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GEOGRAPHICAL VARIATIONS AND FUNCTIONAL OUTCOME AFTER OUT-OF-HOSPITAL CARDIAC ARREST IN DENMARK

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Summary

Survival after out-of-hospital cardiac arrest (OHCA) has dramatically increased in later years, both in Denmark and internationally. In Denmark in particular, we have seen a fourfold increase in survival over the past two decades.(1–3) While several aspects of improving preparedness and survival have been explored, especially in Denmark due to its unique variety of national registries, certain areas remain relatively unexplored.(4) These areas include a geographical approach to the preparedness and a more sophisticated approach to outcome than merely survival.

This thesis aims to fill some of the gap through three manuscripts that

1. Investigates incidence of prior OHCAs in Denmark, and attempts to predict areas of high risk in the future, and provide a model for predicting such areas.
2. Investigate survival of prior OHCAs according to geographical characteristics
3. Investigate the need for antidepressants and anxiolytics after OHCA survival and the influence of pre-hospital factors on outcome

For study one we recorded 12,366 valid OHCAs. 65% of these occurred in 3.6% of the total area, specifically in areas with no public points of interest, 10 or more residents per hectare. The points of interest with the highest annual risk of at least one OHCA were malls (41.6‰) and shopping streets (39.88‰) ; however, these points of interest account for a very small proportion of both geography and incidence. Areas with a nighttime population of 5.6-15 had an annual risk of at least one OHCA of 6.61‰ and areas with a nighttime population of 16-965 had an annual risk of 20.58‰.

For study two we identified 8,971 witnessed OHCAs of which 71.5% happened in residential areas. Of these 53,2% happened in the most densely populated third of the geography (12 persons or more per hectare). This area group had a median EMS response time of six minutes, whereas the most sparsely populated area group (1.8-4 persons per hectare) had a corresponding median of 10 minutes. Witnessed arrests in public amounted to 2,558 and also had a median EMS response time of six minutes. 30-day survival was highest in public arrests (38.5%, 95% Confidence Interval (CI) [36.9;40.1]), and varied only slightly with no statistical significance between OHCAs in densely and sparsely populated areas from 14.8% (95% CI [14.4;15.2]) and 13.4% (95% CI [12.2;14.7]).

Of 2,018 30-day survivors in study III from 2001 to 2011 without prior use of antidepressants and/or anxiolytics 242 (11.2%) were prescribed an antidepressant and 165 (8.2%) were prescribed an anxiolytic drug during the first year after OHCA. Cardiac arrest witnessed by

bystander (Hazard Ratio(HR) 0.63 (95% CI [0.43;0.93]) and bystander cardiopulmonary resuscitation (HR 0.73 (95% CI [0.53;0.99]), were in multivariable analyses associated with less prescriptions of antidepressants within follow-up period. Similar results were seen in prescriptions of anxiolytics: cardiac arrest witnessed by bystander (HR 0.57 (95% CI [0.36;0.90]), and bystander cardiopulmonary resuscitation (HR 0.57 (95% CI [0.39;0.83]).

This thesis shows that the bulk of OHCAs in Denmark happen in densely populated residential areas. Geographical predictors of incidence are certain public points of interest such as malls and shopping streets. Survival was not significantly different in sparsely- and densely populated residential areas, while OHCAs occurring in public places had a significantly higher survival rate than in all residential areas. Among OHCA survivors generally, there was a need for either antidepressants and/or anxiolytics within a year after arrest in roughly one of ten cases, and receiving bystander CPR was negatively associated with such need.

Danish Summary (Danske Resumé)

Overlevelse efter hjertestop udenfor hospital (OHCA) er steget dramatisk både i Danmark og internationalt i løbet af de seneste år. Danmark har gennemgået en særlig flot udvikling med en firedobling i overlevelse over de seneste to årtier.(1–3) Særligt i Danmark, hvor de mange nationale registre giver særlige muligheder, er mange områder undersøgt for at forbedre parathed til- og overlevelse efter hjertestop udenfor hospital, men nogle indgangsvinkler er i det store hele uudforskede.(4) Nogle af disse områder er en mere geografisk tilgang til paratheden og en mere nuanceret tilgang til efterforløbet efter hjertestop udenfor hospital end simpel overlevelse. Denne afhandling stiler efter at udfylde nogle af disse huller igennem tre projekter som:

1. Undersøge områder med tidligere forekomst af hjertestop udenfor hospital og ud fra disse forudsige i hvilke områder risikoen for hjertestop i fremtiden er høj, og lave en model til generel forudsigelse af områder med stor risiko
2. Undersøge overlevelsen efter tidligere hjertestop udenfor hospital fordelt på geografiske områder
3. Undersøge behovet for antidepressiver og angstmedicin efter hjertestop udenfor hospital og hvilke præhospitale faktorer som påvirker dette

Til det første studie fandt vi 12.366 brugbare hjertestop. 65% af disse skete på 3,6% af Danmarks totale areal. Mere specifikt i de områder hvor der ikke var nogen særlig, offentlig aktivitet som gågade eller shoppingcenter og mere end 10 beboere pr. hektar.

Til studie nummer to identificerede vi 8.971 bevidnede hjertestop, hvoraf 71,5% skete i beboelsesområder. Af disse igen fandt 53,2% sted i den tættest befolkede tredjedel af beboelsesområder (12 eller flere personer pr hektar). Disse områder havde en median responstid på seks minutter, mens den tyndest befolkede tredjedel af områderne (1,8-4 personer pr. hektar) havde en median responstid på 10 minutter. I alt 2.558 bevidnede hjertestop fandt sted i det offentlige rum, og disse områder havde også en median responstid på seks minutter. 30-dages overlevelsen var højest efter hjertestop som fandt sted i det offentlige rum (38,5%, 95% sikkerhedsinterval (SI) [36,9;40,1]), mens overlevelsen efter hjertestop i private hjem varierede ganske lidt, og uden statistisk signifikans mellem de tættest og tyndest befolkede områder mellem henholdsvis 4,8% (95% SI [14,4;15,2]) og 13,4% (95% SI [12,2;14,7]).

Ud af 2.018 30-dages overlevere mellem 2001 og 2011 uden tidligere forbrug af antidepressiv- og/eller angstmedicin indløste 242 (11,2%) en recept på antidepressiva og 165 (8,2%) indløste en recept på angstmedicin indenfor det første år efter deres hjertestop udenfor hospital. Bevidnet

hjertestop hazard ratio(HR) 0,63 (95% SI [0,43;0,93]) og hjerte-lungeredning inden ambulancens ankomst HR 0,73 (95% SI [0,53;0,99]) var i multivariat analyse associeret med færre indløste recepter på antidepressiva. Det samme gjorde sig gældende for indløste recepter på angsmedicin: Bevidnet hjertestop HR 0,57 (95% SI 0,36;0,90) og hjerte-lungeredning inden ambulancens ankomst HR 0,57 (95% SI 0,39;0,83).

Denne afhandlinger viser, at langt størstedelen af hjertestop udenfor hospital i Danmark sker i tæt befolkede beboelsesområder. Geografiske med stor risiko for fremtidige hjertestop er bestemte offentlige områder med særlig aktivitet, eksempelvis gågader og shoppingcentre. Overlevelsesraterne var ikke signifikant forskellige i tyndt- og tætbefolkede beboelsesområder, mens overlevelsesraten blandt hjertestop som fandt sted i det offentlige rum var signifikant højere end i alle beboelsesområder. Blandt dem som overlevede havde i omegnen af hver tiende behov for antidepressiv- og angstmedicin indenfor et år efter deres hjertestop, og det er modtage hjerte-lungeredning inden ambulancens ankomst er associeret med et mindre behov.

This PhD is based on the following papers

Predicting OHCA: A geospatial and demographic approach; Kristian Bundgaard Ringgren, Vilde Ung, Thomas Alexander Gerds, Kristian Hay Kragholm, Peter Ascanius Jacobsen, Filip Lyng Lindgren, Anne Juul Jørgensen, Helle Collatz Christensen, Elisabeth Helen Anna Mills, Louise Kollander Jakobsen, Harman Yonis, Carolina Malta Hansen, MD, Fredrik Folke, Freddy Lippert, Christian Torp-Pedersen

Out-of-hospital Cardiac Arrest: Does rurality decrease chances of survival?; Kristian Bundgaard Ringgren, Kristian Hay Kragholm, Filip Lyng Lindgren, Peter Ascanius Jacobsen, Anne Juul Jørgensen, Helle Collatz Christensen, Elisabeth Helen Anna Mills, Louise Kollander Jakobsen, Harman Yonis, Fredrik Folke, Freddy Lippert, Christian Torp-Pedersen
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This PhD was largely conducted in the confinement of my home office. Even before the breakout of COVID, practical circumstances dictated this. This had made for a very different process, and a digital work environment later shared by millions. The deficit of human interaction has no doubt intensified the inward journey and the time has no doubt been a test of self-discipline. Fortunately, solace in the solitariness was found in the profoundness of my collaborators and co-coders who have made for not only an extremely educational, but also evolving time.

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Table of Contents

1 Abbreviations

OHCA	Out of Hospital Cardiac Arrest
AED	Automated External Defibrillator
EMS	Emergency Medical Services
CPR	Cardiopulmonary Resuscitation
BLS	Basic Life Support
ROSC	Return of Spontaneous Circulation
ILCOR	International Liaison Committee on Resuscitation
GPS	Global Positioning System

2 Introduction

Cardiac arrest is the very definition of an acute illness. While is it has been shown that survivors generally fare acceptably in terms of neurological outcome, very little time can have a very large impact on outcome, not only in terms of survival, but also in quality of the life lead after survival.(5–10) This makes it not only interesting in terms of how well, and in particular fast, the health care system performs, but in particular with out-of-hospital cardiac arrest (OHCA) also what happens in the time between recognition of the cardiac arrest and arrival of the pre-hospital emergency medical services (EMS) scene.

To make matters even more interesting, it is well established that lay-persons have the capability to make a life-saving difference with relatively simple, widely applicable measures.(4,9,11–16) This has ignited a plethora of initiatives aimed at utilising and optimising bystander and community first responder effort before EMS arrival.(17–21) This becomes important because in reality, while the EMS is often on scene within very few minutes, it is unrealistic to expect the EMS to be able to provide short response times in more remote areas.(22–24) The pre-EMS effort aims at bringing the essential tools for basic life support (BLS) as close to the distressed person as possible in order to minimise the so-called low- or no-flow period, where both the brain and the heart receive less vital oxygen than needed.(25–31) Trying to bring BLS to the patient faster than the EMS can get there is a multifactorial and complex undertaking. First, it requires that the general population are aware that outcome after OHCA can be greatly improved if they act, and then it requires that they're informed about and trained in HOW to act.(32–36) Furthermore it requires an availability of the tools of the trade, mainly the automated external defibrillator, while useable only in patients with a shockable rhythm has proved to increase survival dramatically.(37–42)

The worldwide focus on OHCA materialised in Denmark in 2001 with the formation of the Danish Cardiac Arrest Registry, systematically recording data on each cardiac arrest where a resuscitative effort was initiated, as later suggested by the Global Resuscitation Alliance (GRA), a worldwide NGO co-founded by Danish researchers, as a basis of improving survival after OHCA.(1,43) Since then Denmark has long superseded the initial GRA goal of increasing survival by 50%, and newest reports indicate a three to four-fold increase in survival after OHCA in Denmark between 2001 and 2020, and Denmark has become a pioneer in the field. Looking at the reports from the Danish registry it is evident that both in terms of bystander intervention and clinical outcome Denmark is in the international OHCA elite. (24) This is in part because of a range of National initiatives to increase BLS knowledge and training including mandatory training in primary schools and drivers academies.(4) To improve the public availability of AEDs, a national AED network was formed in 2006, showing an increase in availability comparable to the one seen for survival up until today.(1,44) As it turns out, cardiac arrests taking place in public areas are easily influenced by the surge of willing- and ableness of the citizens and the increased availability of AEDs. Arrests in residential(non-public) areas, however, account for around 75% of OHCAs in Denmark, and as one would expect, CPR and AED usage before EMS arrival is less common in these areas.(1) This gave birth to the citizen first responder concept, which has since been implemented in different incarnations internationally, and throughout Denmark.(18,21,45–51)

To activate such citizen responders, first the OHCA needs to be recognized. While this might seem like a simple task, research has shown that it is anything but, and that even after focused training of dispatcher personnel the highest dispatch recognition rates are around 90%.(52–59) Recently this has fostered the creation of an artificial intelligence to assist the dispatcher in recognizing the OHCA.(60,61)

When it comes to investigating all the mentioned facets of recognizing and treating OHCA, Denmark offers a unique setting for epidemiological research in the field. On top of having a solid cardiac arrest and AED registry, this is because of the uniform publicly financed health care system and the Central Person Registry which allows linking OHCA data and patients to a range of information from other public registries regarding things such as hospitalizations, medicine, education, employment, economy and housing.(62–67)
This allows for a more refined investigation than simply characterising a patient as suffering an OHCA and being categorised as a survivor or not. Amongst other things, socio-economic and ethnic inequalities in both incidence, exposure and outcome has been demonstrated in Danish and international data.(68–75)

The potential of utilising knowledge of things like demographic risk factors concerning OHCA lies in targeting the pre-hospital health care system efficiently. Bearing in mind that the previously mentioned intervention strategies rely largely on geographical proximity, this requires a geographical interpretation of said risk factors. Previous works have investigated incidence and outcome in relation to geography and demographic characteristics with varying results. (22,76–79) In this aspect, the nationwide Danish registries allow for a detailed geographical mapping of demographic characteristics.

When examining outcome after OHCA, survival is the obvious first step, but it is also a crude measure, as survival can be with a very varying degree of functionality.(80–84) In this aspect the Danish registries are also a source of great opportunity, as they allow for a more detailed evaluation of post-arrest need for amongst other things medication and need for professional care or welfare checks.(10,85)

3 Aims

As is evident from the previous introduction, the time from cardiac arrest ensues to a rescuer, ideally equipped with an AED, or the EMS is present is critical. As this time is not only determined by the travel speed of the aforementioned, it is to an even higher degree determined by the travel distance. Diminishing the latter requires proximity, an area still under-explored in the field of OHCA. This thesis utilizes the potential of the nationwide Danish registries to examine OHCA in a geographical framework, and will investigate geographical differences of both incidence and survival after OHCA in Denmark. We aim to use this historical data to predict the future risk of cardiac arrests according to geographical areas. This will provide a basis of planning for geographical proximity initially by means of AED coverage.

Further, survival figures are stagnating, maybe because a further increase simply isn't biologically plausible, and this calls for a more refined way of measuring outcome if we are to continue to evaluate future efforts. Therefore this thesis will examine the need for psychotropic agents following survival after OHCA as a means of qualifying the quality of life led post-arrest.

4 Methods

4.1 The Danish Cardiac Arrest Registry

The basis of this thesis, like many before it, is the Danish Cardiac Arrest registry. The registry was founded in 2001 to enable research and quality assurance of the effort to improve outcomes after OHCA. The data resources are the five administrative regions in Denmark, and aside from pooling data to a nationwide registry, each region can use its own data for internal quality assurance. The administrative leaders of each administrative region have a seat in the board of the nationwide registry alongside representatives of the Danish Society of Cardiologists, Danish Society of Anaesthesiology and Intensive Care Medicine (this because, in Denmark, the prehospital domain falls under Anaesthesiologists, Danish Resuscitation Council, the Society of Heart Patients in Denmark (Hjerteforeningen) and a few specific clerical and academic members. The board of directors is dynamic, as are the positions represented, but several members of the board have sat since the registry's establishment. The board of directors defined, in 2001, the inclusion criterion for the registry, as any prehospital case where any kind of resuscitative effort was initiated, either before arrival of the EMS, or by the EMS itself.

The registry was formed on the basis of the 1993 *"Uniform reporting of data following out-of-hospital and in-hospital cardiac arrest--the Utstein style"*(86)**,** but while this defined some data points to collect, it was not specified how to define a cardiac arrest in the prehospital setup. This is because while it may be easy to identify abnormal breathing and lack of consciousness, it is somewhat inappropriate to include people who are found dead, and have been so for days, in a registry that aims to evaluate efforts to improve outcome, as being dead for a long time only leads to one possible outcome. Further, as in Denmark, only medical doctors are allowed to pronounce people dead hence terminate resuscitation, and the healthcare personnel often in charge of filling out the case report form were, and are, not medical doctors, but more often emergency medicine technicians or paramedics, the inclusion criterion could not rely on the assessment of a medical doctor. As such, the inclusion criterion was defined as stated above. It is however known to happen, that prehospital physicians arriving simultaneously with the primary ambulance decides that the patient who has ongoing resuscitation are with signs of irreversible death, and therefore counters the filing of an OHCA case report form, even though technically the patient should be included. Further, this caveat of the inclusion criterion makes inclusion rates depend on whether or not a physician is present at the scene. This is because the EMTs/Paramedics present on site are obliged to initiate resuscitation until a physician allows them to disengage, either by arriving on the scene or via radiotelephone. These challenges have led to a change in how survival is measured in general. Initially, survival was measured as a simple fraction of the included arrests that survived. This method was prone to change in account of the above mentioned challenges with uniform inclusion, because this had the potential to alter the denominator as well as the numerator. To avoid this, and impose a stable denominator, amount of people in the general population was implemented, leading to a survival measured as the number of survivors per 100.000 people in the background population, a method of fractionating that has received more resonance during the recent pandemic. Furthermore, the survival in the Utstein comparator group was implemented on recommendation by the International Liaison Committee on Resuscitation and includes only witnessed arrests where the first measured rhythm was measured as shockable.(87) This is a group that selects the best of cases, where the EMS is usually activated instantly after collapse, and while this method omits a large part of the OHCAs it is the most precise denominator when aiming to evaluate what difference the initiatives implemented makes, because the outcome is not predetermined by time form collapse to recognition. This also removes the uncertainty of inclusion, because there is no risk of a witnessed arrest being irreversibly dead on EMS arrival.

Initially, all the prehospital patient charts were analogue, and so too was the case report form, which is found in the appendix. As a digital version of the prehospital patient chart was implemented nationwide by 2016, the case report form was also digitised, and so multiple values were henceforth automatically recorded from the ambulances electronic equipment.

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The recorded values included were:

Variable	Possible values	Method of recording
CPR (Social security number)	All	Manually
Site of arrest	Residential/Nature/Trafficked area/Other	Manually
Date	DATE	Manually/ Automatically
Was the arrest witnessed by bystander prior to EMS arrival	No/Yes	Manually
Was CPR initiated prior to EMS arrival?	No/Yes	Manually
Did an AED deliver a shock prior to EMS arrival?	No/Yes, publicly available AED/Yes, other AED	Manually
Time of first AED shock prior to EMS arrival	TIME	Manually
Was a physician present on site at any time during the resuscitative attempt?	No/Yes, EMS physician/Yes, other physician	Manually
Was the arrest witnessed by the EMS (mutually exclusive with witnessed by bystander)	No/Yes	Manually
Was an ECG obtained by the EMS?	No/Yes	Manually
Time of ECG	TIME	Manually/ Automatically
Did the EMS deliver a shock?	No/Yes	Manually
Time of first EMS shock	TIME	Manually/ Automatically
First rhythm recorded by the EMS	Initially shockable/non-shockable, later free-text.	Manually
Was a return of spontaneous circulation (ROSC) achieved at any time?	No/Yes	Manually

Time of ROSC	TIME	Manually
Status at end of EMS treatment (delivery at hospital/termination of resuscitation)	Dead/Ongoing resuscitation/ROSC and unconscious/ROSC and conscious	Manually
Receiving hospital	TEXT	Manually
GPS coordinate of vehicle stop	GPS coordinate	Automatically

Furthermore, between 2001 and 2015, an approximate time of collapse was recorded, and a presumed cause of arrest was subsequently attached according to later received diagnoses and recorded causes of death.

WIth he implementation of the electronic prehospital patient chart came the opportunity to include not only an automated recording of certain key parameters, but also the option to go through all patient charts, even the ones without filed OHCA case reports, in search of cardiac arrests, but it also allowed for a manual, meticulous validation of each care report form on the basis of the entire prehospital patient chart. This validation process, along with a general validation of already recorded variables, enabled a secondary recording of specific information of interest. This enabled an exclusion of patients with recorded signs of irreversible death and the absence of a resuscitative attempt by the EMS. Further, data on whether or not an AED was applied but did not deliver a shock, if the arrest occurred during sports activities, and whether or not the arrest was caused by trauma, drowning, suicide or overdose, as recommended by the Utstein template to replace the previous presumed cause of arrest.(87) These variables are still being validated for use whereas the new, automatically recorded GPS coordinate of vehicle stop is being used in a plethora of scientific research, including this thesis.

4.2 Methods of geographical and predictive models

In Study I we attempted to predict the risk of a future OHCA for each individual hectare in Denmark. This method of operation deviates from the bulk of the current research on several levels. First and foremost, working with OHCA in a context of demographic features of the geographical setting incorporates the age of the population in the area where the OHCA occurred, not the age of the actual patient who suffered the OHCA. This way of analysing needs some getting adjusted to, as our results from both study I and study II cannot be interpreted as the individual's chance of surviving an OHCA, but rather as the general chance of survival after OHCA in a specific geographical setting. This can be hard to interpret, as we, with good reason, often strive to make research that is patient-centered. However, when the tools for improving patient care we are evaluating are not patient-centered, like providing prophylactic medicine, physical exercise or the like, but rather based on geography, like proximity of a volunteer responder, a publicly available AED or an ambulance, the information included should also be based on geography rather than the individual patient.

Secondly, the use of prediction models often makes clinical interpretation more complex than it would be in a simple descriptive study. This is especially the case when, like in study I, the models used for prediction are less commonly used as is the case for the random forest model. While most clinicians are familiar with the basics of logistic regression also used in study I, the random forest deserves further explanation. The basic cogwheel of the random (decision) forest is the decision tree. The goal of each tree is to predict a value on the basis of one or more attributes about each observation. In its simplest form it does so by making a tree with the root of the tree being the attribute that describes the outcome the most precisely in terms of a yes/no answer. For numeric values, values are split into a number of intervals and treated as either less or more than that value for each split. It then further branches out into, choosing the most descriptive attribute as the next branch. Ultimately, when no further division of data is done, either because there are no more variables to divide by, or because the value is pure, meaning that the returned chance of either outcome is 100%. As such, any decision tree will end up with a number of leaves. The decision made by the tree will then be the majority of outcomes for boolean values, and the mean of all leaf outputs for numeric values. Decision trees have limitations, some of which are being mitigated by constructing a forest of trees. The single decision tree is very sensitive to the specific dataset used, and particularly in smaller sample sizes, small variable variations can lead to radically different leaf decisions. The random forest chooses a random sample of the dataset (bootstrapping) and uses different select variables for each tree. This ultimately results in a series of trees and leaves which are aggregated into a single output value, as would have been the case with the simple decision tree. This process is called bagging (**b**ootstrapping and **agg**regating).

5 Studies

5.1 Study I

5.1.1 Background

Study I utilised data on demography in a geographical framework to make a prediction model in order to identify areas with high risk OHCA and provide a model for providing proximity of the pre-hospital setup, initially by placement of publicly available AEDs.

5.1.2 Methods

Data from the Danish Cardiac Arrest Registry was linked to both demographic and geographical data. All cardiac arrests with a valid GPS coordinate of ambulance arrival on scene from 2016-2019 were included. Cells were classified hierarchically according to presence of special activities within the cell, and in the absence of such by population density. The ranking was done based on an assumption of clinical importance level. As such, each cell was only included in the highest area group that matched the characteristics of the cell and adjusted for factors ranking lower in the hierarchy. Population was defined as the number of people with a registered residential address within the cell, whereas workforce was defined as the number of people registered with employment at an address within the cell.

Followingly, a prediction was made in order to predict the annual risk of OHCA within that cell, where the variables used for prediction were determined by which area group the cell adhered to. Models used for prediction were chosen partially from a clinical assumption that airports and malls were special areas unaffected by lower ranking characteristics. Subsequently, random forest was chosen as the strongest model for area groups with sufficient data and covariates, and logistic regression where these were insufficient for random forest. Models and covariates are shown in Table 1. This prediction was then compared to an assumption that future OHCAs will happen in the same areas as previous OHCAs without including the predator variables presented by comparing mean squared error of predictions.

5.1.2.a Table 1 - Variables and models used for prediction

Area group	**Predictor variables**	**Prediction model**
Airport	None	Average incidence
Mall	None	Average incidence
School	Pedestrian street w/multiple shops, public transport station, major road, night- and workforce, age 60+, non-western ethnicity and lower educational level	Random forest (num. trees =500)
Pedestrian street w/multiple shops	Public transport station, major road, night- and workforce, age 60+, non-western ethnicity and lower educational level	Random forest (num. trees =500)
Public transport Station	Major road, night- and workforce, age 60+, non-western ethnicity and lower educational level	Random forest (num. trees =500)
Major Road	Night- and workforce, age 60+, non-western ethnicity and lower educational level	Random forest (num. trees =40)
No SA, 100-1000 residents	Workforce, age 60+, non-western ethnicity and lower educational level	Logistic regression
No SA, 50-100 residents	Workforce, age 60+, non-western ethnicity and lower educational level	Logistic regression
No SA, 10-50 residents	Workforce, age 60+, non-western ethnicity and lower educational level	Logistic regression
No SA, 0-10 residents	Workforce, age 60+, non-western ethnicity and lower educational level	Logistic regression
No SA, only workforce	Workforce	Logistic regression

5.1.3 Results

19,090 valid OHCAs were included, and the mean annual rate of OHCA per cell peaked in the area group without special activity and a population density of 100-1000 residents per cell with a mean incidence rate of 9.7/year/cell. The area group with 50-100 residents per cell and no special activity also had a relatively high incidence rate of 5.5/cell/year. Area groups with special activities of historical high incidence rate were pedestrian streets with multiple shops and malls with rates of 5.8/year/cell and 4.9/year/cell respectively. These, and the historical incidence rates of the remaining area groups are represented in Table 2.

5.1.3.a Table 2 - Incidence and KM^2 according to area type and year

Area group	**Number**	**2016**	**2017**	**2018**	**2019**	**Mean**
Airport	KM^2 OHCAs (OHCAs/KM^2)	69 12 (0.2)	69 8 (0.1)	69 11 (0.2)	69 9 (0.1)	69 10 **(0.1)**
Mall	KM^2 OHCAs (OHCAs/KM^2)	7 32 (4.8)	7 41 (6.2)	7 28 (4.2)	7 29 (4.4)	7 32 **(4.9)**
School	KM^2 OHCAs (OHCAs/KM^2)	25 42 (1.7)	25 50 (2.0)	25 55 (2.2)	25 36 (1.4)	25 46 **(1.8)**
Pedestrian street w/multiple shops	KM^2 OHCAs (OHCAs/KM^2)	16 99 (6.0)	16 107 (6.5)	16 95 (5.8)	16 78 (4.7)	16 95 **(5.8)**
Public transport station	KM^2 OHCAs (OHCAs/KM^2)	5 16 (3.3)	5 17 (3.5)	5 14 (2.9)	5 11 (2.3)	5 14 **(3.0)**
Major Road	KM^2 OHCAs (OHCAs/KM^2)	1321 419 (0.3)	1321 399 (0.3)	1321 423 (0.3)	1321 380 (0.3)	1321 405 **(0.3)**
No SA, 100-1000 residents	KM^2 OHCAs (OHCAs/KM^2)	41 380 (9.2)	42 454 (10.9)	35 372 (10.7)	44 358 (8.1)	40 391 **(9.7)**
No SA, 50-100 residents	KM^2 OHCAs (OHCAs/KM^2)	79 427 (5.4)	79 459 (5.8)	73 427 (5.8)	82 419 (5.1)	78 433 **(5.5)**
No SA, 10-50 residents	KM^2 OHCAs (OHCAs/KM^2)	1334 2333 (1.7)	1343 2370 (1.8)	1294 2327 (1.8)	1347 2274 (1.7)	1330 2326 **(1.7)**
No SA, 0-10 residents	KM^2 OHCAs (OHCAs/KM^2)	2480 798 (0.3)	2476 811 (0.3)	2686 875 (0.3)	2503 910 (0.4)	2536 848 **(0.3)**
No SA, only workforce	KM^2 OHCAs (OHCAs/KM^2)	191 162 (0.8)	181 158 (0.9)	205 235 (1.1)	204 165 (0.8)	195 180 **(0.9)**

No SA, no residents or workforce	KM^2 OHCAs (OHCAs/KM^2)	37890 319 (0.0)	37894 271 (0.0)	37722 317 (0.0)	37834 273 (0.0)	37835 295 **(0.0)**

The result of benchmarking our prediction model with a "0-model" is shown in Table 3, where the mean squared error of the prediction proves lower in our selected prediction model across the board, indicating a better predictive performance.

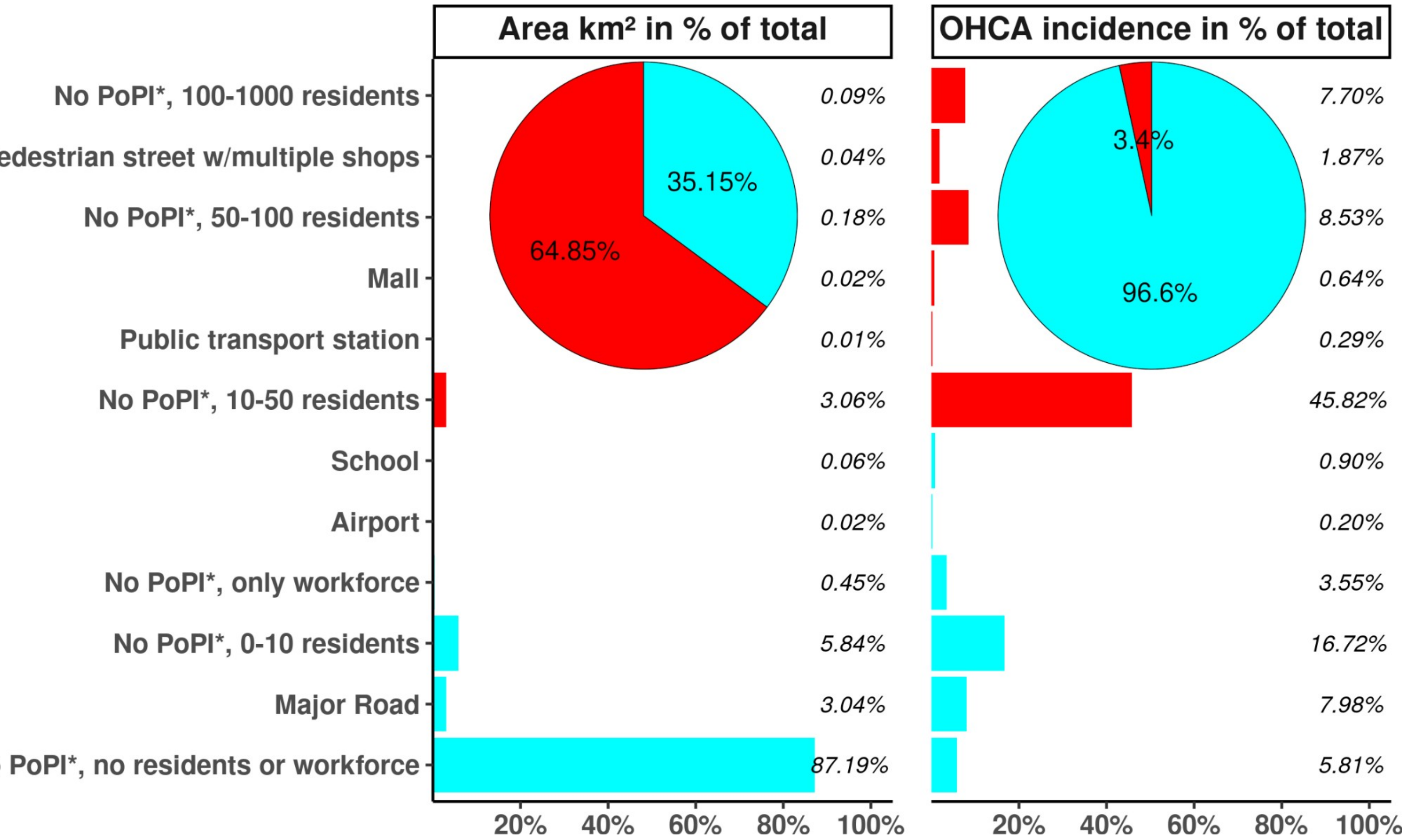
5.1.3.b Table 3 - Predictive performance

Area group	**Benchmark Brier score**	**Our model Brier score**
Airport	0.0019	0.0013
Mall	0.0466	0.039
School	0.0173	0.0129
Pedestrian street w/multiple shops	0.0553	0.0425
Public transport Station	0.0327	0.0228
Major Road	0.0035	0.0028
No PoPI*, 100-1000 residents	0.0811	0.0641
No PoPI*, 50-100 residents	0.0554	0.0444
No PoPI*, 10-50 residents	0.0203	0.0156
No PoPI*, 0-10 residents	0.0045	0.0035
No PoPI*, only workforce	0.009	0.0076

**PoPI: Point of Public Interest*

When including the areas containing public transport stations, schools and the area group 10-50 residents per cell and no special activity, the combined area constitutes 1.496km^2 annually corresponding to 3.4% of the total area of Denmark while they account for more than 65% of the incidence. The fact that the vast majority of OHCAs is concentrated within a very small part of the geographical area is depicted in Figure 1, where the percentages of the total incidence and total area respectively is depicted according to area group.

5.1.3.c Figure 1 - Area and incidence in percent of total, summed over years

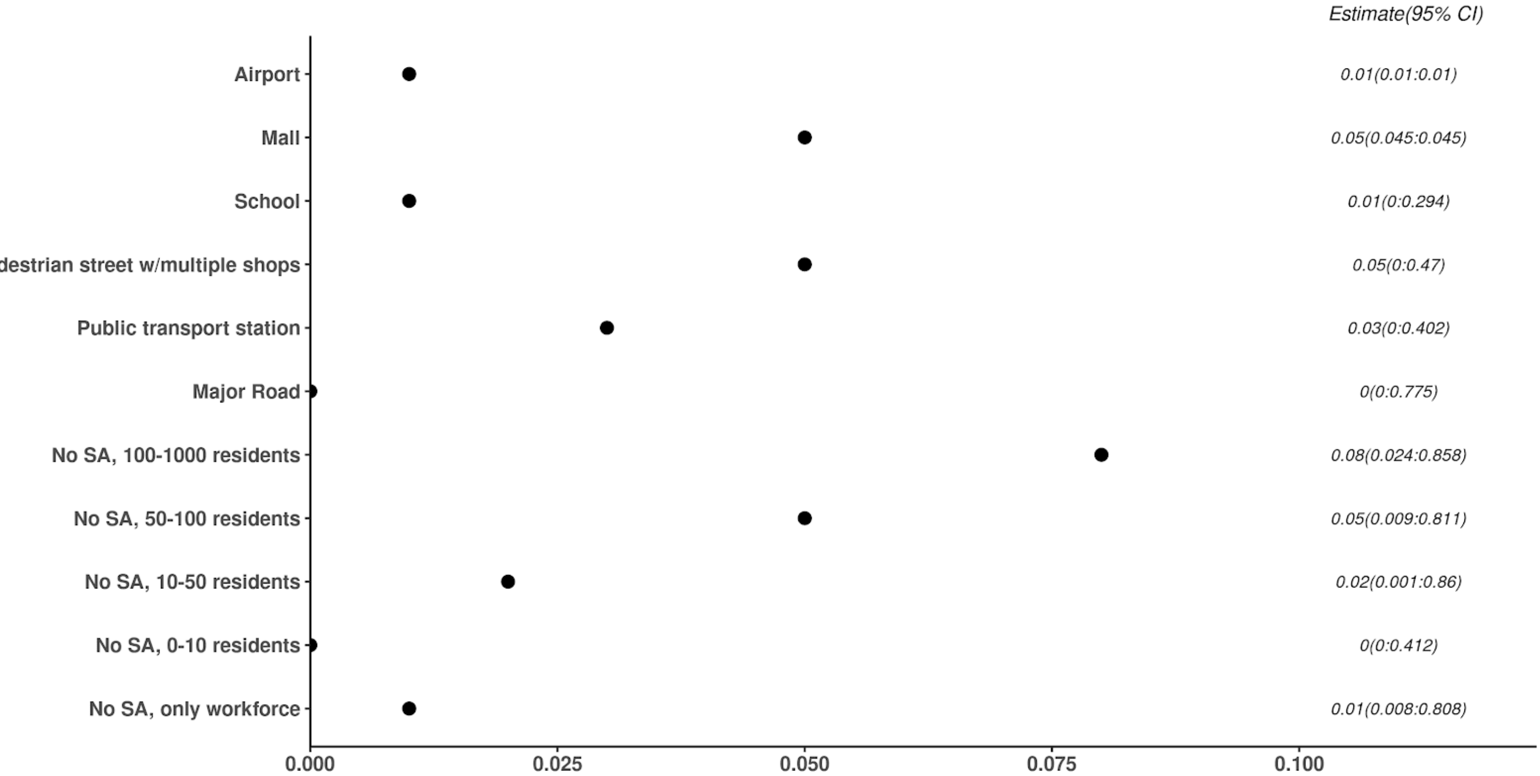


**PoPI: Point of Public Interets*

Barplot indicating area and incidence of each area group respectively, while pie chart depicts accumulated area and incidence of red and blue area groups respectively.

Previously mentioned area groups are correspondingly represented when predicting mean annual risk of at least one OHCA in the cells within each area group as depicted in Figure 2.

5.1.3.d Figure 2 - Mean predicted annual risk of at least one OHCA pr. cell

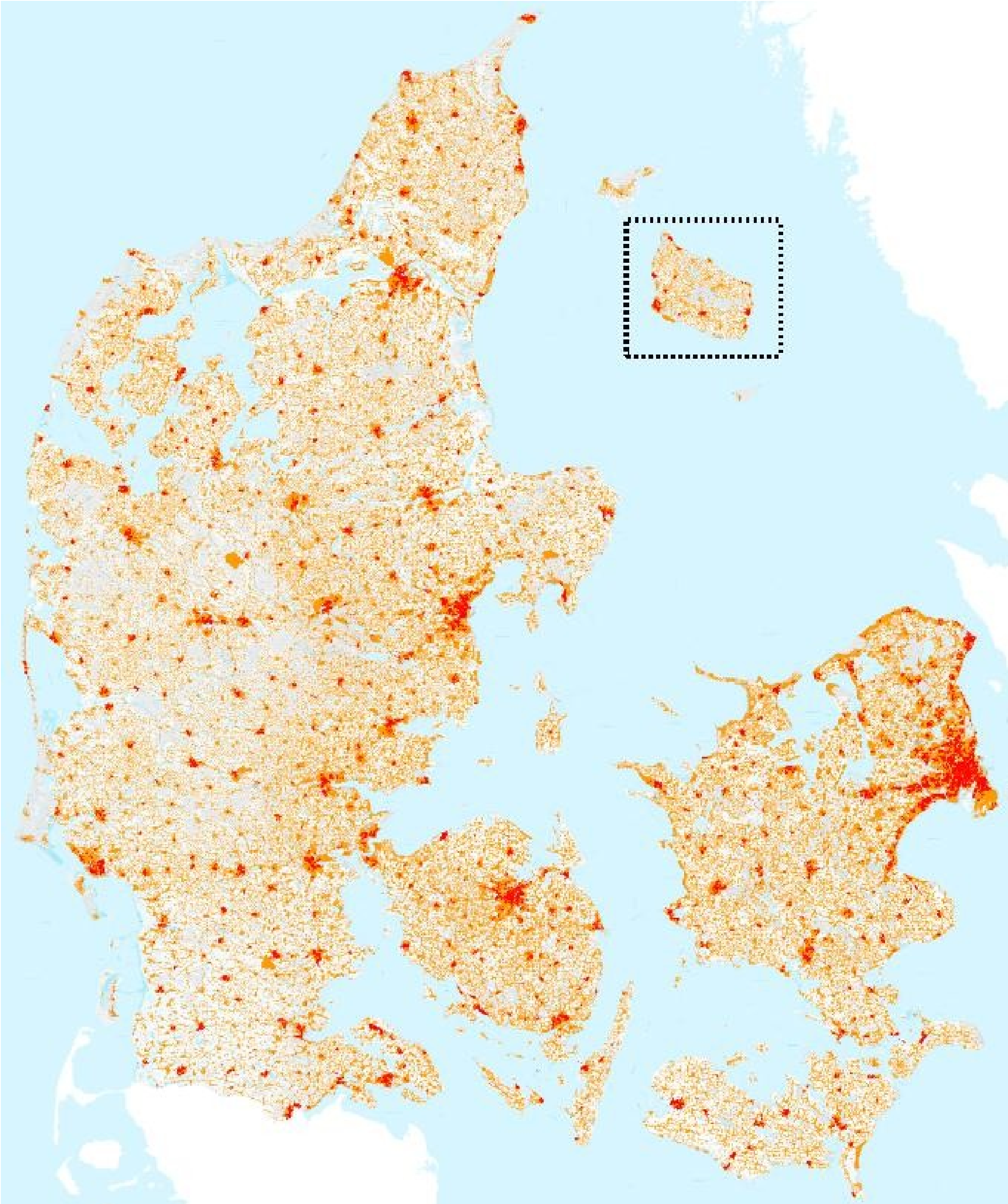


Dots depict point estimate for the mean predicted annual risk of at least one OHCA per cell in the group. 95% confidence intervals are presented as text to the right.

The predicted annual risk of at least one OHCA in the specific, singular cells is drawn on a map of Denmark in Figure 3.

5.1.3.e

5.1.3.f Figure 3 - Geographical representation of predicted annual risk of at least one OHCA



Predicted annual risk of at least one OHCA for each cell is plotted as orange for annual risk between 0 and 0.02, both excluded, and red for 0.02 and above. Cells with no colour have no predicted risk or a risk of 0.

5.1.4 Conclusion

The predicted annual risk of at least one OHCA is highest in certain areas with special activities, namely airports, malls and pedestrian streets with multiple shops and public transport stations and areas with no special activity and more than 10 residents. Combined, these groups constitute 3,6% of the total Danish area, and AED coverage of all these areas would be feasible with only one ninth of the currently available AEDs if placed strategically.

5.2 Study II

5.2.1 Background

Study II investigated the perception that the choice of rural living comes at the cost of good health care. This is in part because it seems obvious that it is going to take longer before any help arrives. This is particularly the case for time critical conditions where the EMS response time plays an important role. Further, the historical incidence and outcome on a geographical level was compared across the administrative regions of Denmark.

5.2.2 Methods

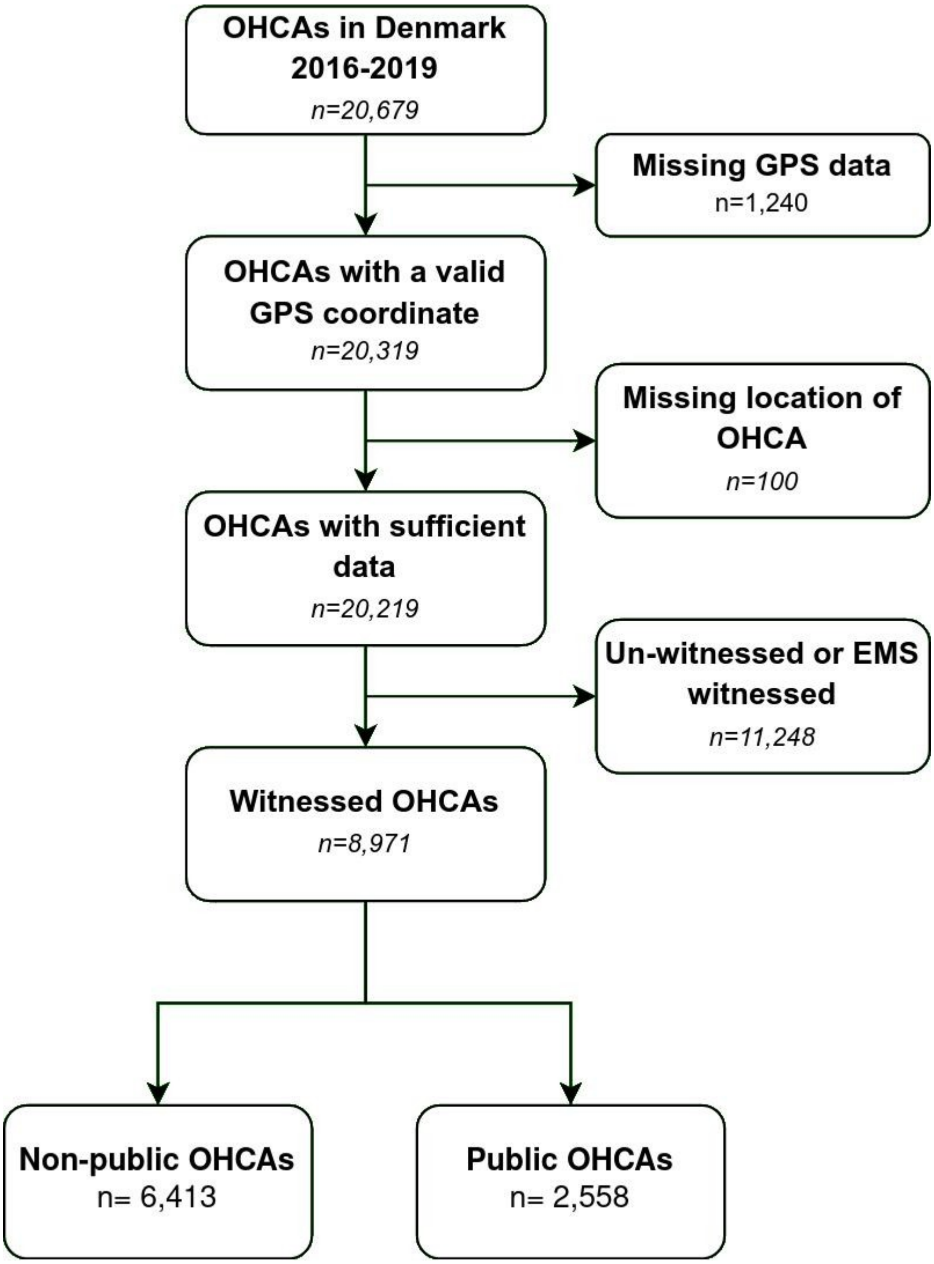
Only witnessed arrests in the period 2016-2019 were included in this study. This was done to minimise the influence of factors that aren't influenced by the health care services, as the medical emergency has to be recognized in order for the system to respond. As such, the time it takes for someone to arrive and alert the health care system might determine the outcome regardless of the quality of the subsequent health care services provided.

Arrests were categorised according to place of arrest as either public or residential using the Danish Cardiac Arrest Registry. The residential arrests were further subdivided into three categories of equal geographic size according to population density on a cell level of 100*100m excluding population densities not represented in all administrative regions and airports. Population was defined as the number of people with a registered residential address within the cell. Then EMS response incidence, EMS response time and 30-day survival was calculated according to geographical category, and further stratified according to which administrative region they occurred in.

5.2.3 Results

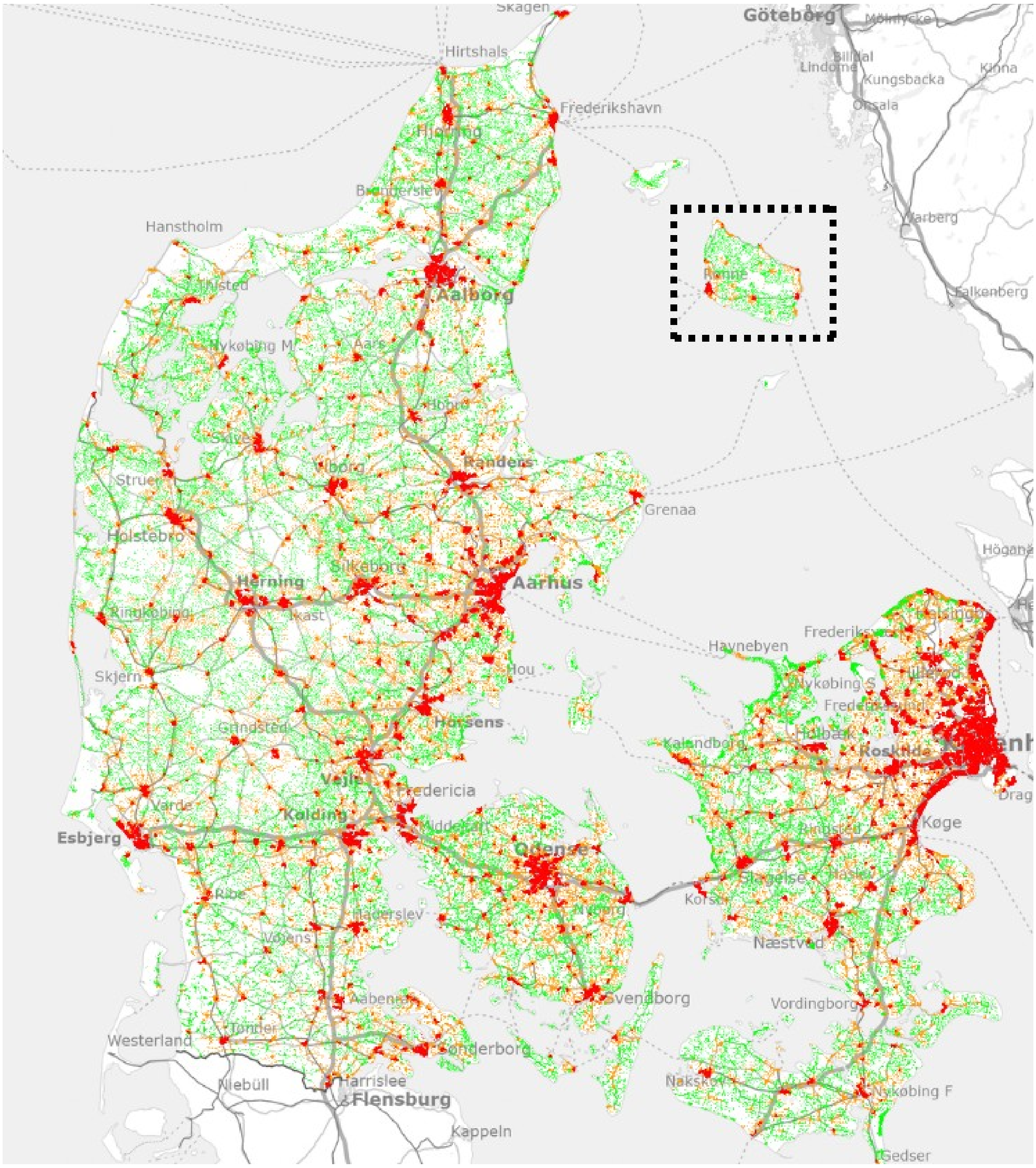
A total of 8,971 witnessed arrests were identified, of which 6,413 (71.5%) happened in residential areas. The full inclusion process is depicted in Figure 4.

5.2.3.a Figure 4 - Flowchart of selection of study population.



Three geographically equally sized groups of population density were formed as [1.8-4), [4-12) and [12-311], [indicating including and) indicating exclusion. The geographical distribution of these groups are depicted in Figure 5. Uncoloured cells are either unpopulated or so densely populated that they are not represented in all administrative regions (>311) or airports.

5.2.3.b Figure 5 - Population density in three groups



Green depicts the least densely populated areas (1.8-4], orange the more densely populated areas (4-12] and red the most densely populated areas (12-311)

5.2.3.c

The incidence distribution of OHCAs is shown in Table 3 as total and as stratified by administrative region. 392 (4.4%) witnessed OHCAs arrests took place in an area not included in the analysis according to above mentioned criteria. The majority (53.2%) of OHCAs happened in the most densely populated third of the geographical area.

5.2.3.d Table 4 - Distribution of OHCA according to population density group and administrative region

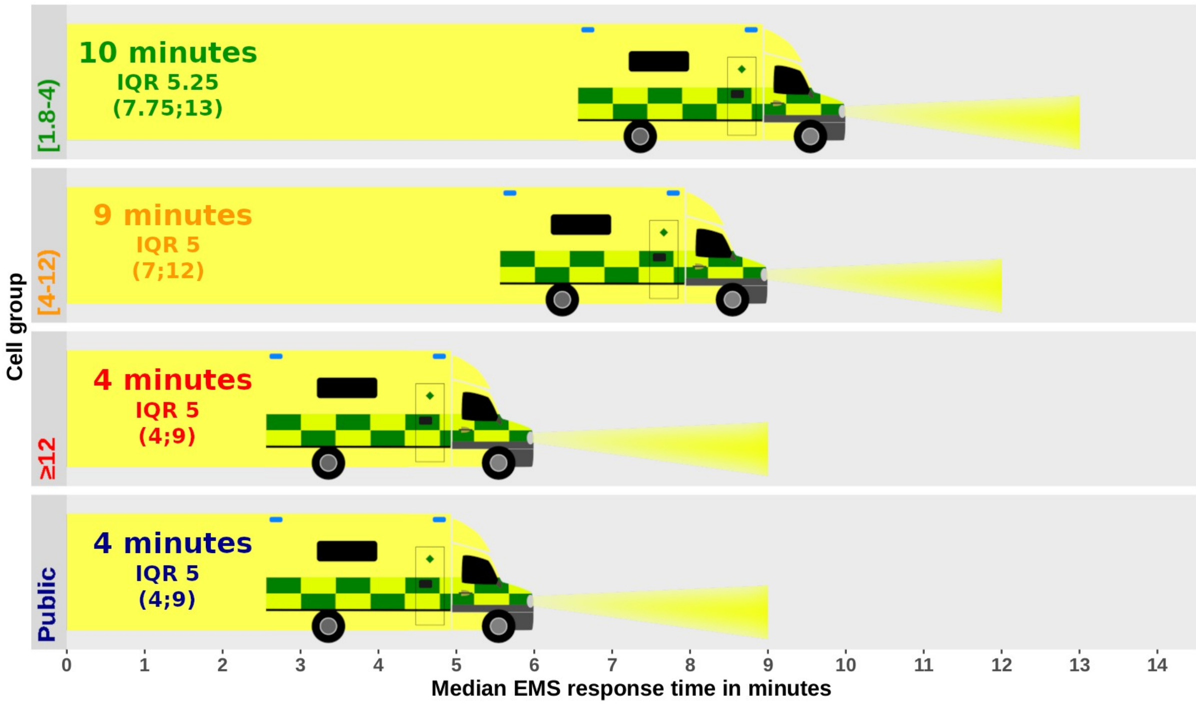
Population density group	***Capital Region***	***Central Denmark Region***	***North Denmark Region***	***South Denmark Region***	***Zealand Region***	***Total***
[1.8-4)	*39 (1.6%)*	*111 (6.0%)*	*84 (7.8%)*	*87 (4.8%)*	*115 (8.6%)*	*436 (5.1%)*
[4-12)	*108 (4.3%)*	*250 (13.6%)*	*173 (16.0%)*	*276 (15.4%)*	*215 (16.0%)*	*1022 (11.9%)*
≥12	*1549 (61.5%)*	*956 (51.9%)*	*495 (45.8%)*	*928 (51.7%)*	*635 (47.3%)*	*4563 (53.2%)*
Public	*822 (32.6%)*	*525 (28.5%)*	*329 (30.4%)*	*504 (28.1%)*	*378 (28.1%)*	*2558 (29.8%)*
Total	*2518 (100%)*	*1842 (100%)*	*1081 (100%)*	*1795 (100%)*	*1343 (100%)*	*8579 (100%)*

[ ]denotes inclusion of number, ( ) denotes exclusion.

EMS response time varied from a median of six minutes in the most densely populated area group and arrests in public places to 10 minutes in the least densely populated group. 732 (8.2%) arrests had missing values for. These response times, along with interquartile range, are depicted in Figure 6.

5.2.3.e

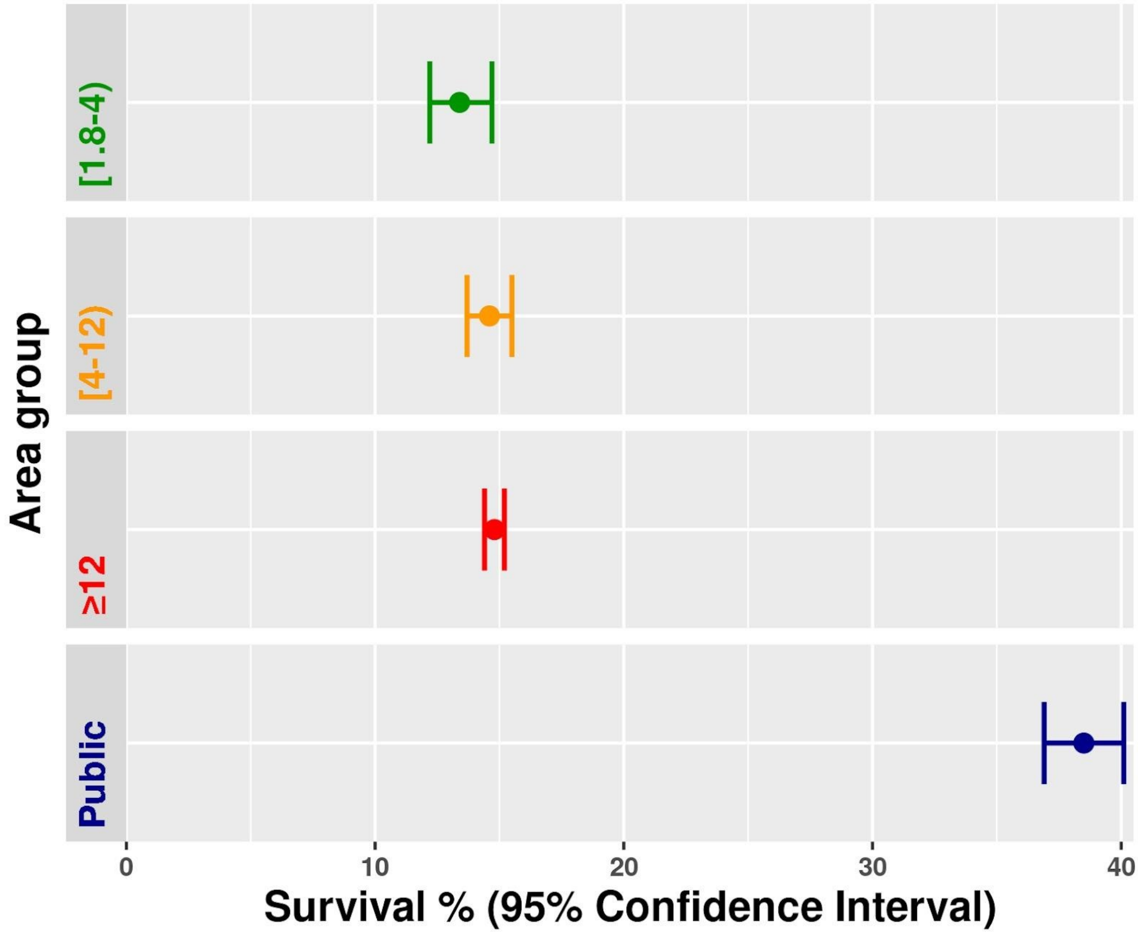
5.2.3.f Figure 6 - Median EMS response time in minutes according to population density



Front end of ambulances showing median response time, end of headlight depicting 3rd quartile and IQR presented under the median as text on to the left.

A total of 1,802 (21.1%) patients were alive 30 days after their OHCA. Figure 7 shows survival percentage stratified by the area group in which the OHCA occurred. The last populated area group had a survival rate of 13.4% (95% confidence interval (CI) [12.2;14.7]). Whereas the more densely populated areas had a survival rate of 14.6% (95% CI[13.7;15.5]), and the most densely populated group had a rate of 14.8% (95% CI[14.4;12.2]). The highest survival rate was found in OHCAs that occurred in public places of 38.5% (95%CI [36.9;40.1]).

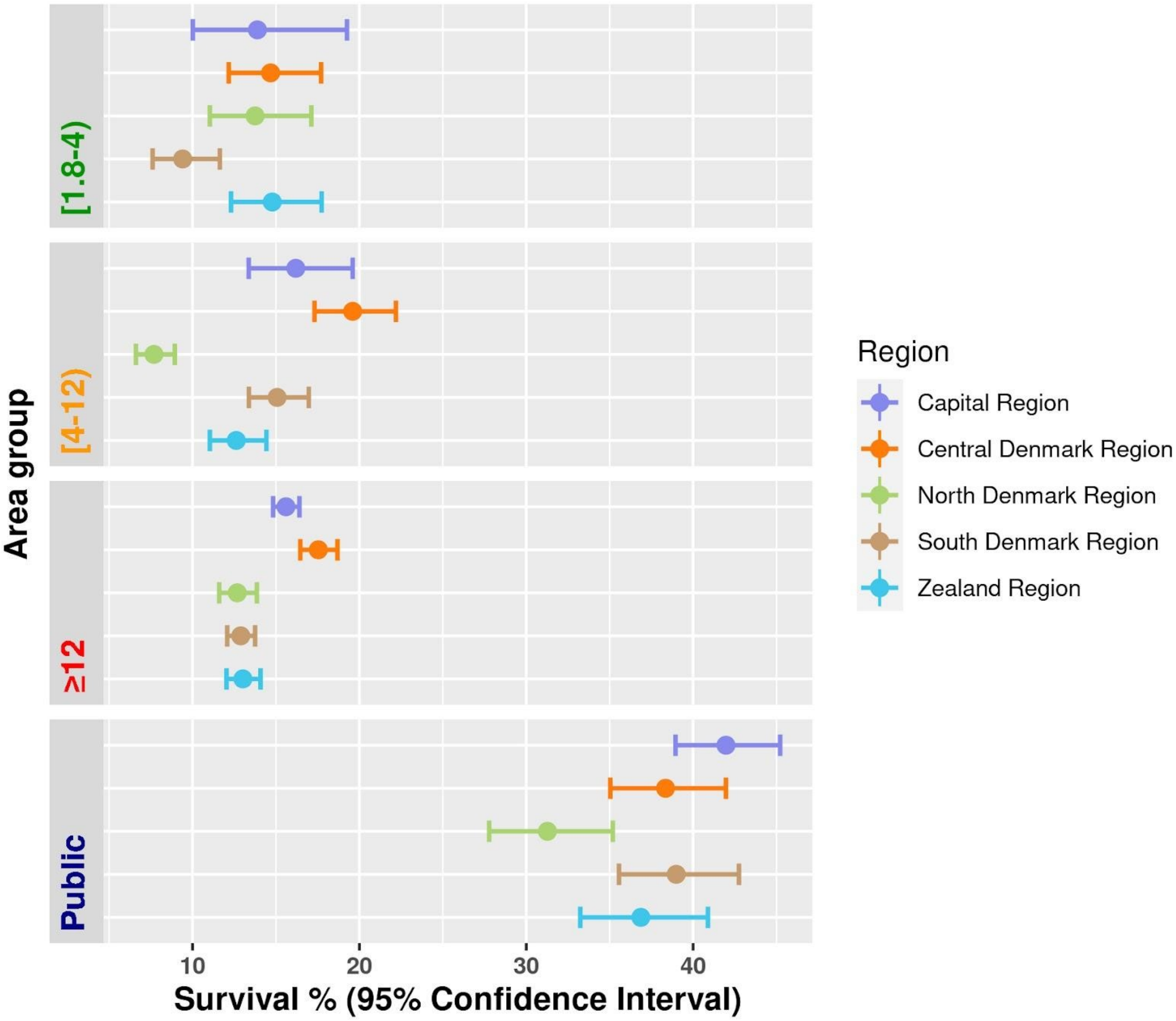
5.2.3.g Figure 7 - Survival in % according to area group



Dots represent survival percentage and lines indicate 95% confidence interval (CI). Colouring of dots and lines are according to area group.

Stratifying on administrative regions does not change this overall picture, and generally the survival rates show overlapping 95% confidence intervals and only a few outliers across regions. In particular, no region can be considered an outlier across area groups. These results are depicted in Figure 8.

5.2.3.h Figure 8 - Survival in % according to area group and administrative region



Dots represent survival percentage and lines indicate 95% confidence interval (CI).
Colouring of dots and lines are according to healthcare-divided.

5.2.4 Conclusion

Our study demonstrates that while EMS response times are longer in the rural areas, there is no statistically significant reduction in survival compared to the most densely populated areas. Further, when comparing survival between the administrative regions, significant differences in survival rates are limited to specific area groups, indicating that what differences there are, is dictated by geography rather than local decisions.

5.3 Study III

5.3.1 Background

Study III investigated frequency of redeemed prescriptions for antidepressants and/or anxiolytics as proxies for a reduced functional outcome after OHCA and investigated possible association between the hazard of redeeming such a prescription and receiving with bystander CPR.

5.3.2 Methods

Adult 30-day OHCA survivors from 2001 to 2011 prior use of antidepressants and/or anxiolytics, defined as redeemed prescriptions within 180 days prior to their arrest, were included. Follow-up period for new use after OHCA was one year. To compare usage with patients who had not experienced an OHCA, two controls matched by age and sex were identified according to dates maching each OHCA.

When comparing outcome of bystander CPR recipients and non-recipients, death was treated as a competing risk in the Cox proportional hazard models of which three were made, all with bystander CPR as exposure. 1) unadjusted; 2) adjusted for age and sex, and 3) adjusted for age, sex, year of arrest, Charlson comorbidity index, witnessed status and socioeconomic status.

5.3.3 Results

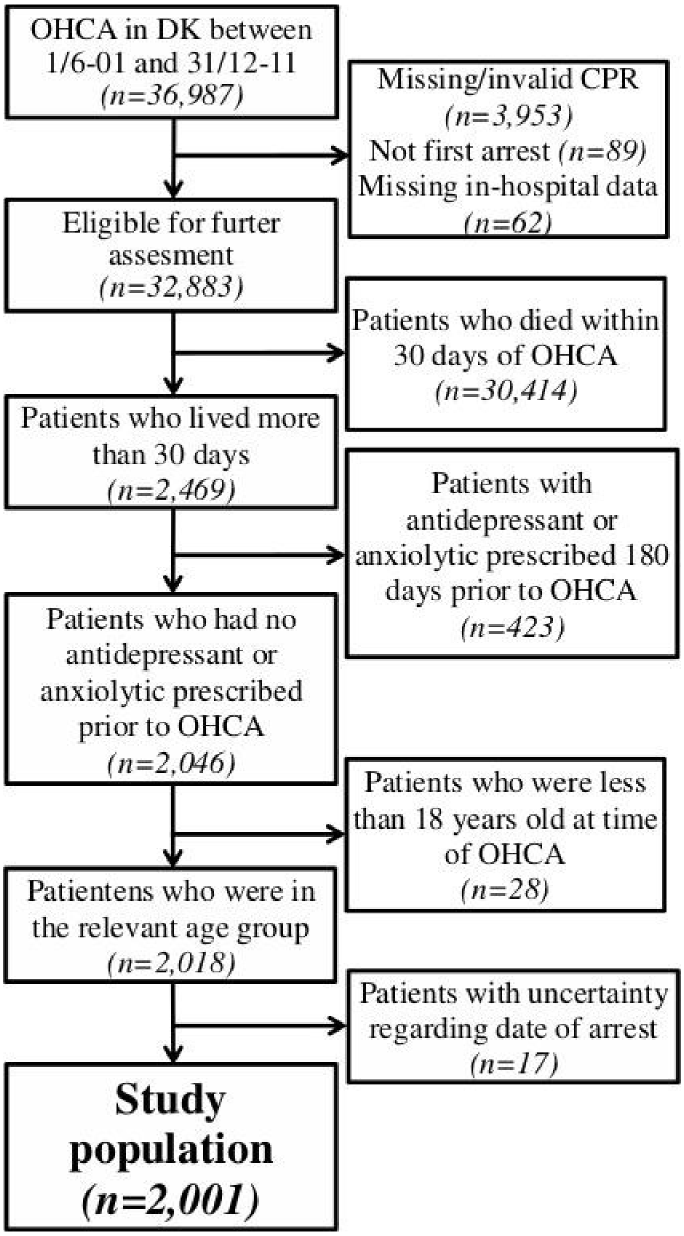
A total of 2,001 30-day survivors were identified with complete enough data to analyze. This inclusion is depicted in Figure 9. Of these patients without prior relevant medical prescriptions, 174 (8.6%) died within one year, whereas 240 (12.0%) and 163 (8.2%) redeemed a prescription for antidepressants and anxiolytics respectively. Persons who had not experienced an OHCA were found to redeem a first prescription for antidepressants in 7.5% of the cases and for anxiolytics in 5.2% of the cases within one year. These figures are depicted in Figure 10.

When comparing the rate of redeemed prescriptions between OHCA survivors that did, and did not receive bystander CPR, recipients were less likely to redeem a first prescription for both antidepressants (6.3% [95% CI 4.9–8.0%] versus 11.1% [95% CI 9.2–13.3%]) and anxiolytics 13.4% [95% CI 10.5–17.0%] versus 17.2% [95% CI 13.9–21.1%]).

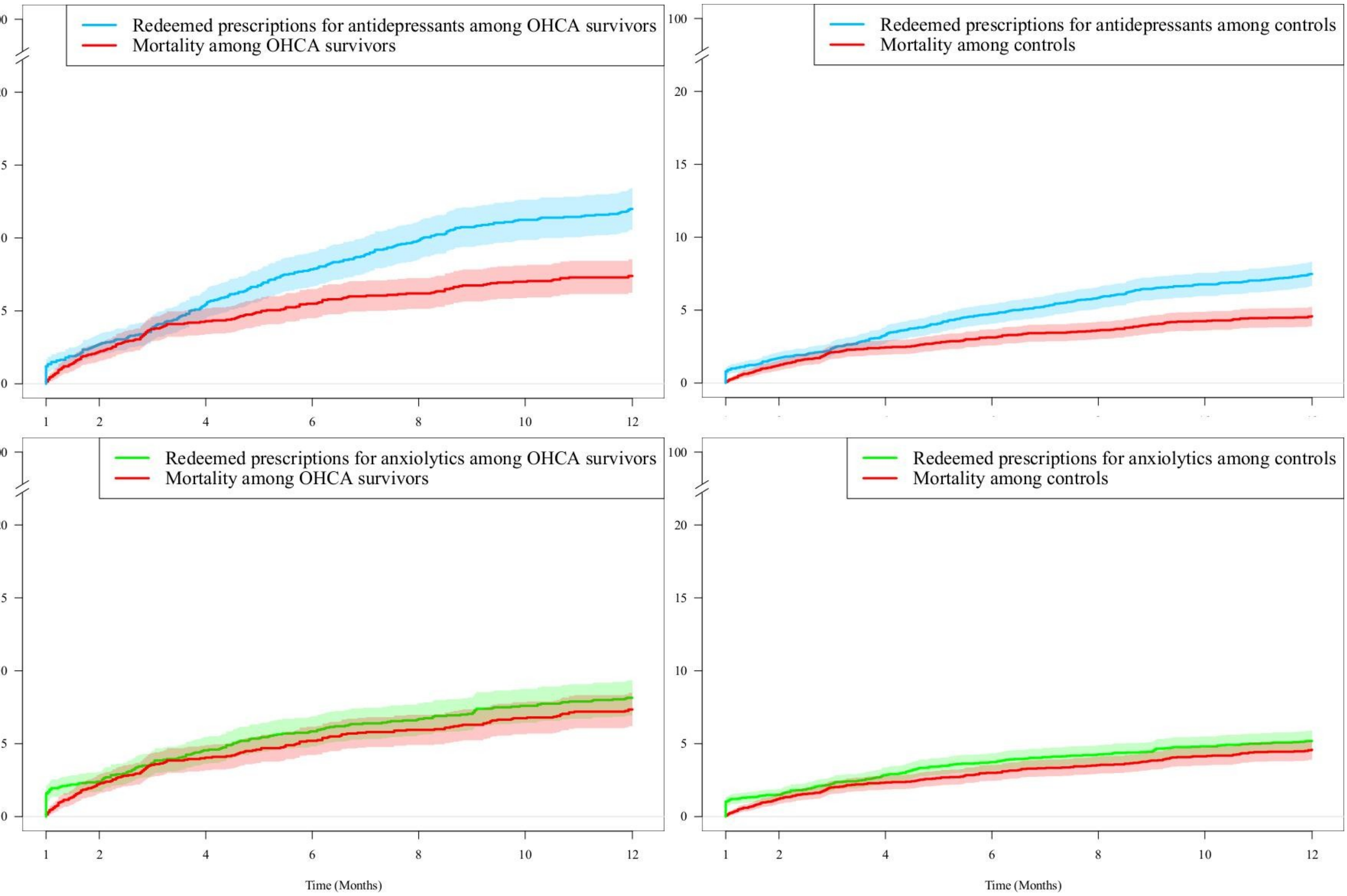
In an unadjusted Cox proportional hazards model the hazard ratio (HR) of redeeming a first prescription for antidepressants was 0.63 (95% CI 0.47-0.86) when receiving bystander CPR when compared to not receiving. When adjusting for age and sex, the corresponding ratio was 0.65 (95% CI 0.48-0.88), and when further adjusting for year of arrest, comorbidity, witnessed status and socioeconomic status the HR was 0.71 (95% CI 0.52-0.98) as per Figure 11.

The hazard ratio of redeeming a first prescription for an anxiolytic agent within one year of OHCA was 0.47 (95% CI 0.33-0.68) in unadjusted analysis, 0.49 (95% CI 0.34-0.70) when adjusting for age and sex and 0.55 (95% CI 0.38-0.81) when further adjusting for year of arrest, comorbidity, witnessed status and socioeconomic status as per Figure 12.

5.3.3.a Figure 9 - Flowchart of selection of study population.



5.3.3.b Figure 10 - Cumulative incidences of redeemed prescriptions for antidepressants and anxiolytics and mortality

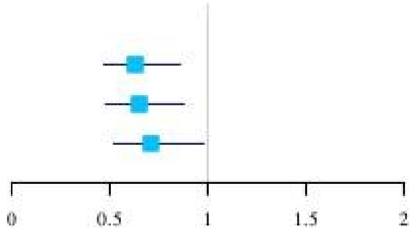


The blue and green lines depict the cumulative incidences of redeemed prescriptions for antidepressant and anxiolytic drugs, respectively, within one year after arrest. The red line depicts mortality. The shaded areas depict the 95% confidence intervals. Vertical axis: Cumulative incidence. Horizontal axis: Time (months).

5.3.3.c

5.3.3.d Figure 11 - Association between bystander CPR and redeemed prescriptions for antidepressants

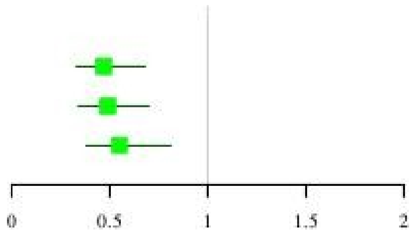
	HR	low 95%	high 95%	P
Bystander CPR, unadjusted	0.63	0.47	0.86	.003
Bystander CPR, adjusted*	0.65	0.48	0.88	.005
Bystander CPR, adjusted**	0.71	0.52	0.98	.035



*The square represents the hazard ratio (HR) and the associated line represents the 95% confidence interval (CI). EMS witnessed cases were excluded in these analyses. *Adjusted for age and sex. **Adjusted for age, sex, year of arrest (2001-2005 vs 2006-2011), Charlson comorbidity index (0 versus above 0), witness status (witnessed versus unwitnessed) and socioeconomic status (low, medium and high educational level).*

5.3.3.e Figure 12 - Association between bystander CPR and redeemed prescriptions for anxiolytics

	HR	low 95%	high 95%	P
Bystander CPR, unadjusted	0.47	0.33	0.68	<.001
Bystander CPR, adjusted*	0.49	0.34	0.70	<.001
Bystander CPR, adjusted**	0.55	0.38	0.81	.002



*The square represents the hazard ratio (HR) and the associated line represents the 95% confidence interval (CI). EMS witnessed cases were excluded in these analyses. *Adjusted for age and sex.**Adjusted for age, sex, year of arrest (2001-2005 vs 2006-2011), Charlson comorbidity index (0 versus above 0), witness status (witnessed versus unwitnessed) and socioeconomic status (low, medium and high educational level).*

5.3.4 Conclusion

Patients suffering from an OHCA have an increased frequency of starting a new use of antidepressants and anxiolytics than the background population. Receiving bystander CPR is associated with a lower hazard of a novel use of both therapies even in adjusted analysis. This supports the notion that bystander CPR has a potential to improve functional outcome among OHCA survivors.

6

7 Discussion

7.1 Study I

The findings in study I, that the risk of future OHCA incidence is high in geographical areas of high population density appears intuitive, but the degree to which the risk areas are consolidated is, to our knowledge, not previously shown in such a concise manner with nationwide, high completeness of data. While the mean predicted risk in the different area groups likely represents a broad spectrum of individual risks, as presented by broad confidence intervals in Figure 2, it is worth noting that even though the mean brier score does not prove a specific level of performance, predictions on a cell level performed better than a 0-model. The relatively small area of high predicted incidence characterised by a public point of interest pin-points a mismatch between the focus that these areas receive in terms of AED placement and the actual need for AEDs. This is a clinical debate that has been discussed previously, and focus on public locations has been suggested.(88) Said study demonstrates a higher rate of shockable rhythms in public arrests, and it can be speculated, that public arrests by proxy constitute a select, healthier OHCA population because their frailty level allows them to go outside. In the Danish cohort, however, which rhythms patients present to an AED prior to EMS arrival is still not systematically recorded, and could provide valuable information to this debate.

A previous study of geographical data has shown the importance of age and socioeconomic status in incidence and outcome, but did not consider population density.(72) Another study on geography of OHCA using a similar methodology did not disclose what factors were included, not allowing for external use.(79) On the contrary, our findings pave the way for predicting sites of OHCAs in the future by specifying socioeconomic factors that should be included in geographical incidence prediction models in order to increase statistical performance.

7.2 Study II

On the same geographical basis the evaluation of survival after suffering a witnessed OHCA shows no statistically significant difference between urban and rural areas, but in accordance with study I also revealed that the largest proportion of OHCAs happened in more densely populated areas. Insignificant differences in survival across population density areas seems counter-intuitive when considering the prolonged EMS-response time in less densely populated areas which is shown to have strong negative association with survival, but indicates that EMS-response time is the sole factor determining survival, as has previously been demonstrated by temporal increase in survival despite prolongation of EMS-response time in the Victorian cohort. (5,7,89,90) When comparing to OHCA occurring in public OHCAs in residential areas survival is substantially higher in public arrests, which is in line with previous Danish studies. (91,92) This is in spite of EMS-response times comparable to residential arrests in densely populated areas, and likely related to an increased defibrillation rate.(24,93) Existing literature is conflicted in terms of survival according to population density. Some found increased survival in more densely populated areas, some found no difference, and some found crude differences that did not persist after adjusting for relevant covariates. (22,23,76–78,94,95) Most previous studies included both witnessed and unwitnessed arrests. Doing so ignores the pivotal role of what happens between collapse and discovery, which in unwitnessed cases might well constitute the most important predictor of survival. This is also a phase of an OHCA that is non-modifiable, and as such may be considered of less interest. Future technologies such as smart-watches detecting OHCAs might alter this perspective. What is modifiable is how the time from recognition to EMS arrival is used, and might be where to look for the explanation of your results. While telephone-assisted CPR which has been developed to great extent within recent years should be uniformly executed regardless of geography, the citizen responder are often, if not universally implemented, implemented in areas where the EMS response time is expected to be prolonged. (18,50)

7.3 Study III

The main findings of study III is that OHCA survivors in general more often redeem prescriptions for antidepressants and anxiolytics than the control population. Receiving bystander CPR, however, is associated with a decrease in redeemed prescriptions for antidepressants and anxiolytics, as a proxy for better functional outcome, among 30-day survivors. This held true even in multivariate logistic regression adjusting for age, sex, burden of comorbidity, socioeconomic status, year of arrest and whether or not the arrest was witnessed by bystanders. Findings that redemption of prescriptions was associated with a diagnosis of anoxic brain damage strengthens the hypothesis that these can be viewed as consequences of increased cerebral hypoxia from no-/low flow time until EMS arrival.

Previous studies have linked OHCA to anxiety and depression, and receiving bystander CPR to increased chances of favourable functional, neurological and quality of life measures.(10,96–100) The effect of intervention, however intact, seems to decrease with elongation of resuscitation time. (101,102) A more recent american study showed no neurologic benefit measured as CPC < 3 of bystander CPR or mechanical CPR, however, this study also did not demonstrate any significant benefit in survival from either, and hence cannot be representative of our study population. (103)

8 Strengths and limitations

8.1 General

All studies included in this thesis is of observational nature, and relies largely on the DCAR. As such, studies inherit both strengths and limitations from the DCAR. DCAR is a well established registry that has mandatory reporting for all resuscitative attempts on a nationwide scale, and since 2016 each entry has been manually validated by healthcare professionals against the prehospital patient chart. This constitutes a data quality og very high standards that, on a nation-wide scale is only paralleled by very few registries.

However, the registry, as mentioned, only included patients in whom a resuscitative effort is initiated. This mainly affects study I as explained in the following section, but affects the overall reports from OHCAs in Denmark as well. Furthermore, Denmark is an optimal setting for conducting large, epidemiological studies because of the plethora of registries available, all linked by a unique personal identifier allowing for cross-registry linkage. At the same time, the tax-financed health-care system ensures that there are no financial barriers keeping low-income individuals from using the system, and thereby being part of the registries. That being said, complete socioeconomic equality in health-care usage cannot be guaranteed and is unlikely.

8.2 Ethical considerations and data permissions

The Danish National Committee on Health Research Ethics does not require ethical approval for registry-based studies so long as no personal information is disclosed by the project, but each project requires an approval of responsible data handling from the data holder in order to ensure this. While the Danish rules are deviant from an international perspective the current studies do not expose individuals and do not directly bring any individual at risk in any manner. I therefore consider the research ethically acceptable from a general perspective.

In terms of data availability and security, Study III, which was conducted first, was carried out using Statistics Denmark linking several public databases using a pseudonymized civil registration number not interpretable by the investigator, and observations with N <3 was not allowed for reporting to ensure no single person was identifiable. The project was approved in the Capital Region with the approval number P-2019-400.

Study I and II was conducted on a regional server in the North Denmark region, using only data anonymized from the DCAR, containing no unique personal identifier, and non-sensitive, geo- and demographical data that was acquired from a private contractor ViaMap. The common approval for both studies is in the North Denmark Region and labelled 2008-58-0028.

8.3 Study I

Study I is particularly affected by the inclusion to the registry being restricted to cases where resuscitation was initiated because OHCAs that were discovered late enough that resuscitation was never initiated might still have been interesting in terms of predicting sites of incidence, because future arrests in similar locations might be discovered within a timeframe of relevant resuscitation. As the approach to prediction used in study 1 is relatively novel, some methodological decisions were based on assumptions. These assumptions, for instance that airports and malls are special categories where prediction including lower ranking factors was not applied can be questioned, just as the decision to alter the reported area of airports. The former could, in future studies be tested with machine learning optimising the model for least possible Brier score in all area groups. The latter would benefit more from different data sources defining the extent of actual buildings rather than including the vast areas of the runways where the person-flow is significantly lower. Further, model selection might be improved by machine learning making several iterations and adjusting the chosen model for the area group along with the number of trees chosen for random forest and a possible weighted inclusion of covariates. Input data in study I is of very fine granularity, and while this strengthens the specific prediction for each area it complicates understanding and external applicability all the while converting to square kilometres to improve interpretability at the same time adds another denominator making the coherence in methods more complex. The methods chosen were chosen in an effort to achieve both external applicability, understanding and at the same time a detailed prediction for practical use in Denmark.
What further complicates the results of a study predicting geographical is that clinicians are accustomed to evaluating the effect of covariates, and as such will find the study wanting, because it is not designed to answer these questions, which have been answered by previous studies with different methodology relevant to these questions.(72,73,104) In stead, this study offers an individual prediction for each small geographical cell, which makes it extremely useful when planning logistical preparedness, and because this is the primary outcome of the study it may seem to have low relevance outside Denmark. This is, however, not the case because the study also

proves that the prediction models and covariates used performs better when predicting future sites of incidence than using historical incidence alone, and that is a result which should prove interesting to anyone wanting to predict future OHCA.

8.4 Study II

Sub-dividing a country into rural and urban areas can be done in a plethora of ways, and the method chosen in study II is not widely accepted, but is used to utilise the low granularity level of Danish data to the fullest. This, however, limits international applicability. While it is relatively simple to multiply the inhabitants per hectare to inhabitant per km2 which has been used in previous studies, but the international standard is swinging towards using Degree of Urbanisation (DEGRUBA) as standard for studies in this category, to which the data format used is uninterpretable.(105) Using DEGRUBA is, however, would not have been viable for study II because large parts of rural Denmark is unclassified by DEGRUBA, and even if it was classified, granularity would have been much larger, decreasing the internal value of the study.

A clinical limitation of study II is. that the study presents a crude survival rate, and does not consider neither patient characteristics nor events happening in the modifiable phase between recognition and EMS arrival, such as bystander CPR, use of AEDs and possible activation of volunteer responder programs even though these factors might indeed be prognostic for 30-day survival. Including these factors, however, poses a methodological challenge in combining person-data with geographical data and the following complex interpretation of results.

8.5 Study III

When evaluating long-term outcome after OHCA in a more sensitive manner than crude survival, we chose to evaluate prescription registries, just as employment registries have previously been utilised on the Danish population.(10) Both proxies rely on the existing Danish registries which are tested, tried, and have a high completion rate, in part because the motivation for registration is rooted governmental finances. This makes quality data on a large scale readily available, but cannot be used as the only marker of quality of survival. The ILCOR has made a recommendation to record cerebral performance category (CPC) at hospital discharge as a key parameter.(87) This has been implemented in numerous studies, and it makes headway towards a more sensitive outcome measure. The benefit is the possibility to collect data systematically on discharge, but while it is more sensitive than survival, it is still a relatively crude measure. Taking a step further in evaluating outcome is the emerging patient reported outcome measures (PROM). Health-related quality of life (HRQoL) has been proposed as a central measurement parameter.(80) While these outcome measures are certainly more sensitive and qualitative than the methods used in this thesis, it remains import to be aware that when compared to the larger registry based studies, PROMs suffers both from relying on the ability to identify patients beyond hospital admission and on identified survivors putting in the effort to respond to questionnaires or interviews.

With regards to the specific findings in Study III, the speculated reduction in frequency of anoxic brain damage and redeemed prescriptions due to no-flow time in patients not receiving bystander CPR prior to EMS arrival comes with the caveat that while we could adjust for witnessed status, we were unable to evaluate EMS response time which is a key determinant to the duration of no-/low flow.

9 Conclusions

Denmark has become a key player in OHCA research over the last decades. This is partially because of the well developed scientific community, in large part driven by the Danish Cardiac Arrest Registry, but moreover it is because of the incredible development in the effort made before EMS arrival and increase in survival. Survival has increased from 3.9 to 11 survivors per 100.000 in the background population and survival in the Utstein comparator group increased from 12% to 44%. While the increase in survival in itself is cause for celebration, the bystander rate, which has proven to be pivotal in determining the quality of the life lived after survival, has increased from 20% to 80% in the same time period.

Survival after suffering a cardiac arrest in a public location in Denmark is relatively high, and future efforts to optimise OHCA preparedness and outcome should be focused on residential areas with a high population density and provided a high bystander rate should be of continued focus, as it increases not only survival, but also quality of survival.

While there seems to be no significant difference in survival rates between rural and urban areas, the residential arrests in general still offer potential for improvement in terms of bystander CPR rates and defibrillation prior to EMS arrival. While part of the reason for the difference between residential and public arrests no doubt lies in early recognition, there is still a potential for optimising the proximity of publicly available AEDs in order to ensure the ability to defibrillate possible shockable rhythms among particularly the residential arrests.

10 Perspectives

While this thesis sheds a shiver of light on the geographical challenges and more refined outcomes after OHCA, much research still needs to be done in the area.

This thesis identifies areas of high risk of event occurring in future years, And identifies areas where publicly available AEDs should be placed. If this prediction is to hold any clinical value, it is to be combined with data on which areas already have publicly available AEDs. This will allow us to pinpoint areas that are currently under-equipped with publicly available AEDs. The predicted risk could also be combined with data on EMS response times, as to identify areas where there is a high or moderate risk of an OHCA, and at the same time a risk of prolonged response time, and a possible need to reinforce either the EMS system or consolidate volunteer responder programmes. The prediction could also form the basis of a more customised volunteer responder programme in Denmark in terms of the needed radius of each volunteer responder in order to cover even the more remote locations of possible future incidence.

What further warrants investigation is the reason for the homogeneity in survival across the different levels of population density despite the prolonged EMS response time in the more sparsely populated areas. One theory is presented in the paper, focusing on witnessed status or bystander/volunteer responder CPR being the key difference, however, the rates of these are yet to be reported. Looking even further, mapping any possible difference of precursors of outcome in OHCA patients according to the site of arrest might be of interest. As such, a future study could include area of arrest in a multivariate analysis of survival incorporating key patient and OHCA parameters as exposure variables.

In further attempt to evaluate the importance of EMS response time to outcome a study is planned to assess how cardiac rhythms measured by publicly available AED change over time until the EMS arrives, for instance estimating the degree ventricular decline according to EMS response time. In the process of evaluating this, important information about initial rhythms will also be added to the Danish cohort, as one of the current limitations of the Danish Cardiac Arrest Registry is, that information on pre-EMS AED usage is solely based on whether or not a shock was delivered, and holds no information on AEDs placed but not activated. As such, a simple descriptive investigation of AED data is an important factor in understanding the nature of AED usage and OHCAs in general.

When it comes to evaluating quality of survival, a lot of ground has already been covered in the Danish context, by this thesis, previously and subsequently published papers. None of these however, have included patient reported outcomes. Investigating patient reported outcomes would add greatly to the current knowledge of what intervention strategies improve outcome beyond mere survival, and several such studies are currently underway.

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12 Appendix

12.1 Analogue Case Report Form

2. Sygehus som patienten indbringes til:

Skriv tydeligt med blokbogstaver |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

3. Stedet for hjertestop: ☐ Privat hjem ☐ Trafikeret område (gade/vej/opgang)
☐ Naturområde ☐ Andet område (butik, institution, arb.plads)

4. Tidspunkt for hjertestop: Dato: |_|_|_|_|_|_| (dag måned år) Klokken: |_|_|_|_|
(Der anføres det bedst mulige skøn for tidspunktet ud fra tidspunkt for anmeldelsen og oplysninger fra dem, som har meldt hjertestoppet).

5. Var der nogen, der direkte observerede, at patienten fik hjertestop? ☐ Nej ☐ Ja

6. Blev hjertemassage påbegyndt *før* ambulancen ankom? ☐ Nej ☐ Ja

7. Blev der givet DC stød *før* ambulancen ankom?

☐ Nej
☐ Ja, offentlig tilgængelig AED
☐ Ja, anden AED

} Hvis ja, angiv tidspunkt klokken: |_|_|_|_|

8. Var en læge involveret i genoplivning *før* ankomst til hospital?
☐ Nej ☐ Ja, læge fra lægeambulance ☐ Ja, anden læge

9. Overværede ambulancepersonalet at hjertestoppet indtraf? ☐ Nej ☐ Ja

10. Analyserede ambulancepersonale patientens hjerterytme (EKG)? ☐ Nej ☐ Ja, klokken: |_|_|_|_|

11. Gav ambulancepersonalet DC-stød? ☐ Nej ☐ Ja, klokken: |_|_|_|_|
(tidspunkt for første stød)

Patientens *__allerførste__* observerede hjerterytme ☐ VT/VF
☐ Anden rytme

12. Fik patienten på noget tidspunkt følelig puls uden samtidig hjertemassage? ☐ Nej ☐ Ja, klokken: |_|_|_|_|

13. Patientens tilstand ved ankomst til sygehus?
☐ Genoplivning indstillet, patient erklæret død af læge før ankomst til sygehus
☐ Fortsat hjertestop, genoplivning fortsatte til sygehuset
☐ Patienten har følelig puls eller andre tegn på at spontant kredsløb er genoprettet
☐ Patienten er vågen – Glasgow coma score større end otte

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Clinical paper

Out-of-hospital cardiac arrest: Does rurality decrease chances of survival?

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Abstract

Background: Geographical setting is seldomly taken into account when investigating out-of-hospital cardiac arrest (OHCA). It is a common notion that living in rural areas means a lower chance of fast and effective helpwhen suffering a time-critical event. This retrospective cohort study investigates this hypothesis and compares across healthcare-divided administrative regions.

Methods: We included only witnessed OHCAs to minimize the risk that outcome was predetermined by time to caller arrival and/or recognition. Arrests were divided into public and residential. Residential arrests were categorized according to population density of the area in which they occurred. We investigated incidence, EMS response time and 30-day survival according to area type and subsidiarily by healthcare-divided administrative region.

Results: The majority (71%) of 8,579 OHCAs were residential, and 53.2% of all arrests occurred in the most densely populated cell group amongst residential arrests. This group had a median EMS response time of six minutes, whereas the most sparsely populated group had a median of 10 minutes. Public arrests also had a median response time of six minutes. 30-day survival was highest in public arrests (38.5%, [95% CI 36.9;40.1]), and varied only slightly with no statistical significance between OHCAs in densely and sparsely populated areas from 14.8% (95% CI 14.4;15.2) and 13.4% (95% CI 12.2;14.7).

Conclusion: Our study demonstrates that while EMS response times in Denmark are longer in the rural areas, there is no statistically significant decrease in survival compared to the most densely populated areas.

Keywords: Out-of-hospital cardiac arrest, OHCA, Survival, Geography, Population density, EMS response time

Introduction

Out-of-hospital cardiac arrest (OHCA) is a well known time-critical condition, and has for a long time received great attention from both clinicians, prehospital administration and mainstream media. This partly results from the use of survival after OHCA as a proxy to benchmark the performance of the Emergency Medical Services (EMS). Worldwide, a culture of excellence has spread, encouraging friendly competition in increasing survival.[1]

Abbreviations: OHCA, Out of Hospital Cardiac Arrest, EMS, Emergency Medical Services, HEMS, Helicopter Emergency Services, BLS, Basic Life Support, ALS, Advanced Life Support, AED, Automated External Defibrillator, IQR, Interquartile Range, GPS, Global Positioning System.

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This way of benchmarking has spread to the political and economic debate, and is used whenever a new hospital is to be built, as there is a general conception that experiencing an OHCA far away from an established hospital, with potentially longer EMS response times, decreases the chance of survival. Nevertheless, it remains debated whether specific geographical parameters influence important factors such as EMS response time and survival.

In Denmark, the EMS are obliged by contract to live up to a certain median EMS response time. This mechanism can work either of two ways: It could incline the EMS to station ambulances scattered across the country, but innately, remote areas are prone to longer response times if the vehicle which was originally stationed in the given area is otherwise occupied. It could also invoke a strategy of centralization to a certain degree, as most medical events will inevitably happen where most of the population is settled. This way, the EMS can keep the median response time down by reaching the majority of the events rapidly, and downgrade more remote areas with fewer events. It is a constant worry of politicians and citizens alike that more remote, thinly populated areas have a lower chance of a rapid response and lower odds of favourable outcome when an acute event like an OHCA occurs. This registry based, follow-up study aims to investigate whether living in rural, sparsely populated, areas comes at the cost of a lower chance of survival and simultaneously benchmark the five healthcare-divided administrative regions in Denmark.

Methods

Study setting

Denmark comprises 4,345,831 cells of 100 m by 100 m of mixed population density. The geography is divided into five healthcare-divided administrative regions as shown in supplementary, eFigure 1.

Each region is an administrative unit, responsible for the in- and out-of-hospital systems and services within itself. In each region the EMS consists of a dispatch center (one per region), ambulances providing basic life support (BLS) and physician-staffed cars and helicopters providing advanced life support (ALS). Furthermore, some regions employ paramedic-staffed cars providing ALS. Ambulance services providing BLS are either public (and thus administered by the region) or provided by private contractors. All physician-staffed cars (which are dispatched to all suspected OHCAs) and helicopters (HEMS) are public. Paramedic-staffed cars can be either.

The specific number of vehicles available to each region is largely undisclosed, and in part determined by the private contractors. Notable interregional differences between regions are that while the Central Denmark Region employs the largest amount of physcician staffed vehicles, the Zealand Region does not uliize this response form. HEMS is cross-regionally administrated, and three of such vectors were available from 2016 to 2018 where a fourth was implemented.[2]

Multiple volunteer responder programes were active in the time period, and while no one, national system was implemented until 2020, all regions had a form of volunteer responder programme in the period, either by SMS- or app activation.

All regions utilized a nationwide criterion-based emergency medical dispatch system (Danish Index) throughout the period, and there was one acute, percutan cardiac intervention center in each region except the Zealand Region from which patients are brought to Rigshospitalet in The Capital Region.[3]

Regardless of the administrative setup, the EMS services are publicly financed, and in each region, there is a political council which, on the basis of professional counseling and political considerations, determines the highest acceptable median EMS response time.[4] Population density and comprisement varies across regions and geography.

Data collection

Inclusion data was based on OHCAs registered in the Danish Cardiac Arrest registry.

All initiated resuscitative efforts in Denmark are required to be registered by the EMS by filing a case report form to this registry. To allow geographical analysis, only reports filed after logging of GPS coordinates began in 2016 were collected, and subsequently matched to a geographical hectare by the coordinates of the ambulance on arrival.

Data on geographical extents of healthcare-divided administrative regions was gathered using data from the Danish Map Supply. Further, data on population density was acquired on a square hectare (cell) level, defined by the coordinate of the lower-left corner from a private data supplier.

Each cell is re-evaluated once per year, and as such the total number of hectares does not vary between years, but the population density of the cells might. In order to avoid person-sensitive data, the population density data received on sparsely populated areas was a mean over an area to a minimum of 1.8 people per cell.

Data analysis

Cell groups

Each cell has one representation for each year between 2016 and 2019. The pool of cells was divided into three groups with an approximately equal number of cells in each group according to population density. Population was defined as night-time population to reflect the amount of people residing in the cell and thereby correspond to residential arrests. Cells with a population of zero and a population so dense that it was not represented in all regions were not included in analysis. In addition, cells containing airports were not included in the analysis due to the mismatch between living population and actual flow of people.[5] A cell was allowed to change groups each year. OHCAs that happened in public were treated as a separate group regardless of population and were not included in population and cell analysis.

Population was summed over the years and presented as an absolute number. Residential OHCAs were summarized according to population density group and subsequently, along with public OHCAs according to healthcare-divided administrative region. When presenting population density intervals, inclusion of af number in a group is denoted by a bracket [or] and exclusion of the number from the group is denoted by a parenthesis ().

Incidence

Arrests without valid GPS data or with missing data on the arrest site were excluded. Only bystander witnessed arrests were included. This was done in order to minimize pre-recognition time bias and optimize regional comparability. Incidence was summed for each cell across years according to the healthcare-divided administrative region and reported as raw numbers with column percentages.

OHCAs were categorized according to the case file as being either residential or any three of “Trafficked area”, “Nature area” or “Other”. OHCAs happening in nursing homes are defined as residential if the patient suffering the OHCA is registered as a permanent resident. All but residential arrests were categorized as public.

Inclusion and exclusion process is depicted in Fig. 1.

EMS response times

Response times were treated univariately as time in minutes from the call received at the emergency medical dispatch center to the first EMS-vehicle at the scene. It was received from the registry as integers, and reported as medians with 25% and 75% quartiles and interquartile ranges (IQR) according to cell group.

Survival

Survival was reported unadjusted in univariate analysis as the percentage of patients with valid survival data who survived to day 30 after OHCA and 95% confidence intervals for rates (CI) were calculated and presented in brackets [;]. Survival was stratified according to cell group and healthcare-divided administrative region.

Data analysis was conducted using R statistical software version 4.1.1 and RStudio v. 1.4.1103 with attached packages for the data analysis.[6–13]

Data permissions

The study was approved by the Danish Data Protection Agency. The Danish National Committee on Health Research Ethics does not require ethical approval for registry-based studies. The use of the Danish Cardiac Arrest Registry used for the conduct of this study was approved in the North Denmark Region (2008-58-0028).

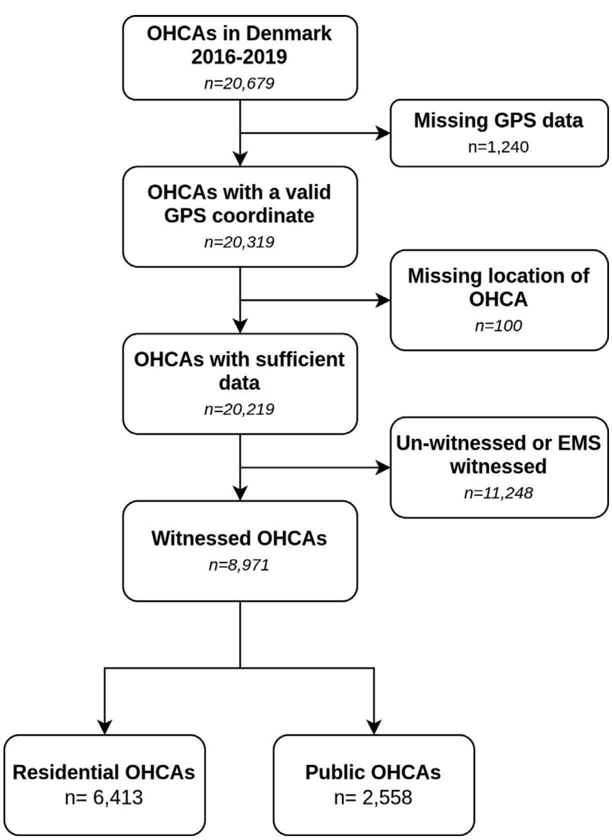

Fig. 1 – Inclusion flowchart.

Results

Cell groups

The analysis included data for four years, and as such, the distribution of accumulated cells is shown in eTable 1 according to population density and region. 1,318 (0,008%) cells had a population so dense that it was not represented in all regions (greater than 311), 27,792 (0.16%) cells were airports, and 15,671,533 (90,2%) had no population. A total of 178,132 (1.0%) cells were not assigned to a region of which 4,307 (0.02%) had a population of 311 or less and above zero with no airport. The geographical distribution is depicted on a map in supplementary eFigure 2. For the purpose of this illustration, population data for 2019 is chosen.

The accumulated population in each cell group is shown in Table 1, stratified by region. Notably, the Capital Region had the largest span, with 28,663 and 140,941 cells in the least- and most densely populated cell group respectively. Correspondingly, these areas contributed 87,400 and 5,940,000 inhabitants respectively summed across four years. The other health-care administrative regions have a quite different distribution, with 60%-70% of the population living in the most densely populated cell groups compared to 93% in the Capital Region of Denmark and accordingly 28%-31% of the area being densely populated, as opposed to 64% in the Capital Region.

Incidence

Table 2 shows the distribution of OHCAs stratified by cell group and healthcare-divided administrative region. A total of 392 (4.4%) OHCAs were witnessed, but happened in a cell that was not included in the analysis (eg. population of zero, more than 311 or in an airport). More than half of all the arrests (53.2%) occurred in the most densely populated cell group. OHCAs that took place in residential areas accounted for 6,021 (70,2%).

EMS response times

A total of 732 (8.2%) arrests had missing values for EMS response time. Median EMS response times in cell groups ranged from 10 (IQR 5.25) minutes in the least densely populated cell group to 6 (IQR 5) minutes in the most populated cell group and public arrests as depicted in Fig. 2. Overall, EMS response time shortened as population density increased, while the spread of the interquartile range was uniformly between two minutes less and three minutes more than the median. Individual EMS response times spanned from 1 to 240 minutes.

Survival

Survival data was missing in 430 (4.8%) of included OHCAs. Of the remaining, a total of 1,802 (21.1%) survived to 30 days after OHCA. Of the survivors, 66 (3.7%) happened in areas not included in analysis (eg. population of zero, more than 311 or in an airport). Fig. 3 depicts survivors in percentages according to cell group as a dot with 95% CI. In the least populated cell group survival was 13.4% (95% CI 12.2;14.7). In the medium populated cell group survival was 14.6% 95% CI13.7;15.5), and in the most densely populated cell group 14.8% (95% CI 14.4;12.2). OHCAs that occurred in public had the highest survival with a rate of 38.5% (95% CI 36.9;40.1).

When further stratifying on healthcare-divided administrative region, as is depicted in Fig. 4, the overall picture remains the same, with significantly higher survival rate in public arrests, and generally

Table 1 – Population in 100,000 according to population density and region, 2016–2019*

Cell group	Missing Region	Capital Region of Denmark	Central Denmark Region	North Denmark Region	Region of Southern Denmark	Region Zealand	Total
[1.8–4)	0.03 (4.2%)	0.87 (1.4%)	4.73 (9.3%)	3.39 (14.5%)	3.95 (12%)	4.96 (10.3%)	17.9 (8.2%)
[4–12)	0.1 (13.9%)	3.35 (5.3%)	10.51 (20.7%)	5.24 (22.4%)	7.1 (21.6%)	10.79 (22.5%)	37.1 (16.9%)
≥12	0.6 (83.3%)	59.41 (93.4%)	35.65 (70.1%)	14.75 (63.1%)	21.79 (66.4%)	32.3 (67.2%)	164.5 (74.9%)
Total	0.72 (100%)	63.64 (100%)	50.89 (100%)	23.38 (100%)	32.84 (100%)	48.05 (100%)	219.5 (100%)

[]denotes inclusion of number, () denotes exclusion.
* Rounding errors occur.

Table 2 – Distribution of OHCA according to cell group and region.

Cell group	Capital Region	Central Denmark Region	North Denmark Region	South Denmark Region	Zealand Region	Total
[1.8–4)	39 (1.6%)	111 (6.0%)	84 (7.8%)	87 (4.8%)	115 (8.6%)	436 (5.1%)
[4–12)	108 (4.3%)	250 (13.6%)	173 (16.0%)	276 (15.4%)	215 (16.0%)	1022 (11.9%)
≥12	1549 (61.5%)	956 (51.9%)	495 (45.8%)	928 (51.7%)	635 (47.3%)	4563 (53.2%)
Public	822 (32.6%)	525 (28.5%)	329 (30.4%)	504 (28.1%)	378 (28.1%)	2558 (29.8%)
Total	2518 (100%)	1842 (100%)	1081 (100%)	1795 (100%)	1343 (100%)	8579 (100%)

[]denotes inclusion of number, () denotes exclusion.

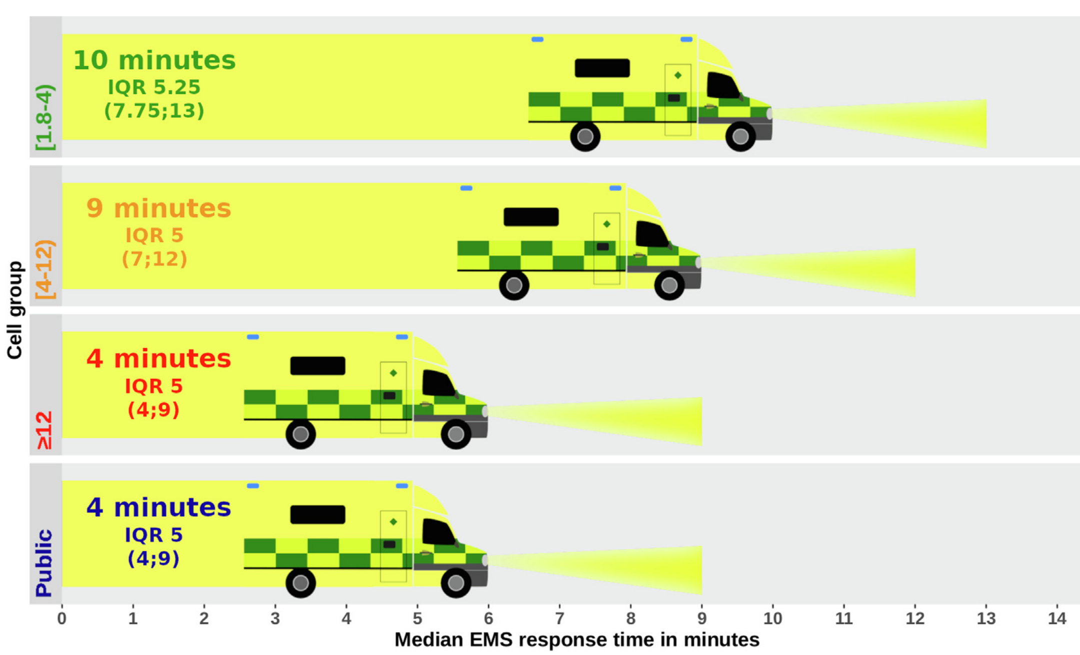

Fig. 2 – Median EMS response time in minutes according to population density. Front end of ambulances showing median response time, end of headlight depicting 3rd quartile and IQR presented under the median as text on to the left.

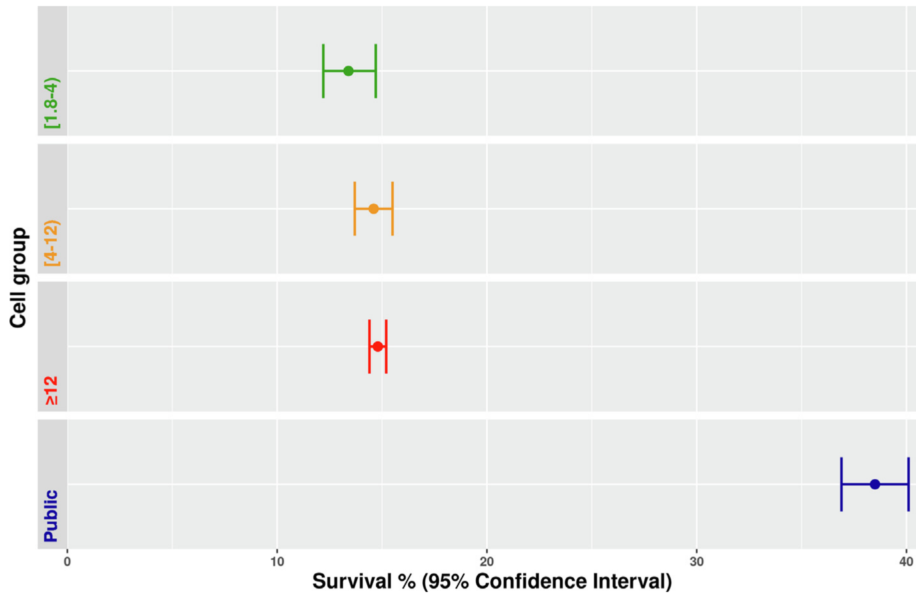

Fig. 3 – Survival in % according to cell group. Dot represents survival percentage and lines indicate 95% confidence interval (CI). Colouring of dots and lines are according to cell group.

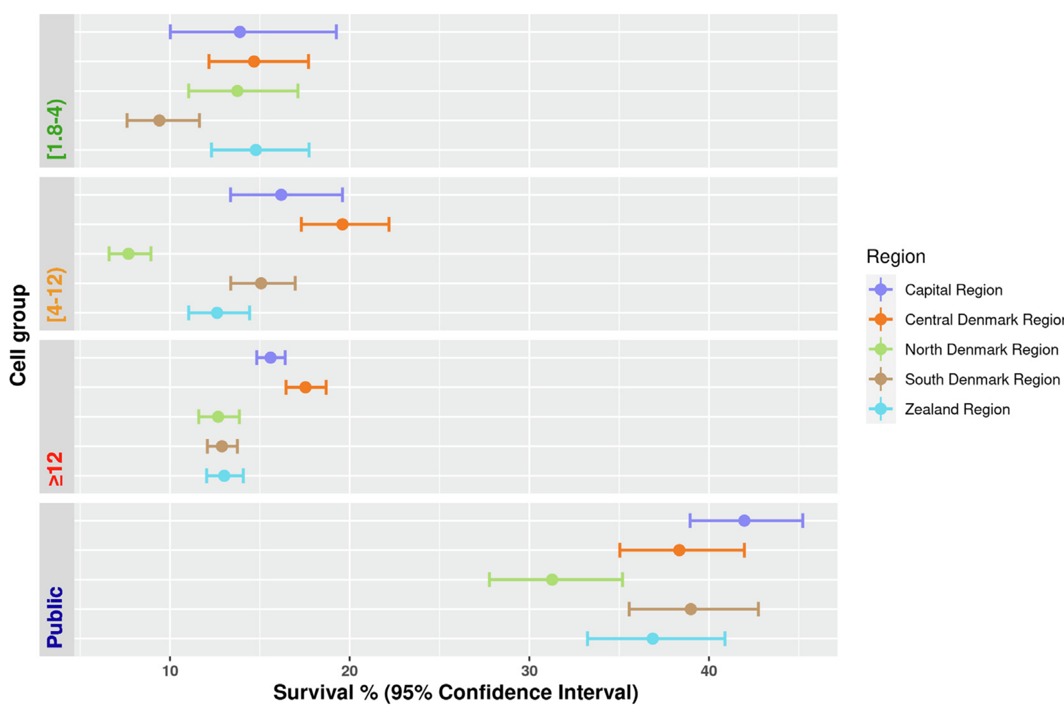

Fig. 4 – Survival in % according to cell group and healthcare-divided administrative region. Dot represents survival percentage and lines indicate 95% confidence interval (CI). Colouring of dots and lines are according to healthcare-divided.

overlapping 95% CIs. In the least densely populated cell group, the South Denmark Region stands out with a survival rate of 9.41% (95% CI 7.6;11.6) but with 95% CI overlapping with both North Denmark Region and Capital Region. In the medium densely populated cell group, the North Denmark Region falls behind with a survival rate of 7.7% (95% CI 6.6;8.9) with no overlaps of 95% CI. In the most densely populated cell group, the Capital Region and the Central Denmark Region have the highest survival rates of 15.6% (95% CI 14.3;16.4) and 17.5% (95% CI 16.5;18.7). The remaining three regions have lower survival rates with 95% CIs that do not overlap with the two first. For public arrests, survival rates are lowest in the North Denmark Region at 31.3% (95% CI27.8;35.2) and highest in the Capital Region at 42.0% (95% CI 39.0;45.2), both with 95% CIs overlapping other regions.

Discussion

This study aimed to investigate differences in residential OHCAs across different geographical areas, compare them to public OHCAs and further stratify by healthcare-divided administrative region. In summary, by far the largest proportion of OHCAs occurred in the most densely populated third of Denmark, but surprisingly the survival rate was not significantly lower in less populated areas. Survival rates after public OHCAs were found to be significantly higher than all residential arrests, in accordance with previous findings.[14,15]

Looking at differences across the healthcare-divided administrative regions, it is clear that not one region stands out across cell groups. While some particular administrative regions do perform either better or worse in specific cell groups, the same administrative regions have survival rates comparable to the other regions in other cell groups. This indicates that the actual pre-hospital effort does not vary significantly between regions, and considering that each healthcare-divided administrative region only has one primary intervention center it would seem that differences in geography and demographic composition between the regions are determinants of specific survival rates in different cell groups.

Concerning the consequences of having a cardiac arrest in a rural area in Denmark, the disparities in the EMS response time are relatively high with a difference in median times between the most densely populated and rural areas of four minutes. Although the response times in general may not be long, there is still a rough 50% increase between the highest and the lowest median, thus long enough for single-person cardiopulmonary resuscitation (CPR) quality and survival to decrease significantly.[16,17]

Previous similar studies have shown an apparent increase in OHCA survival in more densely populated areas compared to less densely populated areas.[18–21] However, other studies find no significant differences.[22,23] One study found, in line with our finding, that while in crude analysis survival-rate depended on rurality, it was not an independent prognostic factor.[24] Most previous studies included both witnessed and unwitnessed arrests. Doing so factors that are non-modifiable by the EMS plays a pivotal role in determining outcome and is, by extension, less relevant to the political debate.

When examining witnessed arrests only, on the other hand, the only parameters that are not in the healthcare providers' hands are delay from discovery of OHCA to phone call which we assume to be short, and the actual quality of CPR provided by the witness which is actively sought to be improved by dispatcher assisted CPR.[25,26]

Previous studies have used the actual number of survivors pr. 100,000 inhabitants not taking geographical variance into account. This is, as depicted in Fig. 2, associated with a large difference in EMS response time, a key parameter in securing long-term survival.[17,27–29] To adjust for or stratify by EMS response is an irrelevant strategy when benchmarking administrative regions, as it is one of the key parameters of interest that the healthcare-divided administrative regions can influence in order to improve outcome.

When comparing with previous studies of rural versus urban another aspect to consider is the definition of rurality, which is innately relative, and followingly applicability of both present study and previous depends on this very definition. There is no uniform standard for defining rurality, and present study uses a definition based on the Danish geography and a granulation of hectare level, allowing a minimum population density corresponding to 180 per km^2. Correspondingly, categories were set to [180–400), [400–1200) and ≥1200 pr km^2 where previous studies have defined the most rural categories with a maximum of between 10 and 663.[18–20,22,23,30]

The choice to live rurally alone might not entirely be a matter of choice, as it is influenced by both social and economic capabilities, but it is a parameter that the healthcare-divided administrative regions and the EMS cannot be held accountable for. Interestingly, the hermitization is most common in the most densely populated healthcare-divided administrative region, the Capital Region.[31]

The health care system is already trying to mitigate the possible consequences of potential prolonged EMS response times in more rural areas by initiating a number of citizen responder programs. This is true both in Denmark and internationally.[32–35] Whether or not this is part of the explanation for the absence of difference in survival despite the longer EMS response times as uncovered in this study remains to be explored.

Strengths

This study was performed on a national scale, with inclusion criteria that is uniform across all healthcare-divided administrative regions. Furthermore, each patient chart is subsequently manually validated by health care professionals to ensure correctness of inclusion and each variable. As such, not only is capture as complete as can be, but data is also of high quality.

Limitations

First, only including witnessed arrests limits the study population. We do, however, argue that this exact population, regardless of size, is the one best suited for the purpose of this study.

Second, what happens at the site of arrest during the EMS response time is unaccounted for, and might influence outcome.

Third, some cells were defined by a coordinate in a south-eastern shoreline and thus could not be linked to a healthcare-divided administrative region, as shoreline has no such geographical definition. This will, however, only affect the summation of cells within each healthcare-divided administrative region and not OHCA data, as these allow tying each OHCA to a region and a cell.

Fourth, the health-care system in Denmark is not to be directly compared to the health-care system in every other setup, neither in terms of pre-hospital setup nor post-resuscitative care. This is especially true when comparing to other countries that might not have a publicly-fininanced health care systems, and comparative research is required in diffrerent healt-care in before assuming applicability.

Fifth, this study did not include analysis of population-centered data, which could in part introduce bias. Further studies should explore the impact difference in age, socioeconimic status and burden of comobidity across area categories.

Sixth, while Danish Society of Cardioligsts publish nationwide recommandation for post-resuscitative care, cross-regional differences in specific practices for which we have not accounted may occur.

Conclusion

Our study shows that in Denmark, despite longer EMS response times to residential OHCAs in rural areas, survival is not significantly different from OHCAs in urban areas of Denmark, and regional differences across cell groups was absent. Only arrests that happened in public locations had a significantly higher survival rate.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2022.100208.

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Clinical paper

Association between bystander cardiopulmonary resuscitation and redeemed prescriptions for antidepressants and anxiolytics in out-of-hospital cardiac arrest survivors

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ABSTRACT

Aim: This study aimed to examine rates of redeemed prescriptions of antidepressants and anxiolytics, used as markers for cerebral dysfunction in out-of-hospital cardiac arrest (OHCA) survivors, and examine the association between bystander CPR and these psychoactive drugs.

Methods: We included all 30-day survivors of OHCA in Denmark between 2001 and 2011, who had not redeemed prescriptions for antidepressants or anxiolytics in the last six months prior to OHCA. Main outcome measures were redeemed prescriptions of antidepressants and anxiolytics within one year after OHCA.

Results: Among 2,001 30-day survivors, 174 (8.6% died and 12.0% redeemed a first prescription for an antidepressant and 8.2% for an anxiolytic drug within one year after arrest. The corresponding frequencies for redeemed prescribed drugs among age- and sex-matched population controls were 7.5% and 5.2%, respectively. Among survivors who received bystander CPR, prescriptions for antidepressants and anxiolytics were redeemed in 11.1% [95% CI 9.2–13.3%] and 6.3% [95% CI 4.9–8.0%] of the cases, respectively, versus 17.2% [95% CI 13.9–21.1%] and 13.4% [95% CI 10.5–17.0%], respectively, among patients who had not received bystander CPR. Adjusted for age, sex, year of arrest, comorbidity, witnessed status and socioeconomic status, bystander CPR was associated with significant reductions in redeemed prescriptions for antidepressants, Hazard Ratio (HR) 0.71 [95% CI 0.52–0.98], $P = 0.031$; and anxiolytics, HR 0.55 [95% CI 0.38–0.81], $P = 0.002$.

Conclusion: Relative to no bystander CPR, redeemed prescriptions for antidepressants and anxiolytics were significantly lower among 30-day survivors of OHCA who received bystander CPR, suggesting a cerebral dysfunction-lowering potential of bystander CPR.

Introduction

Survival following out-of-hospital cardiac arrest (OHCA) has increased substantially in recent years following improvement in the “chain of survival” including bystander interventions and

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advanced post-cardiac arrest care [1–4]. In Denmark, rates of both bystander cardiopulmonary resuscitation (CPR) and 30-day survival nearly tripled during the past decade [2]. With such improvements, it is essential to examine the function and quality of life in survivors and how bystander CPR relates to such outcomes, as underscored by a recent American Heart Association consensus document and the more recent Institute of Medicine report [5,6].

Survival after OHCA can be followed by anxiety, post-traumatic stress disorder (PTSD) and depression, with rates of depression varying between 8 and 45% and anxiety and PSTD between 13 and 42% and 19–27%, respectively [7–9]. These conditions can be debilitating for survivors' ordinary life and societal activities causing them to seek medical attention and physicians to prescribe psychoactive drugs. However, the extent to which survivors are prescribed antidepressants and anxiolytics is not known, and redeemed prescriptions of these drugs may indicate impairment of function and quality of life. Using nationwide registry data, we cannot examine compliance to prescription of psychoactive drugs, but we assessed whether such drugs were prescribed and redeemed. However, recent data has shown that around 95% of prescriptions for antidepressants and anxiolytics were redeemed in a general Danish population [10].

Previous studies have linked cerebral hypoxia to onset of depression, as seen in patients with stroke and traumatic brain damage [11,12]. Furthermore, micro arthrosclerosis as well as embolic and white matter lesions have been suggested to form a vascular pathway to depression [13–15]. Antidepressant and anxiolytic drugs may therefore be prescribed to survivors with minor brain damage as a result of insufficient cerebral perfusion during OHCA. CPR ensures a small, but crucial blood flow to vital organs including the brain, which potentially reduces cerebral anoxia. Since CPR during OHCA will not directly affect a patient's perception of the event and thus psychological reaction following the OHCA, we hypothesized that differences in rates of redeemed prescriptions for antidepressants and anxiolytics may therefore be attributed to cerebral anoxia during OHCA. Bystander CPR may therefore lower rates of redeemed prescriptions for these drugs through preservation of cerebral perfusion.

Therefore, we examined differences in redeemed prescriptions for antidepressants and anxiolytics according to bystander CPR status among 30-day survivors of OHCA. Also, rates of redeemed prescriptions were compared to age- and sex-matched population controls (ratio 1:2) without prior OHCA.

Methods

Study setting

We used OHCA data from Denmark collected between June 1st 2001 and December 31st 2011. Denmark covers ≈16,600 mi^2 including rural, suburban and urban areas and has a population of 5,580,516 residents by January 1st 2012 (5,349,212 in 2001). The Emergency Medical Services (EMS) consist of ambulances staffed by technicians or paramedics, and mobile emergency care units staffed by paramedics or anesthesiologists dispatched as rendezvous with ambulances. Throughout the study period, treatment has been provided in accordance with the latest guidelines [16,17].

Study population

The Danish Cardiac Arrest Registry includes all OHCA patients, in whom a resuscitative attempt is initiated, either by bystanders or EMS personnel. Thus, patients with obvious signs of death with no attempt of resuscitation are not included. Case capture is considered complete since: (1) the EMS is activated to all emergencies in Denmark including OHCA; and (2) EMS personnel are required to complete a case report form for every OHCA. An average incidence of 57.4 per 100,000 persons per year between 2001 and 2011 is comparable to other European and US registry data [18–20].

From the Danish Cardiac Arrest Registry, we included 30-day survivors ≥18 years of age and excluded survivors who had redeemed prescriptions of antidepressants or anxiolytics within six months before arrest to avoid prior psychoactive drug use to influence our outcomes.

Study design

This study is a registry-based matched cohort study. From the Danish Cardiac Arrest Registry, we obtained information on date of arrest, location of arrest (public versus at home), whether the arrest was unwitnessed, bystander- or EMS-witnessed, whether bystander CPR was initiated, the first recorded heart rhythm, and time interval between arrest recognition and first rhythm analysis by EMS.

Using the Civil Personal Registration number unique to each Danish citizen we linked cardiac arrest data to the National Patient Register and the National Presription Registry to obtain a Charlson Comorbidity Score [21,22].

A list of the specific antidepressants and anxiolytics with Anatomical Therapeutic Chemical (ATC) Classification codes assessed from The National Prescription Registry is shown in Supplement eTable 1. We measured prescription redemptions until one year post-arrest, based on recommendations in existing literature [12,23–25]. Information on highest achieved educational degree as proxy of socioeconomic status was derived from Statistics Denmark [26,27]. In agreement with the International Standard Classification of Education (ISCED), patients were divided in three groups: ISCED 0–2 including early childhood education to lower secondary educations; ISCED 3–5 including upper secondary to short-cycle tertiary educations; and ISCED 6–8 including bachelor's degree to a doctoral degree.

To compare redeemed prescriptions for antidepressants and anxiolytics in survivors of OHCA to population controls, two Danish citizens from the Danish Civil Personal Registry without prior OHCA were matched to each study case.

We performed risk set matching to match on age, sex and date of arrest, ensuring controls were alive and included at the time cases had arrest. Similar to arrest survivors, we excluded controls who had redeemed relevant prescriptions six months prior to the arrest date.

To support redeemed prescriptions for antidepressants and anxiolytics as markers of cerebral dysfunction, we compared the cumulative incidence of anoxic brain damage among survivors who redeemed these psychoactive drugs to survivors who did not redeem these drugs during the one-year follow-up period. We also compared the cumulative incidence of these redeemed prescriptions among survivors, who were diagnosed with anoxic brain damage in the time frame between the incident arrest and one year post-arrest, to the corresponding incidence among survivors who were not diagnosed with anoxic brain damage. Information on anoxic brain damage was derived from the National Patient Register and cases with known anoxic brain damage before arrest were excluded from these analyses.

Outcome measures

The main outcome measures were redeemed prescriptions for antidepressants and anxiolytics in the course between OHCA and one year post-arrest. Secondary outcomes were one-year mortality and anoxic brain damage.

Statistical analyses

We summarized categorical variables using percentages and frequencies and continuous variables using medians and 25%–75% percentiles (1st quartile [Q1] −3rd quartile [Q3]). Descriptive data were compared with chi-squared tests for categorical data and Kruskal-Wallis test for continuous data. We estimated and depicted cumulative incidences of death and redeemed prescriptions for antidepressants and anxiolytics using Aalen-Johansen estimations [28]. Missing data were handled by multiple imputation methods (Multivariate Imputation in Chained Equations) in our fully adjusted multivariable modeling [29]. We constructed ten imputed datasets (complete datasets with observed and imputed values) using information from all variables in Table 1. Estimates were then calculated from the imputed datasets and combined using multiple imputed pooled analysis. Before imputation, missing data patterns and mechanisms were investigated and we found no indication of informative missing. We treated redeemed prescriptions for antidepressants and anxiolytics as dependent variables in Cox proportional hazard models, separately for the drug groups. Three models were constructed, with bystander CPR as main exposure variable: (1) unadjusted; (2) adjusted for age and sex; and (3) adjusted for age, sex, year of arrest (2006–2011 versus 2001–2005), Charlson comorbidity index (0 versus >0), witnessed status (witnessed versus unwitnessed) and socioeconomic status (using the three ISCED educational groups defined above). These covariates were selected based on current literature on the association between bystander CPR and functional outcomes as well as current literature on psychiatric disorders, both related and unrelated to OHCA [26,30–34]. The assumption of proportional hazards was tested and not violated. A *P*-value <0.05 was considered statistically significant. Data management and statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA), and R [35].

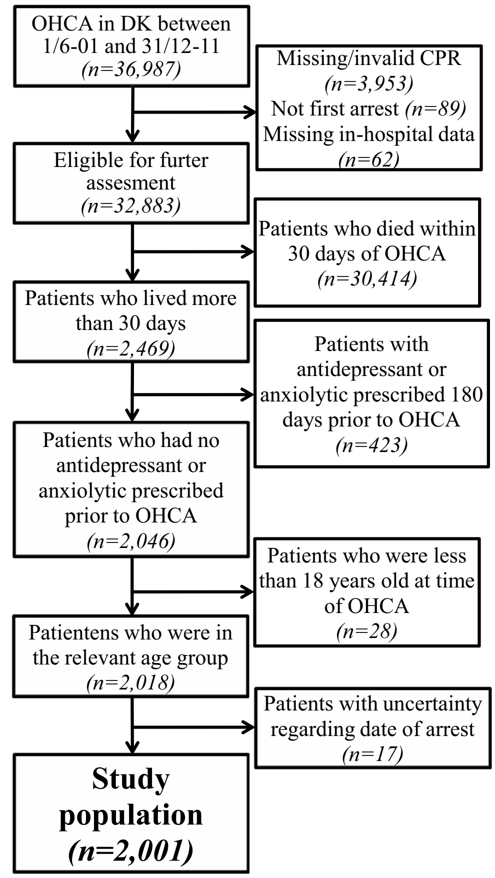

Fig. 1. Flowchart of selection of study population.
Selection process of patients from the Danish Cardiac Arrest Registry.

Results

Patients and characteristics

We included 2,001 30-day survivors between 2001 and 2011 (Fig. 1). Patient characteristics and outcomes of the study population according to bystander CPR and EMS-witness status are displayed in Table 1. Relative to patients who did not receive bystander CPR, patients who received bystander CPR were younger, more likely men, more likely to have arrest in years 2006–2011 relative to 2001–2005, had less comorbid conditions and arrests in public places, and more likely to have a witnessed arrest, a shockable rhythm, a longer time to arrival of EMS personnel, and a higher socioeconomic status (Table 1). Three patients in the survivor group and four in the control group were lost to follow-up.

Redeemed prescriptions for antidepressants and anxiolytics in survivors

Of 2,001 patients, 240 (12.0%) redeemed prescriptions for antidepressants within one year after OHCA, and 163 survivors (8.2%) redeemed prescriptions for anxiolytics. The cumulative incidences with 95% confidence intervals are depicted in Fig. 2, in comparison with the corresponding incidences for controls: 7.5% redeemed prescriptions for antidepressants and 5.2% for anxiolytics. Among 240 survivors, who redeemed prescriptions for antidepressants, 23.0% (n = 56) also redeemed prescriptions for anxiolytics; and the corresponding figure for population controls was 20.4%.

Associations between bystander CPR and redeemed prescriptions

Redeemed prescriptions for antidepressants were lower in survivors who received bystander CPR relative to survivors who did not receive bystander CPR (11.1% [95% CI 9.2–13.3%] versus 17.2% [95% CI 13.9–21.1%]) and the corresponding results for anxiolytics were 6.3% [95% CI 4.9–8.0%] versus 13.4% [95% CI 8.5–12.3%]. The incidence of redeemed prescriptions for antidepressants among EMS-witnessed survivors was similar to those who received bystander CPR: 10.0% [95% CI 10.5-17.0%] and for anxiolytics 7.8% [95% CI 6.9–10.4%]. In cause-specific Cox proportional hazard models, bystander CPR was associated with a reduction in redeemed prescriptions for antidepressants in unadjusted modeling: hazard ratio (HR) 0.63 [95% CI 0.47–0.86], *P* = 0.003, and when adjusting for age, sex, year of arrest, comorbidity, witnessed status and socioeconomic status (Fig. 3). Likewise, bystander CPR was associated with a reduction in redeemed prescriptions for anxiolytics in unadjusted and adjusted modeling (Fig. 4). No signs of interactions were found between bystander CPR and the included covariates. The analyses using imputed data were comparable to analyses in which data with missing observations were omitted (see Figs. 3–4 and Supplement eTables 3–4).

Anoxic brain damage and redeemed prescriptions

Among survivors who redeemed prescriptions for antidepressants, the cumulative incidence of anoxic brain damage was 22.1% [95% CI 17.3–27.7%] versus 5.7% [95% CI 4.7–7.0%] among survivors who did not redeem prescriptions for antidepressants. The cumulative incidence of anoxic brain damage was 17.2% [95% CI

Table 1
Characteristics and outcomes for the study population according to bystander CPR and EMS witness status.

Variable	No bystander CPR[a] (n = 418)	Bystander CPR (n = 909)	EMS[a]-witnessed (n = 561)	P value[f]
Characteristics				
Age median [Q1–Q3[a]], n (%)	63 [53–72]	61 [52–69]	64 [53–73]	<0.001
Arrest in 2006–2011[b], n (%)	267 (63.9)	699 (76.9)	350 (62.4)	<0.001
Male sex, n (%)	317 (75.8)	754 (82.9)	429 (76.5)	0.001
Charlson score >0[c], n (%)	133 (31.8)	236 (26.0)	169 (30.1)	0.053
Public location of arrest, n (%)	216 (63.0)	288 (35.1)	219 (49.0)	<0.001
Missing, n	75	88	114	
Bystander-witnessed, n (%)	329 (81.0)	804 (89.1)	–	<0.001
Missing, n	12	7	561	
Interval[d] (min), median, [Q1–Q3[a]]	7 [4–10]	9 [6–13]	–	<0.001
Missing, n	43	121	561	
First rhythm VF/VT[a], n (%)	294 (75.0)	740 (85.0)	238 (46.0)	<0.001
Missing, n	26	38	44	
High SES[a,e] n (%)	45 (11.4)	148 (17.0)	60 (11.7)	<0.001
Missing, n	23	38	48	
Outcomes				
Redeemed prescriptions for antidepressants	72 (17.2)	101 (11.1)	56 (10.0)	<0.001
Redeemed prescriptions for anxiolytics	56 (13.4)	57 (6.3)	44 (7.8)	<0.001

Data show characteristics and outcomes across bystander CPR and EMS-witness status for 1,888 of 2,001 30-day survivors (n = 113 patients had missing bystander CPR status and were excluded from these analyses). No substantial differences were seen between these analyses and analyses including patients with missing bystander CPR status (see Supplement eTable 2).

[a] Abbreviations: CPR, cardiopulmonary resuscitation; EMS, emergency medical service; Q1–Q3, 1st and 3rd quartiles; VT/VF, ventricular tachycardia/ventricular fibrillation; SES, socioeconomic status.
[b] Compared to arrest in 2001–2005.
[c] Compared to Charlson comorbidity score of 0.
[d] Time interval between emergency dispatch call or recognition of arrest and first rhythm analysis performed by EMS on scene.
[e] Socioeconomic class measured by highest educational degree, using the International Standard Classification of Education (ISCED): ISCED 0–2 including early childhood education to lower secondary educations, ISCED 3–5 including upper secondary to short-cycle tertiary educations, and ISCED 6–8 including bachelor's degree to a doctoral degree; highest educational level (ISCED 6–8) across groups are depicted.
[f] P values are for equality test across the groups.

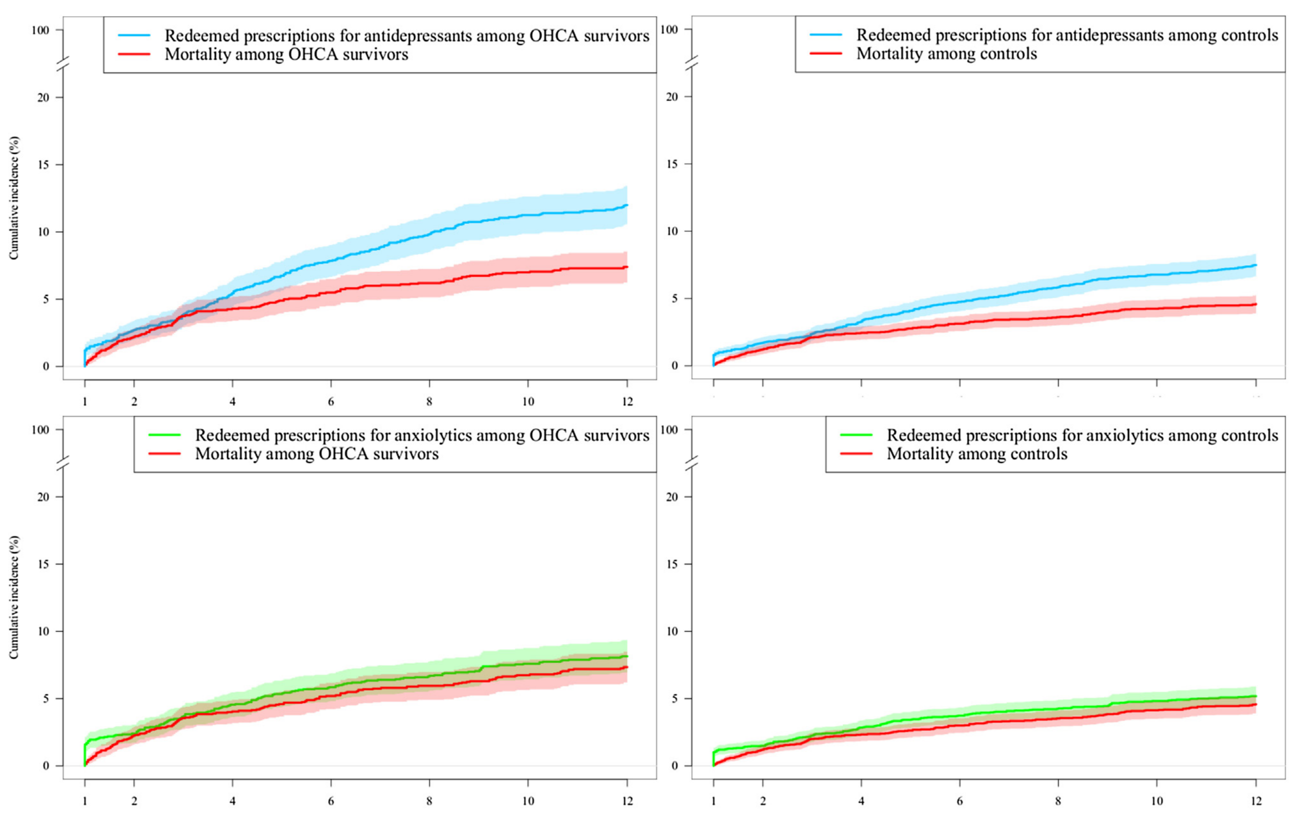

Fig. 2. Cumulative incidences of redeemed prescriptions for antidepressants and anxiolytics and mortality.
The blue and green lines depict the cumulative incidences of redeemed prescriptions for antidepressant and anxiolytic drugs, respectively, within one year after arrest. The red line depicts mortality. Vertical axis: Cumulative incidence. Horizontal axis: Time (months). The two figures on the left hand side depict values for study population, while the two figures on the right depict values for the control population.

	HR	low 95%	high 95%	P
Bystander CPR, unadjusted	0.63	0.47	0.86	.003
Bystander CPR, adjusted*	0.65	0.48	0.88	.005
Bystander CPR, adjusted**	0.71	0.52	0.98	.035

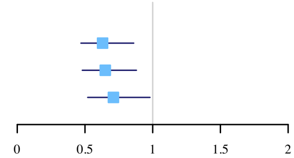

Fig. 3. Association between bystander CPR and redeemed prescriptions for antidepressants in non-EMS witnessed cases.
*The square represents the hazard ratio (HR) and associated line represents the 95% confidence interval (CI). EMS witnessed cases were excluded in these analyses. *Adjusted for age and sex. **Adjusted for age, sex, year of arrest (2001–2005 vs 2006–2011), Charlson comorbidity index (0 versus above 0), witness status (witnessed versus unwitnessed) and socioeconomic status (low, medium and high educational level).

	HR	low 95%	high 95%	P
Bystander CPR, unadjusted	0.47	0.33	0.68	<.001
Bystander CPR, adjusted*	0.49	0.34	0.70	<.001
Bystander CPR, adjusted**	0.55	0.38	0.81	.002

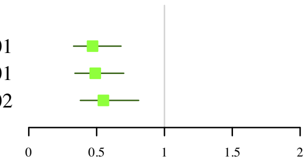

Fig. 4. Association between bystander CPR and redeemed prescriptions for anxiolytics in non-EMS witnessed cases.
The square represents the hazard ratio (HR) and associated line represents the 95% confidence interval (CI). EMS witnessed cases were excluded in these analyses. *Adjusted for age and sex.** Adjusted for age, sex, year of arrest (2001–2011), Charlson comorbidity index (0 versus above 0), witness status (witnessed versus unwitnessed) and socioeconomic status (low, medium and high educational level).

11.9–24.1%] among survivors who redeemed prescriptions for anxiolytics versus 7.1% [95% CI 6.0–8.5%] among survivors who did not redeem prescriptions for anxiolytics. Correspondingly, the cumulative incidence of redeemed prescriptions for antidepressants was higher among survivors diagnosed with anoxic brain damage (n = 166), when compared to survivors without anoxic brain damage (31.9% [95% CI 25.3–39.4%] versus 10.2% [95% CI 8.9–11.7%]). Redeemed prescriptions for anxiolytics were also more frequent among survivors diagnosed with anoxic brain damage relative to survivors without anoxic brain damage (16.9% [95% CI 11.9–23.3%] versus 7.4% [95% CI 6.3–8.7%]).

Discussion

In this nationwide study of a large number of 30-day survivors of OHCA in Denmark during 2001–2011, bystander CPR was associated with lower rates of redeemed prescriptions for antidepressant and anxiolytics and rates for patients who received bystander CPR were comparable to those with EMS-witnessed arrests. These findings support that bystander CPR not only increases chancesof survival but may also lower rates of cerebral anoxia-induced depression, anxiety or PTSD. Thus, not only does bystander CPR improve survival following OHCA, but bystander CPR also seems to improve long-term outcomes of function and quality of life among survivors.

OHCA is a major life event that can lead to depression, anxiety and stress disorders [7,8]. Bystander CPR is initiated while the patient is unconscious and is therefore not experienced by the patient. As such, we postulate that the observed difference in the rates of redeemed prescriptions for antidepressants and anxiolytics between the groups who did, and who did not, receive bystander CPR, cannot be attributed to a difference in psychological trauma, but instead to a difference in no or low-flow time and by extension, cerebral perfusion. OHCA patients who received CPR before the arrival of the EMS will likely have had a better cerebral perfusion during the arrest than patients who did not receive bystander CPR. This is supported by our results, showing that rates of redeemed prescriptions for antidepressants and anxiolytics were lower in survivors who received bystander CPR or had EMS-witnessed arrest, relative to survivors of non-EMS-witnessed arrest who did not receive bystander CPR. These findings were consistent in multivariable adjusted modeling. In support of our findings are studies that have linked bystander CPR to increased chances of favorable functional, neurological and quality of life measures [3,26,36,37]. Additionally, rates of redeemed prescriptions for antidepressants and anxiolytics were notably higher among survivors diagnosed with anoxic brain damage relative to those without anoxic brain damage. While this association does not necessarily implicate causality, it indicates that bystander CPR reduces cerebral damage and thereby potentially lowers the risk of subsequent depression or other mental disease.

Consequently, it is plausible that the increased rates of redeemed prescriptions among patients who did not receive bystander CPR can be related to mechanisms of cerebral hypoxia leading to memory impairment and cognitive dysfunction as well as anxiety and depression, as seen in patients with stroke and traumatic brain injury [11,12,38]. The finding that population controls had rates of redeemed prescriptions for antidepressants and anxiolytics that were much closer to survivors who received bystander CPR also speaks towards a direct neurobiological damage from inadequate oxygenation in survivors who did not receive bystander CPR. Thus, there appears to be two main mechanisms leading to redeemed prescriptions for antidepressants and anxiolytics following OHCA, (1) being that OHCA is major life-altering event that can lead to psychological distress, PTSD, anxiety and/or depression and (2) being a direct brain injury following insufficient cerebral perfusion during a cardiac arrest that is further aggravated, the longer the time until CPR is initiated.

In Denmark, several initiatives have been taken in attempt to increase the rate of bystander CPR including an increase in voluntary CPR courses and implementation of mandatory CPR courses for elementary school students between 12 and 16 years of age since 2005 and when acquiring a driver's license since 2006; also, healthcare professionals were introduced in emergency dispatch centers from 2009 to guide and assist laymen in initiating CPR [2]. These initiatives likely led to more than a doubling of bystander CPR rates and survival during 2001–2010 in Denmark [2]. Our results extend these findings to better functional outcome that further emphasizes the importance of bystander CPR. Our findings should encourage (1) laymen to learn and maintain CPR skills, (2) politicians to mandate and widely disseminate CPR courses in communities and (3) healthcare professionals and other trained volunteers to teach laymen these life-saving skills. Every effort that is likely to improve bystander CPR and survival should be strengthened or implemented.

Limitations

This study had a number of limitations. First of all, the observational nature of our study does not allow any causal relationships to be made and results are merely associations. Nevertheless, bystander CPR remained significantly associated with lower rates of redeemed prescriptions for antidepressants and anxiolytics in fully adjusted modeling.

Second, a number of patients had missing data in arrest-related variables. However, no substantial differences were found between analyses using pooled imputed datasets and analyses using data in which missing observations were omitted. Thus, we did not find missing data to alter our main findings.

Third, the extent to which patients suffer from psychological distress, in which drugs are not used to intervene, was not captured by our study. As such, we have likely not estimated the entire range of survivors with psychological problems following arrest. Nonetheless, our primary endpoints likely reflect the more severe burden of psychological difficulties, in which psychoactive drugs are indicated.

Fourth, thresholds for prescriptions of anxiolytics and antidepressants may vary between prescribing physicians. Further, data on indication is unavailable. As such, we cannot examine the underlying reason or mechanism for prescription. Clinically, it can be difficult to distinguish cognitive impairments as part of anoxic brain damage from cognitive impairments related to depression. Consequently, it is possible that anoxic brain damage has acted as indication in some patients. In either case, psychoactive drug prescription serves as a proxy for impairment of function.

Fifth, data regarding patients' detailed neurological function (such as the modified Rankin scale) or on quality of life was not available. To support redemption of prescriptions of antidepressants and anxiolytics as measures of functional impairment, we assessed the proportion of 30-day survivors who were discharged from hospital with a diagnosis of anoxic brain damage. Although we did not have access to further details regarding anoxic brain damage including signs and symptoms, on which the diagnosis was based and what it means for the patients' everyday life, the proportion diagnosed with anoxic brain damage was significantly higher among patients who also had redeemed relevant prescriptions. In a previous study of 30-day survivors of OHCA in Denmark, the proportion of patients diagnosed with anoxic brain damage significantly decreased during 2001–2011, concurrent with a significant increase in the proportion of patients returning to work [26]. Although these data cannot be extrapolated to 30-day survivors beyond working age that also were included in this study, it is likely that a lower rate of redeemed prescriptions for antidepressants or anxiolytics can be interpreted as a measure of more favorable outcome.

Conclusions

This nationwide study from Denmark showed that rates of redeemed prescriptions for antidepressant and anxiolytic drugs were significantly lower among OHCA survivors who received bystander CPR or who had an EMS-witnessed arrest, relative to survivors who did not receive bystander resuscitative efforts. As such, bystander CPR appears not only to increase patient survival but is also associated with lower rates of redeemed prescriptions for antidepressants and anxiolytics. Our findings stress the importance of early interventions in cardiac arrest care management to improve not only survival but also long-term outcomes of function and quality of life among survivors.

Conflict of interest disclosures

The corresponding author has no conflicts of interests to disclosure. Dr. Wissenberg is supported by the Danish Foundation TrygFonden, the Danish Heart Foundation and the Health Insurance Foundation. Dr. Hansen is supported by an unrestricted grant from the Danish Foundation TrygFonden. Dr. Gislason is supported by an unrestricted clinical research scholarship from the Novo Nordisk Foundation and reports research grants from Pfizer, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim and Bayer. Dr. Kragholm is supported by the Danish Heart Foundation, The Laerdal Foundation and the Fund of Herta Christensen, Denmark. None of these institutions had any influence on the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript for submission. All other authors have no conflicts of interests to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2017.03.032.

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