). Had bystander CPR been the same for lowest-income patients (Q1) as for highest-income patients (Q4), then survival would be 25.3% (95%CI 21.5%-29.0%) higher in highest-income patients compared to lowest, resulting in elimination of 0.79% (95%CI 0.08%-1.50%) of the income-disparity in survival (Figure 3). Similar trends, but smaller were observed in low- (Q2) and high-income patients (Q3), the other three subgroups, and with education instead of income.

<u>Figure 3: Probability for 30-day survival according to patient income</u>

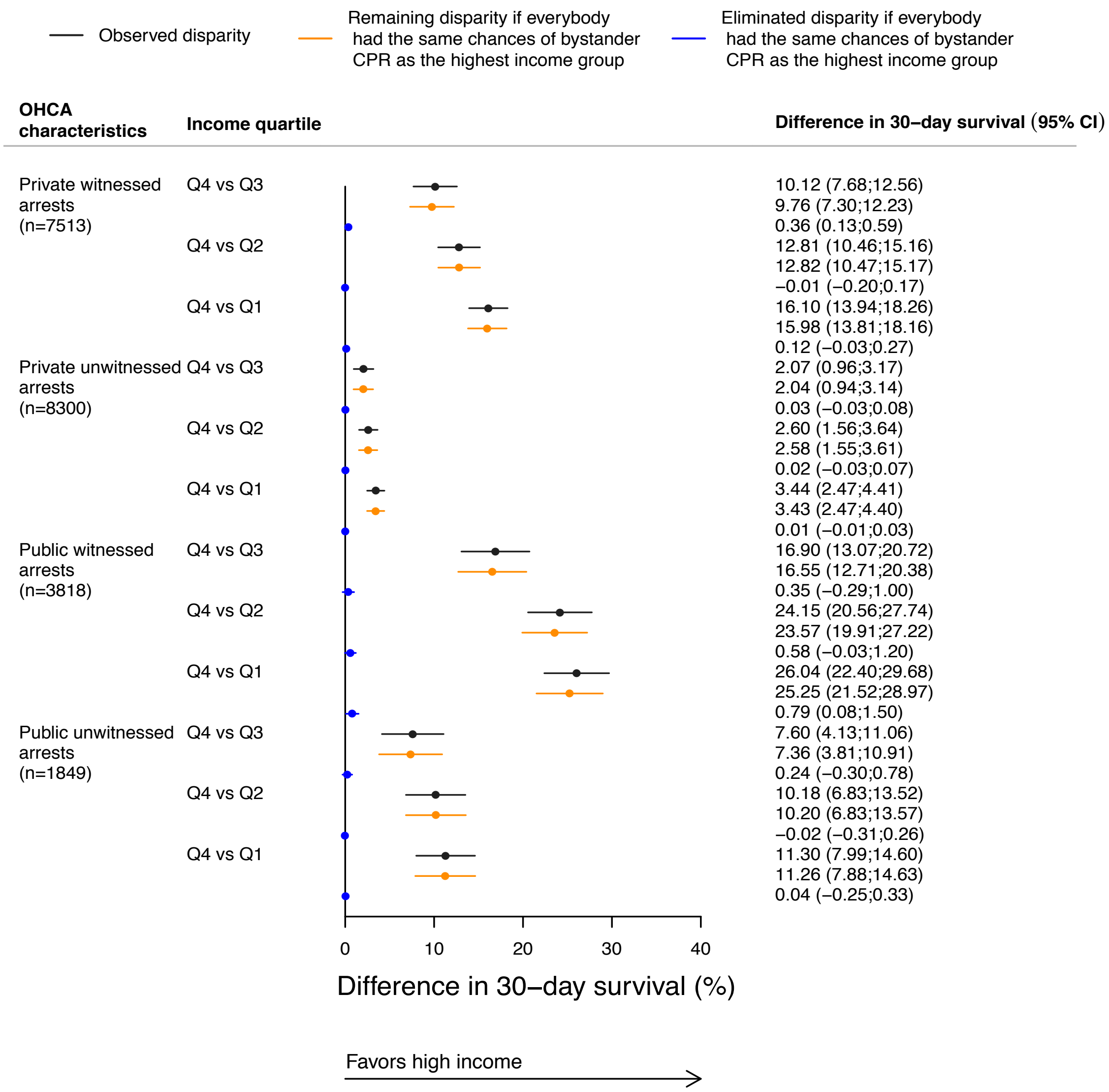

Figure 4 from Paper I: Socioeconomic disparities in pre-hospital factors and survival after out-of-hospital cardiac arrest, by S. Møller et al. Heart. 2021, Jan 8.

6.1.3. Conclusion:

In this nationwide study we demonstrated that despite improvements in bystander CPR and 30-day survival from 2002 to 2014, significant socioeconomic differences were observed with higher income patients receiving more bystander CPR and having higher 30-day survival compared to lower income patients. These results persisted when we included important both patient- and cardiac arrest-related factors as well as when we included the observed socioeconomic difference in bystander CPR. Other factors than socioeconomic disparities in bystander interventions may therefore explain the observed socioeconomic differences in survival.

6.2. Paper II: Socioeconomic differences in coronary procedures and survival after out-of-hospital cardiac arrest: A nationwide Danish study.

6.2.1. Background and objectives:

The most common cause to OHCA is ischemic heart disease and coronary artery disease and the guidelines focuses on early coronary angiography and revascularization (PCI and CABG). Socioeconomic gradients in these procedures have earlier been observed in primary myocardial infarction patients, but remained unknown for OHCA patients. The objective was therefore to examine socioeconomic differences in coronary procedures and survival after OHCA both overall and over time.

6.2.2. Main results:

A total of 6,105 OHCA patients with a hospital admission of ≥30 years of age of presumed cardiac cause and not witnessed by the EMS were included from 2001 to 2014. The patients were divided according to income quartiles with 1,587 patients with highest income (Q4), 1,573 with high income (Q3), 1,522 with low income (Q2) and 1,423 patients with lowest income (Q1). Patients with highest income (Q4) compared to patients with lowest income (Q1) were younger (median age: highest 58 years vs. lowest 76 years), more often male (highest 81.9% vs. lowest 68.5%), had higher education, less comorbidities (Charlson Comorbidity Index = 0: highest 74.0% vs. lowest 44.6%), higher chance of public arrests (highest 49.8% vs. lowest 33.2%), more often bystander CPR (highest 74.4% vs. lowest 48.2%) and an initial shockable rhythm (highest 73.0% vs. lowest 47.0%). Highest income patients (Q4) compared to lowest income patients (Q1) received more often coronary angiographies (highest 63.5% vs. lowest 26.9%) and had higher 30-day survival (highest 58.9% vs. lowest 22.9%). Though no statistically significant difference was observed in revascularization procedures (PCI and CABG) among patients with coronary angiographies. The majority of coronary angiographies (80.5%) were performed day 0-1 after OHCA. From 2001 to 2014 increases were observed for both coronary angiographies performed day 0-1 after OHCA as well as 30-day survival in all income groups.

In adjusted analyses significantly higher incidence rates for coronary angiographies after OHCA were observed in highest income patients (Q4) compared to lowest income patients (Q1) both day 0-1 (IRR 1.79, 95%CI 1.46-2.21), and day 2-7 (IRR 2.14, 95%CI 1.26-3.83) after OHCA (Figure 4). Among the patients with coronary angiography, 54% received either PCI or CABG. No difference was observed among three of the four groups, whereas low-income patients (Q2) had lower IRR (IRR 0.74, 95%CI 0.61-0.89) compared to lowest (Figure 4).

<u>Figure 4: Age-standardized incidence rates and incidence rate ratios for coronary procedures according to patient income</u>

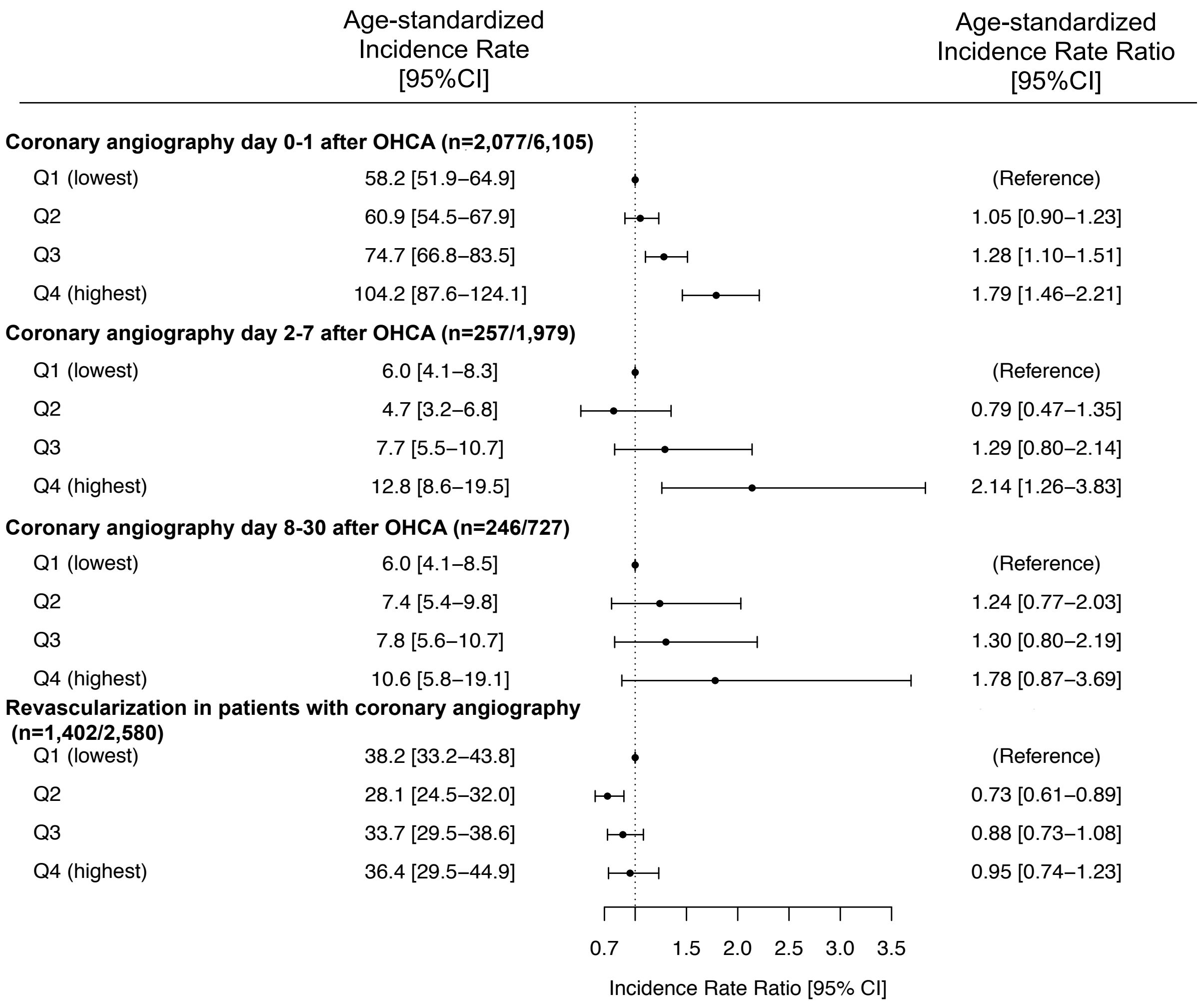

Figure 3 from Paper 2: Socioeconomic differences in coronary procedures and survival after out-of-hospital cardiac arrest: A nationwide Danish study by S. Møller et al. Resuscitation. 2020 Aug; 153:10-19.

In relation to survival, highest income patients (Q4) compared to lowest income patients (Q1) also had higher odds for 30-day survival, both in patients with coronary angiography day 0-1 (OR 1.61, 95%CI 1.12−2.32) and without coronary angiography day 0-1 (OR 2.54, 95%CI 1.83−3.53) (Figure 5). The same trends were observed in subgroups of witnessed arrests with bystander CPR, arrests with initial shockable rhythm, and using education instead of income as exposure.

Figure 5: Odds ratios for 30-day survival according to patient income

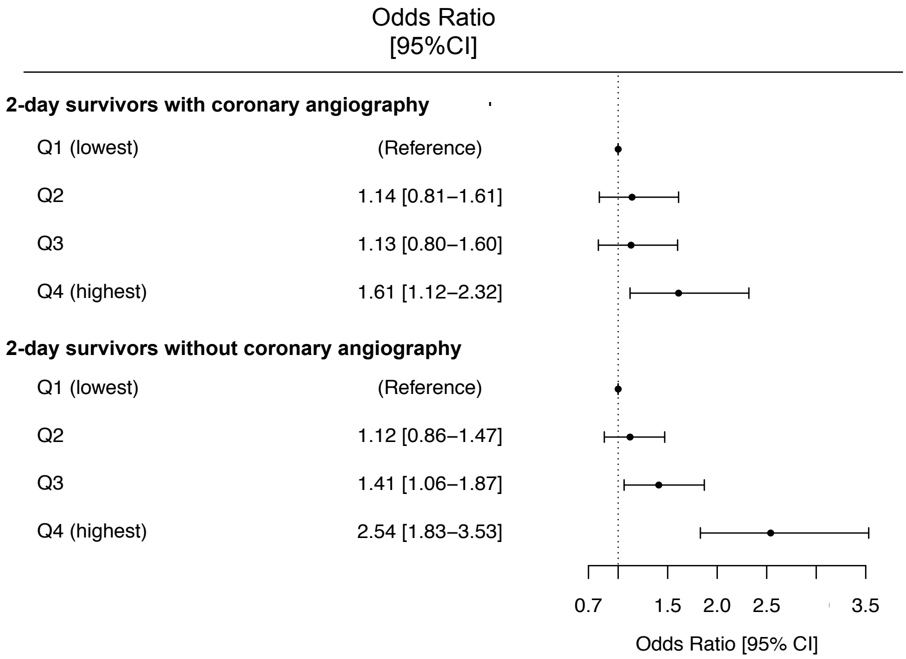

Figure 5 from Paper 2: Socioeconomic differences in coronary procedures and survival after out-of-hospital cardiac arrest: A nationwide Danish study by S. Møller et al. Resuscitation. 2020 Aug; 153:10-19.

6.2.3. Conclusion:

This study showed that even in a tax-financed public healthcare system in Denmark with free access for all inhabitants independent of socioeconomic position, patients of higher socioeconomic status were found associated with a higher frequency of both coronary angiographies and survival.

6.3. Paper III: Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status

6.3.1. Background and objectives:

In addition to survival after OHCA increased focus has been on outcomes of the functional status of the patient such as onset of anoxic brain damage and nursing home admission as well as return to work within a longer time period after OHCA. However, socioeconomic differences in these outcomes remained unknown and therefore, this study aimed to explore the potential effect of socioeconomic factors on (1) 1- and 5-year survival, (2) 1- and 5-year risk of anoxic brain damage or nursing home admission, and (3) 1- and 5-year probability of returning to work after OHCA.

6.3.2. Main results:

A total of 2,309 thirty-day survivors after OHCA of ≥30 years of age of presumed cardiac cause and not witnessed by the EMS were included from 2001 to 2014. The patients were divided according to income tertiles with 780 with high income [Q3], 777 with medium income [Q2] and 752 with low income [Q1]). High-income patient (Q3) compared to low-income patients (Q1) were younger (median age: high 57 years vs. low 70 years), more often male (high 85.8% vs. low 74.3%), had higher education, less comorbidities (Charlson Comorbidity Index = 0: high 80.1% vs. low 58.0%), higher chance of public located arrests (high 58.6% vs. low 47.6%), bystander CPR (high 83.5% vs. low 67.1%) and shockable rhythm (high 86.8% vs. low 78.0%). High-income patients (Q3) compared to low-income patients (Q1) had the highest 1- (high 96.4% vs. low 84.2%); and 5-year survival (87.6% vs. 64.1%), lowest 1- (high 7.4% vs. low 11.3%) and 5-year (8.6% vs. low 13.7%),) onset of anoxic brain damage and nursing home admission, and the highest 1- (high 76.4% vs. low 58.8%) and 5-year (85.3% vs. low 70.6%) return to work among the 831 previously workers below 66 years of age.

In standardized analyses we observed that high-income patients (Q3) compared to low (Q1) had 8.2% (95%CI 4.7 to 11.6%) higher 1-year survival (Figure 6) and 11.9% (95%CI 6.9 to 16.9%) higher 5-year survival. We observed that high-income patients (Q3) compared to low (Q1) had -4.5% (95%CI -8.2 to -1.2%) lower 1-year risk of anoxic brain damage/nursing home admission (Figure 7) and -5.0% (95%CI -8.6 to -1.5%) lower 5-year risk of anoxic brain damage/nursing home admission. At last we observed that high-income patients (Q3) compared to low (Q1) had 18.0% (95%CI 3.8-32.7%) higher probability of returning to work within one year (Figure 8) and 14.1% (95%CI 1.0-28.2%) higher probability within five years. The overall trends persisted in pre-defined subgroups of witnessed arrests with bystander CPR, patients with initial shockable heart rhythm, and when using patient education instead of income as socioeconomic exposure.

Figure 6: The probability of 1-year survival according to patient income

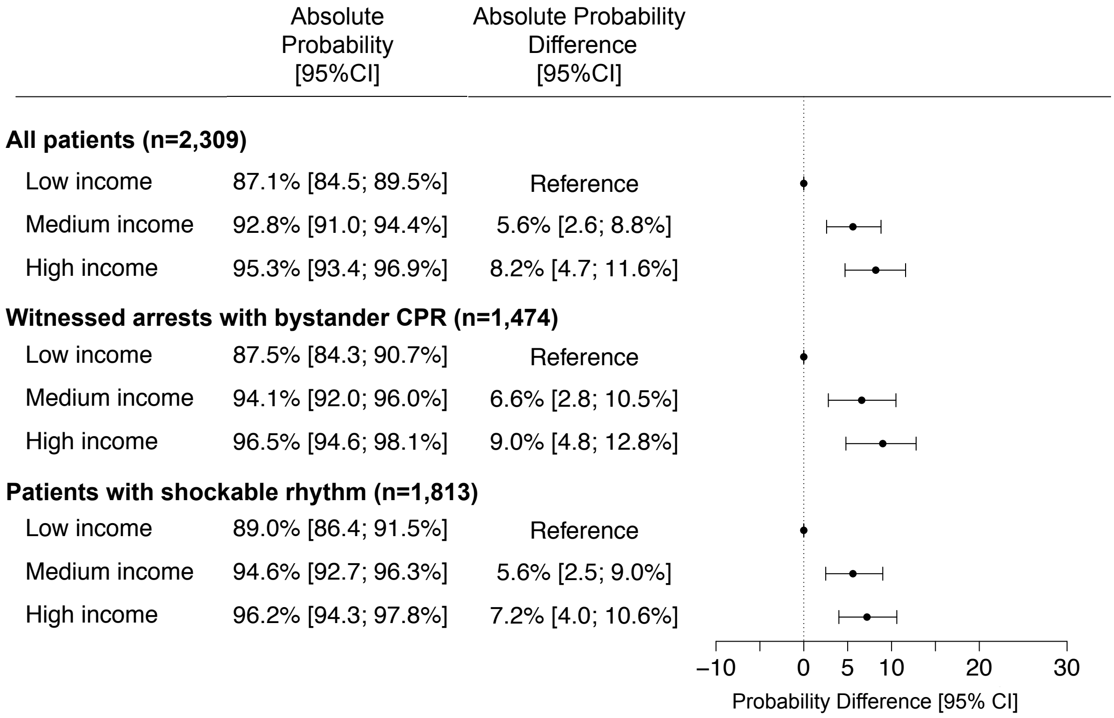

Figure 1 from Paper 3: Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status by S. Møller et al. Submitted.

<u>Figure 7: The 1-year risk of anoxic brain damage or nursing home admission according to patient income</u>

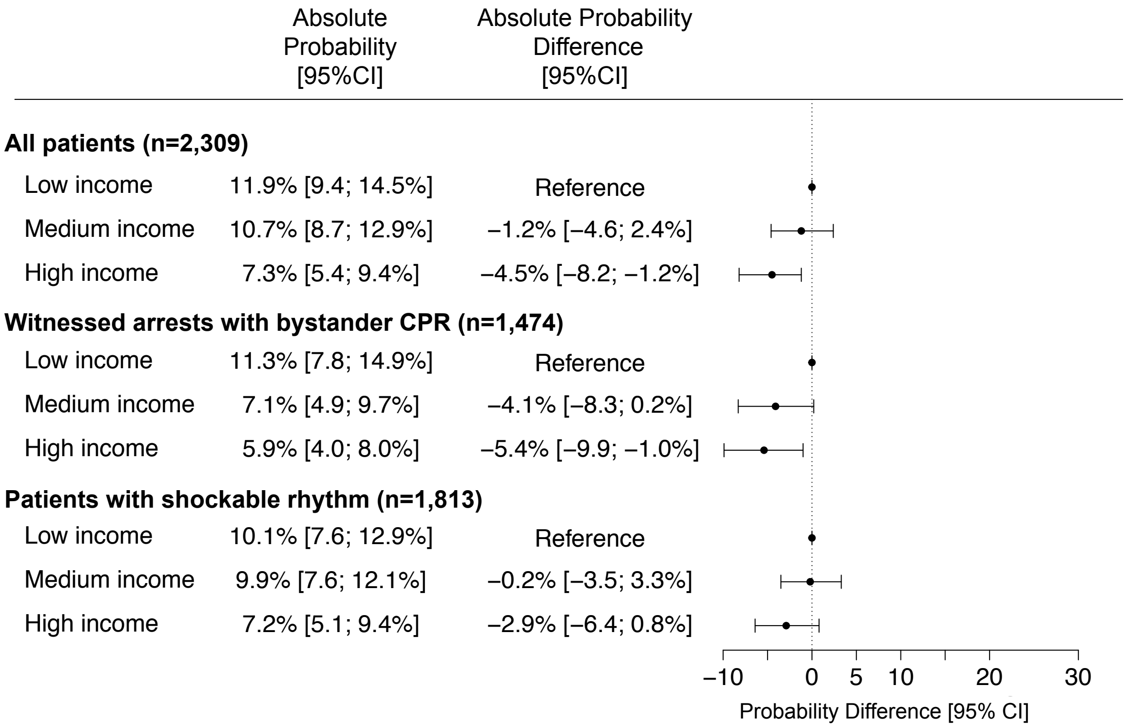

Figure 3 from Paper 3: Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status by S. Møller et al. Submitted.

Figure 8: The probability of 1-year return to work according to patient income

	Absolute Probability [95%CI]	Absolute Probability Difference [95%CI]
All patients (n=831)		
Low income	56.7% [43.1; 70.6%]	Reference
Medium income	69.3% [63.8; 75.1%]	12.6% [−2.0; 27.4%]
High income	75.0% [71.0; 78.6%]	18.0% [3.8; 32.7%]
Witnessed arrests with bystander CPR (n=582)		
Low income	52.2% [33.5; 72.2%]	Reference
Medium income	73.8% [67.3; 80.1%]	21.6% [1.1; 41.0%]
High income	78.1% [73.8; 82.0%]	25.7% [6.2; 45.5%]
Patients with shockable rhythm (n=690)		
Low income	60.5% [45.2; 76.2%]	Reference
Medium income	69.3% [63.1; 75.9%]	8.8% [−7.3; 25.6%]
High income	73.5% [69.2; 77.6%]	13.0% [−0.4; 29.7%]

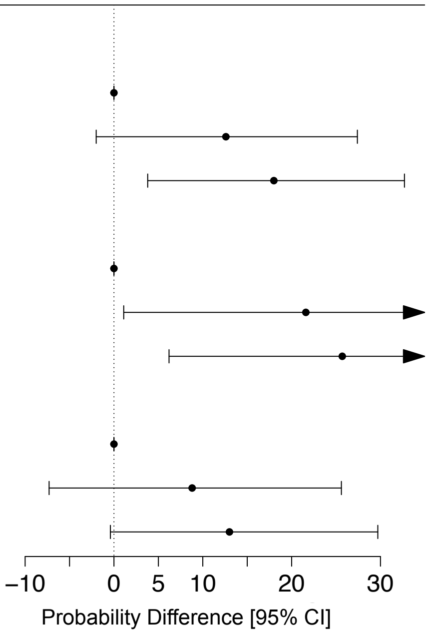

Figure 5 from Paper 3: Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status by S. Møller et al. Submitted.

6.3.3. Conclusion:

This study found that patients with higher income or education had a higher probability of 1- and 5-year survival and return to work, as well as lower risk of anoxic brain damage or nursing home admission compared to patients with low income or basic education.

7. Discussion

7.1. Summary of results

Despite improvements over time OHCA remains a significant health challenge worldwide associated with an overall poor prognosis that calls for further improvements. However, large variations have been observed in survival outcomes after OHCA providing hope that it is possible to improve prognosis after OHCA further [6-11]. Socioeconomic differences have been widely investigated in health in general, and have also found interest in OHCA patients as an explanatory factor for the variation observed in care and survival after OHCA. Therefore, the main objective of this thesis was to explore potential effects of patient socioeconomic factors in OHCA patients in a nationwide setting in relation to three main areas: (1) pre-hospital factors focusing on bystander CPR and survival (Paper I), (2) in-hospital care with performed coronary procedures and survival (Paper II), and (3) long-term outcomes of survival, onset of anoxic brain damage or nursing home admission as well as return to work (Paper III), after OHCA. Whereas previous literature on this field has focused on area-level socioeconomic factors, we chose to focus on individual-level socioeconomic factors as patient income and education. The overall results of this thesis showed a higher frequency of positive prognostic patient- and cardiac arrest-related characteristics in patients with higher income or education (Paper I-III) including a higher chance of receiving bystander CPR (Paper I), as well as receiving coronary angiography procedures as part of the in-hospital treatment (Paper II). The results also showed that patients with higher income or education showed better short- and long-term survival (Paper I-III), lower risk of anoxic brain damage or nursing home admission and a higher probability of returning to work after OHCA (Paper III).

7.2. Socioeconomic differences in pre-hospital factors after OHCA

In all three papers, we observed that patients of higher socioeconomic status were associated with both better prognostic non-modifiable and modifiable patient- and cardiac arrest-related factors [15-23, 32, 38, 112, 113]. Patients of higher socioeconomic status were younger, had less comorbidities, and had a higher chance of having a public and witnessed arrest, as well as a higher chance of receiving bystander CPR and defibrillation. These findings support previous literature of socioeconomic differences in pre-hospital factors and especially in bystander CPR, where higher rates of bystander CPR have been found in areas of higher socioeconomic status [49-52, 56, 58].

Overall different patient- and cardiac arrest-related factors have been suggested as explaining factors for the observed socioeconomic difference in bystander CPR. One study even suggested that a substantial part of the association between area-level socioeconomic factors and bystander CPR may be due to individual demographic and socioeconomic factors that had not yet been explored [114]. Paper I is to our knowledge the first study examining the association between individual-level (patient) socioeconomic factors and bystander CPR. Paper I found, in accordance with previous OHCA studies on area-level socioeconomic factors, higher odds for bystander CPR after OHCA in patients with higher income or education. The association persisted when including both patient- and cardiac arrest-related factors in the analyses through adjustment of the patient factors age, sex, comorbidities and patient education, and in stratified groups of location of arrest and witnessed status. Other factors than the included may therefore explain the observed differences.

For example could it be a result of socioeconomic differences in knowledge about and training in CPR as observed in studies from the United States [115, 116]. One could also imagine that people or areas of higher socioeconomic status have a greater investment in their local neighborhood and neighbors, with a wider social network and thereby potentially more help in case of an emergency. Unfortunately we were not able to obtain such information or other area-level factors, but studies combining area- and individual-level factors, and thereby including effects of for example both the bystanders providing CPR and the patients receiving CPR, could be important and interesting in order to explore this association further.
Importantly, we observed in Paper I increased bystander CPR in all income groups over time, indicating that the initiatives in cardiac arrest management taken over the last decades, with focus on involvement of the public, seem to work irrespectively of the patient's socioeconomic status [15-23]. Though, throughout the time period (2002-2014) investigated in the paper, patients with higher income still received more bystander CPR than patients with the lowest income. Recent programs working with activating citizen responders through mobile phone applications have showed an increase in bystander CPR in cases where citizen responders are dispatched compared to cases where no citizen responders are dispatched [28, 29]. Perhaps these programs could reduce the socioeconomic differences in the future.

In addition to bystander CPR, another very important pre-hospital Chain of Survival factor is defibrillation. In all three papers we found a higher proportion of bystander defibrillation in patients of higher socioeconomic status compared to patients with lower socioeconomic status. Whether this finding is a result of a socioeconomic difference in AEDs applied to the patients by a bystander prior to EMS arrival or a result of a socioeconomic difference in the heart rhythm prior to EMS arrival is unfortunately unknown. Though a combination is probably likely, and especially the latter is supported by our found socioeconomic difference in initial recorded heart rhythm by the EMS. A study from the United States has showed a higher rate of bystander applied AEDs to OHCA patients in neighborhoods with a high proportion of people with a high-school degree or higher [53]. This finding supports the idea about a socioeconomic difference in applied AEDs prior to EMS arrival. A socioeconomic difference in AED application could be a result of the same patient- and cardiac arrest-related factors as mentioned in relation to bystander CPR, as well as it could be a result of socioeconomic differences in knowledge about the importance of AEDs in case of an OHCA. Other factors as differences in publicly available AEDs including bystander knowledge about AED locations or dispatch guidance to AEDs could also affect whether an AED was applied or not by bystanders. The other factor that needs to be present for defibrillation is shockable heart rhythm. Notably, in all three papers we observed a socioeconomic difference in the initial recorded heart rhythm by the EMS, with a higher chance of having an initial recorded shockable rhythm among patients of higher socioeconomic status.
The observed socioeconomic difference in the initial recorded heart rhythm is an interesting finding. The difference could be a result of patient-related factors as age, sex and comorbidities [32, 35-37, 112, 113], as well as cardiac arrest-related characteristics where especially time of and quality of intervention seems important [16, 39, 117]. The etiology of arrest could also play a role for the socioeconomic difference in initial recorded shockable rhythm, and even though we only included

OHCAs of presumed cardiac cause in all three papers, differences in the specific etiology to arrest could still exist. The observed socioeconomic difference in the initial recorded shockable rhythm could also be a result of an initial shockable rhythm transforming to non-shockable rhythm due to delay in recognition of OHCA and thereby important interventions as bystander CPR prior to EMS arrival. This is supported by our observed higher proportion of public located witnessed arrests in higher income patients in all three papers. In these arrests the time from recognition to important actions such as emergency call, bystander intervention and EMS arrival may be shorter than in non-witnessed arrests where it is more difficult to estimate the exact time for the OHCA. Notably, EMS response time did not differ between the socioeconomic groups in all three papers indicating that other factors besides the time from emergency call to EMS arrival seems to be central for the observed socioeconomic differences in both initial recorded heart rhythm and survival after OHCA. Unfortunately, we do not have data on other time variables than EMS response time, though it is a very interesting area for future research.

7.3. Socioeconomic differences in in-hospital care after OHCA

Following the pre-hospital care of the OHCA patients the next link in the Chain of Survival is the post-resuscitation in-hospital care. In relation to this we chose to focus on potential socioeconomic differences in coronary procedures after OHCA in Paper II, since it remained unexplored whether socioeconomic differences existed in these procedures after OHCA.

Overall, we found in Paper II that patients of higher socioeconomic status compared to patients of lower socioeconomic status were more likely to receive a coronary angiography after OHCA. The results overall persisted in adjusted and stratified analyses which included patient factors as age, sex, comorbidities, patient education and cardiac arrest-related factors as location of arrest, witnessed status, bystander CPR and initial shockable rhythm. The observed socioeconomic difference in coronary procedures is supported by previous literature primarily in patients suffering from myocardial infarction [67-71], as well as new study in OHCA patients [118]. As in our study, a new study from Sweden by Lagedal et al. also found both a higher rate of initial shockable heart rhythm and a higher rate of early coronary angiography procedures (within day 1 after OHCA) in patients with higher income. However, when they included first recorded heart rhythm by the EMS in their analysis for coronary angiography procedures the difference between income groups was found non-significant [118]. In comparison, our study found persisting socioeconomic differences in coronary angiography after OHCA and also when only including patients with initial shockable rhythm. However, the socioeconomic difference in coronary angiography was less pronounced in patients with initial shockable rhythm. These findings are overall not surprising since the guidelines recommend immediate coronary angiography in survivors with ST-elevation for all patients (and in patients without ST-elevation but a high suspicion of ongoing myocardial ischemia) [65, 66]. Though, we still observed a socioeconomic gradient in coronary angiography that overall was not explained by either important patient- or cardiac arrest-related factors. Additionally, the found socioeconomic difference in initial recorded shockable rhythm is interesting and has been discussed in *Section 7.3*. Interestingly, we observed that among the patients receiving a coronary angiography there was overall no socioeconomic trend in the revascularization procedures, indicating that socioeconomic factors did not define the probability of the patient having a coronary occlusion in the patients receiving a coronary angiography.

Overall, we expected a smaller or no socioeconomic gradient due to the acute setting of OHCA and the public tax-financed healthcare system in Denmark with equal access for all inhabitants and with wide access to the procedures. Though as for the pre-hospital factors a socioeconomic gradient was observed, and other factors than the ones we included in our study (age, sex, comorbidities, education, witnessed status, bystander CPR and initial heart rhythm) must therefore explain the observed socioeconomic difference. However, supporting our findings of socioeconomic differences in the in-hospital care of OHCA patients in Denmark, another Danish study by Winther-Jensen et al has also found a socioeconomic difference in the implementation of implantable cardioverter defibrillators (ICD) in OHCA patients [119]. In this study they could not exclude an underutilization of ICD implantation in the lowest income patients, but suggested that the observed socioeconomic difference in both the implementation of ICDs and survival was likely multifactorial and may be a result of a healthier lifestyle [119]. They also pointed out that the observed results could in part be due to a higher frailty burden in the lowest income patients beyond what can be captured by the Charlson Comorbidity Index [119]. The same could be argued in our study as well, since we also used the Charlson Comorbidity Index for this study. However, in Paper I we included several comorbidities and not Charlson Comorbidity Index and still observed a socioeconomic gradient in the pre-hospital factors and 30-day survival.

7.4. Socioeconomic differences in outcomes after OHCA

Together with bystander CPR, survival after OHCA is the most investigated outcome in relation to socioeconomic differences in OHCA research. As we found in both Paper I and Paper II, patients with higher income and education had higher rates of bystander CPR and coronary angiography procedures, as well as a higher chance of 30-day survival compared to patients with lower income or education. Existing literature has overall shown conflicting results on whether or not socioeconomic differences exist in survival after OHCA, but mainly support our findings [49, 54, 57-62, 64]. The observed socioeconomic differences in survival have previously thought to be a result of differences in patient factors, pre-hospital factors and in-hospital factors. However, when we included the found socioeconomic differences in these factors in Paper I and Paper II we still observed higher 30-day survival in patients with higher income or education. In Paper I we included bystander CPR as a mediator in our analyses for survival. This was done due to the observed socioeconomic gradient in this factor, and in order to examine if increasing the chance for bystander CPR amongst lower income patients to correspond to the chance for bystander CPR amongst highest income patients would improve survival for the lower income patients. Interestingly and unfortunately, changing the chance of bystander CPR among lower income patients did not change the survival difference between the income groups markedly. However, other factors related to bystander interventions can be important for the observed socioeconomic difference in survival. For example, differences in the time for recognition of arrest, time to emergency call and time to intervention, as well as a potential difference in quality of provided CPR [120]. Previous studies have also showed a socioeconomic gradient in CPR training that easily could affect both bystander interventions and survival after OHCA [115, 116]. Unfortunately, we were not able to obtain information on most of these factors, but investigating these factors could help enlighten the important first minutes after a patient suffers an OHCA.

Since either patient- or cardiac arrest-related factors explained the observed socioeconomic difference in 30-day survival in Paper I we focused on the in-hospital care and especially coronary procedures in Paper II. However, when we examined 30-day survival in patients with or without a coronary angiography day 0-1 after OHCA, we still found a socioeconomic difference in survival. So the higher rate of coronary angiography in patients with higher income did not explain the observed socioeconomic difference in survival.

In addition to the observed socioeconomic differences in 30-day survival found in both Paper I and II, Paper III examined whether socioeconomic differences also existed in long-term outcomes after OHCA of 1- and 5-year survival, 1- and 5-year risk of anoxic brain damage or nursing home admission as well as 1- and 5-year return to work (among previous workers younger than 66 years of age) in 30-day survivors. As in both Paper I and Paper II we found a socioeconomic gradient in the outcomes with higher survival, higher probability of returning to work and lower risk of anoxic brain damage or nursing home admission in patients of higher income or education, also when including important patient and cardiac arrest-related factors in the analyses. Previous studies in this area are limited, but our findings support one study from Australia by Pemberton et al. that found improved, but lower long-term survival after OHCA in patients living in more remote locations and of lower socioeconomic status [76]. Socioeconomic differences in return to work has also been found in patients with myocardial infarction and stroke [88, 121], and could be related to both available rehabilitation programs as well as the work the patients are returning to, since studies show that white collar workers with more sedentary jobs are more likely to return to work than blue collar workers [121]. Together with previous studies on this field, overall OHCA survivors were found to have a relatively high probability of both 1- and 5- year survival and a low 1- and 5-year risk of onset of anoxic brain damage or nursing home admission, as well as a high probability of 1- and 5-year return to work after OHCA [73, 74]. But our found socioeconomic gradient in these outcomes overall highlights a potential for targeted focus and interventions in future cardiac arrest management in order to improve these outcomes after OHCA and hopefully minimize the observed socioeconomic gradient. The focus on long-term outcomes after OHCA is in line with the recently recommendation by the American Heart Association of adding a sixth link to the Chain of Survival focusing on long-term physical, cognitive, and psychosocial recovery after OHCA [14].

All together, these results indicate that the observed socioeconomic differences in all these outcomes may be caused by other factors than differences in pre-hospital interventions and in-hospital coronary procedures, as well as neither important patient-related factors as age, sex, comorbidities and patient education, nor cardiac-arrest-related factors as location of arrest, witnessed status and initial recorded heart rhythm explained the observed socioeconomic difference in 30-day, 1- and 5-year survival, onset of anoxic brain damage or return to work after OHCA. The observed socioeconomic differences may be explained by other factors and the mechanisms are likely multifactorial [119]. A patient's socioeconomic status may reflect accumulations of different risk factors throughout life, as well as patients with higher socioeconomic status may in general may have a healthier lifestyle, have better insight and knowledge of own health – data we unfortunately do not have in hand, and perhaps patients with higher socioeconomic status even use the healthcare system more effectively than patients with lower socioeconomic status [71, 120, 122-124].

This thesis overall shows that socioeconomic differences exist in all levels of care in OHCA patients in Denmark. Denmark is often considered as relatively homogenous country, but no matter what available factors we included in our analyses, the socioeconomic differences persisted. With this in mind, the observed socioeconomic differences may be even bigger in other parts of the world. Future research focusing on other factors that may help explain the observed socioeconomic differences than the ones we were able to examine in this thesis could help us improve the understanding of this area further.

7.5. Strengths, limitations and methodological considerations

All three papers in this thesis are observational studies based on the nationwide Danish Cardiac Arrest Registry combined with other nationwide administrative registries using the unique Danish civil registration number assigned to every inhabitant in Denmark. This made it possible to examine associations in a national setting with large patient groups, where most other studies are based on data from smaller geographical areas or patient samples [125, 126]. Studies based on high-quality nationwide data as the Danish registries gives the ability to study real-life populations without the restrictive inclusion/exclusion criteria used in randomized controlled trials otherwise considered as the gold standard in research, with often compromised generalizability. Nationwide OHCA studies are still relatively rare and randomized trials with OHCA patients are challenging to conduct and might even be impossible for studies like the ones included in this thesis.

However, there are several noteworthy limitations to these three papers. First of all, the observational nature of the studies makes the results considerable only as associations rather than causal relations. This is contrasting the randomized controlled trials, where the results can be interpreted as causal effects, since the randomization causes potential confounders to be evenly distributed between the investigated groups and thereby the exposed and unexposed patients are exchangeable [99, 100, 102].

7.5.1. Causal inference in observational studies

Even though randomized controlled trials have better terms for causal inference, they are as stated challenging to conduct in OHCA research. However, in both Paper I and Paper III we applied causal inference analyses using G-formula and average treatment effect analyses to our data, and in a perfect world with no unmeasured confounders this would allow a causal interpretation of the results equal to the randomized trials [99-102]. As described in the *Methods section 5.7.1. Causal Inference* there are three assumptions (positivity, consistency, exchangeability) that need to be fulfilled for a causal interpretation of the results. Whereas the assumptions about positivity and consistency are easier to fulfill, the assumption about exchangeability and no unmeasured confounders is often difficult if not impossible to achieve in observational studies. In our case we were for example not able to obtain data of certain modifiable risk factors such as smoking, alcohol consumption, diet, physical activity etc. All risk factors with a potential socioeconomic gradient that could contribute to the explanation of some of the observed associations between patient socioeconomic factors and the outcomes. We sought to take these factors into consideration by including comorbidities as proxies in all our analyses. However, we acknowledge that merely including comorbidities from diagnoses obtained from hospital contacts and prescriptions do not summarize and include all potential risk factors. We were also unable to obtain clinical data on factors such as blood pressure measurements, electrocardiograms, etc. as well as data on other in-hospital care such as target temperature management, echocardiograms etc.

Confounding is in general one of the major limitations in observational studies, and often confounders are used interchangeable with mediators, as these can be difficult to separate [101]. Figure 1 shows the difference between confounders and mediators. A confounder is defined as a factor that has a direct effect on both the exposure and the outcome, whereas a mediator is a factor or intermediate step between the exposure and the outcome and thereby a potential causal consequence of the exposure on the outcome. OHCA research often looks at many different factors that are often subdivided in: patient-related factors, cardiac arrest-related factors, in-hospital factors etc., and in previous OHCA research most often many of these factors have been treated as confounders and used as covariates in adjusted analyses. However, as of recent we have become more aware of the distinction between confounders and mediators and how to handle them different in analyses. In this case DAGs can be helpful (Figure 1) [98].
In all three papers we considered age, sex and comorbidities as confounders due to a believed effect of these factors on the exposure: patient socioeconomic status at time of OHCA and the outcomes: bystander CPR (Paper I), coronary angiography procedures (Paper II), 30-day survival (Paper I-II) and long-term outcomes (Paper III) after OHCA. Opposite to this, we considered the cardiac arrest-related factors as location of arrest and witnessed status, bystander CPR as well as initial shockable heart rhythm, as mediators, since we believed these factors were intermediate factors between the patient socioeconomic factors and the outcomes. This is especially due to the fact that the time of different factors is an important element in OHCA research. If we simply adjusted for the mediators, we would eliminate a potential effect between patient socioeconomic factors and the outcome, if the mechanism for this effect was to pass through one of these factors. Instead of adjustment, we therefore conducted stratified analyses of the factors perceived as mediators in all three papers. In Paper I we conducted an actual mediation analysis for the association between patient socioeconomic factors and 30-day survival including bystander CPR as a mediator. We did this due to an interest in estimating how much of the socioeconomic difference in survival that potentially could be explained by the observed socioeconomic difference in bystander CPR. However, unfortunately, only a small part of the socioeconomic difference in survival, if any at all, was driven by the socioeconomic difference in bystander CPR. With this in mind, mediation analysis is likely to have a greater impact in OHCA research in the future due to our often asked research questions based on time from OHCA to survival with some kind of intermediate factor in between as for example bystander CPR, defibrillation, EMS arrival etc.

7.5.2. Choosing the right exposure (patient socioeconomic factors)

As previously noted, there are no generally accepted definitions for socioeconomic status and existing literature have it defined in various ways. The most commonly used measures are education, occupation and income either individually or in combination [40]. Even though the factors correlate, they measure different things and act in different causal mechanisms [40, 42]. We chose to include both patient household income and last completed educational level, and used income as primary exposure and education as supplementary to support the potential socioeconomic gradient that we found. Income was chosen as primary exposure, as the median age for the OHCA population was around 67 years, and we believed that the patients' socioeconomic position in the society at the time of their OHCA would be more determined by their current income status rather than their educational level obtained early in life. Income is often preceded by education, which we acknowledged in our analyses by adjusting for patient education when examining the association between income and the outcomes. In all three papers we observed the same socioeconomic trend in the outcomes whether using income or education as exposure.

Data was obtained from the nationwide Danish registries with limited missing information [89-91]. However, limitations to the socioeconomic information could lead to misclassification of the patients. For income, we used the gross household income before taxes. This income does not include information of for example income-dependent benefits such as rent subsidies that would increase the disposable income primary for citizens of lower income that qualify for this benefit. Further it does not include capital gains, a benefit more likely for citizens of higher income, which would also increase the disposable income. Furthermore, the income does not include accumulated assets of wealth that could result in misclassification of income group primarily in citizens above the retirement age, where the income consists mostly of pension. The income is therefore lower after age 65 (the retirement age in Denmark) than among citizens of age below 65 years and still working. For this reason we included analyses in all three papers of patients <66 years and >65 years showing overall the same socioeconomic trends as the main analyses. Another limitation to income could also be due to the time in life where it is measured. We chose to include income as an average from the year prior to OHCA and five years backwards to account for potential variation over the years and thereby minimize the risk of potential variation due to acute illness and minimize the risk of misclassification.

For education we used the patients' last completed educational level. This information does not include for example continuing education or other skill improvements, and there could be a risk of the patients being misclassified in a lower educational group than actually achieved, whereas the opposite situation of patients being misclassified in higher educational groups than actually achieved are less likely. However, we would not expect this to change our findings in all three papers where we observed a socioeconomic gradient in all the outcomes when using education as exposure instead of income. Though the consequence of such misclassification could be a weakened social gradient due to the group of lower educational patients being mixed with actual high educational patients.

8. Conclusions

The three papers in this thesis overall showed that despite nationwide improvements in cardiac arrest management over time and subsequent improved survival, socioeconomic differences exist in all levels of care, in both short and long-term outcomes of survival, onset of anoxic brain damage or nursing home admission as well as return to work after OHCA. Patients with higher income or education was found associated with generally positive prognostic patient- and cardiac arrest-related characteristics including a higher chance of having a witnessed arrest and receive bystander CPR. Patients of higher income or education was also found associated with a higher chance of receiving coronary angiography, as well as a higher chance of 30-day, 1-year and 5-year survival. Further, patients of higher income or education was associated with a higher chance of return to work, and a lower risk of onset of anoxic brain damage or nursing home admission after OHCA. The observed differences could not be explained by important patient- or cardiac arrest-related factor. The mediation analysis in Paper I did not show a major mediated effect through bystander CPR either, when examining whether the observed socioeconomic difference in bystander CPR explained some of the socioeconomic difference observed in survival. The observed socioeconomic differences may therefore be explained by other factors. Highlighting the need for more research into this field where understanding disparities between different patient groups including understanding socioeconomic differences further is a first step towards minimizing these differences and potentially save more lives in the future.

9. Implications and future research

The socioeconomic differences in care and outcomes after OHCA found in this thesis, that were not explained by any of the included covariates, agrees with previously observed socioeconomic differences in health in general and within cardiovascular diseases [40-46]. A direct causal relationship between a patient's socioeconomic status and outcomes after OHCA is not credible in a strictly biological sense. More intermediate factors must play a role, yet the mechanisms remain unknown. As suggested a patient's socioeconomic status may reflect accumulations of different risk factors throughout life as well as patients with higher income or education may be healthier, have better insight and knowledge of their own health, and use the healthcare system differently than patients with lower income or education [71, 120, 122-124]. Reducing socioeconomic differences in care and outcomes after OHCA is challenging, especially since the mechanisms behind the socioeconomic differences remains unknown. Strategies to reduce socioeconomic differences in OHCA patients are highly needed as of now. However, until we gain more specific knowledge on how we can explain and reduce the socioeconomic differences in OHCA patients, focus most be on improving the links of the Chain of Survival in a way where the initiatives target all people equally regardless of socioeconomic status. Potential interventions that could help reduce the socioeconomic differences in relation to the Chain of Survival could be to identify people and areas of lower socioeconomic status and target training in CPR and AED use to these people and areas. It could also be to supply these areas with more available AEDs with linkage to the dispatch centers and to enable dispatcher to guide the bystanders to nearest AED in case of an OHCA. Another way for applying areas with more accessible AEDs is to use drones to transport AEDs to remote cardiac arrest patients [127]. Such initiatives could potentially help increase the use of AEDs in lower socioeconomic patients or areas and thereby improve survival. Other interventions could also be to dispatch citizen responders through a mobile phone application as recently implemented in Denmark with the HeartRunner project [29]. Since citizen responders should be dispatched regardless of the patient's socioeconomic status, this could potentially help reduce the socioeconomic difference in bystander interventions. In addition to this, for the current studies we only have information on whether there was performed CPR by a bystander or not. Unfortunately we do not have information on for example the time for or the quality of the performed CPR. This can potentially be enlightened with an on-going project in Denmark where on-scene streaming of the bystander intervention for the dispatch centers to see, help and guide. Estimating the quality of CPR could be of great importance for further improvements in cardiac arrest management, since the quality of the bystander intervention naturally depends on the person who intervenes, which might differ according to socioeconomic position [120]. Hopefully all these initiatives will help improve general cardiac arrest management, as well as reduce the observed socioeconomic differences in the future. Future projects with an important socioeconomic aspect could also be to explore different time measures other than EMS response time, as for example time from collapse to emergency call or time from collapse to CPR initiation.

Other future projects could also focus on the observed socioeconomic difference in initial recorded shockable rhythm where again the different time measurements from OHCA to important actions could be very interesting to look at, as well as the etiology of the cardiac arrest hopefully could help explore this area further. For the included three papers in this thesis with data from 2001-2014 we only had the possibility to differentiate between presumed cardiac and non-cardiac cause to arrest, which was in line with the Utstein guidelines from 2004 [1]. However, from 2016 more information about other etiologies to the cardiac arrest has been collected and studies on this could hopefully help enlighten this area in OHCA research.

Other studies with collecting information about comorbidities from general practitioners, as well as other clinical factors (blood samples, electrocardiograms etc.) could also help enlighten socioeconomic differences in health. Another angle to this area could also be studies based on questionnaire on either survivors from OHCA or a sample of a general population that could be followed over several years. Such questionnaire could collect information on for example lifestyle including smoking, diet, exercise etc., social relations and family history, as well as information of the patient's understanding and knowledge of own health. All kind of information that potentially could help enlighten physiological and psychological resources of the OHCA patient that again potentially can help explain the observed socioeconomic differences further.

Summing-up: the socioeconomic aspect is important in nearly all aspects of OHCA care and survival, hence identification of any explaining factors is of great importance.

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11. References

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12. Appendix (Paper I-III)

12.1. Paper I: Socioeconomic disparities in pre-hospital factors and survival after out-of-hospital cardiac arrest.

Original research

Socioeconomic disparities in prehospital factors and survival after out-of-hospital cardiac arrest

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ABSTRACT

Objective It remains unknown whether patient socioeconomic factors affect interventions and survival after out-of-hospital cardiac arrest (OHCA), and whether a socioeconomic effect on bystander interventions affects survival. Therefore, this study examined patient socioeconomic disparities in prehospital factors and survival.

Methods From the Danish Cardiac Arrest Registry, patients with OHCA ≥30 years were identified, 2001–2014, and divided into quartiles of household income (highest, high, low, lowest). Associations between income and bystander cardiopulmonary resuscitation (CPR) and 30-day survival with bystander CPR as mediator were analysed by logistic regression and mediation analysis in private witnessed, public witnessed, private unwitnessed and public unwitnessed arrests, adjusted for confounders.

Results We included 21 480 patients. Highest income patients were younger, had higher education and were less comorbid relative to lowest income patients. They had higher odds for bystander CPR with the biggest difference in private unwitnessed arrests (OR 1.74, 95% CI 1.47 to 2.05). For 30-day survival, the biggest differences were in public witnessed arrests with 26.0% (95% CI 22.4% to 29.7%) higher survival in highest income compared with lowest income patients. Had bystander CPR been the same for lowest income as for highest income patients, then survival would be 25.3% (95% CI 21.5% to 29.0%) higher in highest income compared with lowest income patients, resulting in elimination of 0.79% (95% CI 0.08% to 1.50%) of the income disparity in survival. Similar trends but smaller were observed in low and high-income patients, the other three subgroups and with education instead of income. From 2002 to 2014, increases were observed in both CPR and survival in all income groups.

Conclusion Overall, lower socioeconomic status was associated with poorer prehospital factors and survival after OHCA that was not explained by patient or cardiac arrest-related factors.

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INTRODUCTION

Despite improvements in out-of-hospital cardiac arrest (OHCA) management and survival over time,[1 2] OHCA still remains a major health problem worldwide.[1–4] A common aim has been to identify factors that could guide future healthcare investments. Especially bystander interventions with cardiopulmonary resuscitation (CPR) and defibrillation have been a main focus with observed effect on survival.[1 2] However, further improvements are warranted, and in 2015 the Institute of Medicine, USA, published a report calling for studies focusing especially on socioeconomic differences in patients with OHCA to help target future interventions.[5]

Socioeconomic differences can be challenging to examine due to its multiple dimensions and complexity that are often affected by many different factors.[6–8] Furthermore, socioeconomic differences can be examined both on area level of the OHCA location illuminating important areas for targeted interventions, and on patient level that has been found with a higher predictive value for outcomes.[7] Until now, OHCA studies have primarily focused on area-level socioeconomic factors with associations noted between higher socioeconomic status and positive prognostic factors as higher rates of witnessed arrests, bystander CPR and defibrillation,[9–12] whereas data on survival are more conflicting.[10 12]

However, it still remains unclear how patient socioeconomic factors are associated with bystander CPR and survival after OHCA overall and over time, as well as whether a potential socioeconomic difference in bystander CPR might be associated with disparities in 30-day survival. Therefore, to help improve future strategies, this nationwide study explored patient socioeconomic factors in patients with OHCA overall and over time with the hypothesis that higher socioeconomic position would be associated with higher survival, potentially mediated through increased bystander CPR.

METHODS

Data sources

This nationwide study was based on the Danish Cardiac Arrest Registry[2] that includes all patients with a resuscitation attempt and holds detailed information of date and location of OHCA (private/public location), witnessed status by bystander or the emergency medical services (EMS), bystander CPR or defibrillation, first registered heart rhythm (shockable/non-shockable), estimated time interval from recognition of arrest to EMS rhythm analysis (based on time of 911 call and/or interview of on-scene bystanders) and survival status on

12.2. Paper II: Socioeconomic differences in coronary procedures and survival after out-of-hospital cardiac arrest: A nationwide Danish study.

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Clinical paper

Socioeconomic differences in coronary procedures and survival after out-of-hospital cardiac arrest: A nationwide Danish study

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Abstract

Aim: It remains unclear whether socioeconomic differences exist in post-resuscitation care in out-of-hospital cardiac arrests (OHCA). We aimed to examine socioeconomic differences in coronary procedures and survival after OHCA.

Methods: OHCA patients ≥30 years of cardiac cause with a hospital admission from the Danish Cardiac Arrest Registry, 2001–2014, were divided according to quartiles of household income (lowest, low, high, highest). Associations of income, coronary procedures and 30-day survival were examined by age-standardized incidence rates and incidence rate ratios (IRR), and by logistic regression.

Results: A total of 6105 patients were included. Higher-income patients were younger, males and had less comorbidity-burden. Higher-income patients had higher incidence rates for coronary angiographies both day 0–1 and day 2–7 after OHCA (day 0–1: highest: IRR 1.79, 95%CI 1.46–2.21; high: IRR 1.28, 95%CI 1.10–1.51; low: IRR 1.05, 95%CI 0.90–1.23), compared to lowest. Fifty-four percentage of the patients undergoing a coronary angiography received percutaneous-coronary-intervention or coronary-artery-bypass-grafting with no difference among three of the four groups, but lower IRR in low-income patients (IRR 0.74, 95%CI 0.61–0.89) compared to lowest. Higher-income patients had also higher odds for 30-day survival compared to lowest, both in patients with (highest: OR 1.61, 95%CI 1.12–2.32; high: OR 1.13, 95%CI 0.80–1.60; low: OR 1.14, 95%CI 0.81–1.61) and without (highest: OR 2.54, 95%CI 1.83–3.53; high: OR 1.41, 95%CI 1.06–1.87; low: OR 1.12, 95%CI 0.86–1.47) coronary angiography day 0–1.

Conclusion: Higher-income patients were found associated with more performed coronary angiographies after OHCA, and higher odds for 30-day survival.

Keywords: OHCA, Survival, Socioeconomic status, Coronary procedures

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12.3. Paper III: Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status.

Long-term outcomes after out-of-hospital cardiac arrest in relation to socioeconomic status

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Abstract

Aims: This study aimed to examine whether socioeconomic differences exist in long-term outcomes after OHCA.

Methods: We included 2,309 30-day OHCA survivors ≥30 years from the Danish Cardiac Arrest Registry, 2001-2014, divided in tertiles of household income (low, medium, high). Standardized absolute probabilities and probability differences of the outcomes were estimated using g-formula based on logistic regression and adjusted for potential confounders.

Results: High-income compared to low-income patients had the highest 1-year (96.4% vs. 84.2%) and 5-year (87.6% vs. 64.1%) survival, and the lowest 1-year (11.3% vs. 7.4%) and 5-year (13.7% vs. 8.6%) risk of anoxic brain damage/nursing home admission. The corresponding standardized probability differences were 8.2% (95%CI 4.7 to 11.6%) and 11.9% (95%CI 6.9 to 16.9%) for 1- and 5-year survival, respectively; and -4.5% (95%CI -8.2 to -1.2%) and -5.0% (95%CI -8.6 to -1.5%) for 1- and 5-year risk of anoxic brain damage/nursing home admission, respectively. Among 831 patients <66 years working prior to OHCA, 72.1% returned to work within 1 year and 80.8% within 5 years. High-income compared to low-income patients had the highest chance of 1-year (76.4% vs. 58.8%) and 5-year (85.3% vs. 70.6%) return to work with the corresponding absolute probability difference of 18.0% (95%CI 3.8-32.7%) for 1-year and 14.1% (95%CI 1.0-28.2%) for 5-year.

Conclusion: Patients of high socioeconomic status had higher probability of long-term survival and return to work, as well as lower risk of anoxic brain damage or nursing home admission after OHCA compared to patients of low socioeconomic status.

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