The impact of bystanders and emergency medical services on out-of-hospital cardiac arrest outcomes in children

By

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Abstract

Survival after out of hospital cardiac arrest (OHCA) in the paediatric populations is rare and often results in poor neurological outcomes. Bystander cardiopulmonary resuscitation (BCPR) intervention has been linked to improving survival outcomes. Several factors, including demographic, prehospital and socioeconomic status (SES) may influence the rate of the BCPR. However, limited evidence exists regarding the relationship of these factors and the rate of BCPR, and the association between BCPR and eventual survival outcomes in England.

To improve the knowledge about the impact of BCPR on survival outcomes we conducted a systematic review compared bystander versus no bystander CPR in paediatric OHCA and found a higher chance of achieving return of spontaneous circulation (ROSC) (pOR 2.30(95% CI 1.17-4.52)) , survival to hospital discharge (pOR 2.30(95% CI 1.41-3.75) and survival at one month (pOR 1.43 (95% CI 1.27-1.60)) in those who received BCPR; however, data was limited and there was no study from England.

Using the English OHCA outcomes registry and the Office of National Statistics (ONS) databases, the incidence rate of paediatric OHCA in England was calculated as 5.3 per 100,000 person-years, with a higher incidence in infants less than one year (27.3 per 100,000). Two thirds of OHCA cases received BCPR. Survival to hospital discharge was 11.0% and varied across Emergency Medical Services (EMS) regions.

Using the OHCA registry, patients receiving BCPR were compared with no-BCPR. BCPR was associated with improved rates of ROSC but not with survival at hospital discharge. The rate

of BCPR varied significantly across EMS geographic regions (range 57.7% (206/367) to 83.7% (139/166)).

Finally, the geographical variation was examined by exploring the impact of SES population factors on rate of BCPR. BCPR was less likely to be performed in areas of higher deprivation, higher proportion of ethnic minorities and low work levels. However, after adjusting for prehospital factors, only areas with a higher proportion of people with white ethnicity were associated with increased delivery of BCPR. Further research is needed to describe the effect of SES factors on survival outcomes.

In this thesis, based on the information provided in the systematic review, we concluded that although BCPR is associated with improved survival outcomes, there is limited data regarding the impact of BCPR on long-term survival with good neurological outcomes, suggesting that further studies are required in the future. This thesis provides essential knowledge on the epidemiology, incidence rate, regional variations in clinical factors (e.g. BCPR rate, the status of witness), and survival outcomes in paediatric OHCA in England. The overall survival to hospital discharge observed in this thesis was comparable to that reported in previous studies on paediatric OHCA. Further, this thesis suggests that the impact of BCPR on survival to hospital discharge in paediatric OHCA in England is clearly affected by whether the CA was witnessed. Therefore, further studies should explore factors that affect the willingness to provide BCPR in witnessed cases. Results also suggest that SES could impact the BCPR rate, although further studies are needed to describe the impact of BCPR on survival outcomes in geographical areas with higher and lower SES.

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Declaration and inclusion of previously published work

I, Hussin Albargi, declare that the work presented in this thesis is my own work, except where otherwise stated.

Part of chapter five was published prior to the submission of this thesis. Part of chapter three was presented at the Resuscitation Council (UK) conference, and part chapter five was presented at the European Resuscitation Council conference. I was the first author for the publications and presentations. As first and lead author I undertook all data collection, analysis and interpretation with support of my supervisors and created the first draft of the publication and presentations. The listed co-authors partly contributed to intellectual input, editing and revision of the final draft of the publication. Further information is contained in the acknowledgement section of each chapter.

Abbreviations

AHA: American Heart Association

aOR: Adjusted Odds Ratio

BCPR: Bystander Cardiopulmonary Resuscitation

CA: Cardiac Arrest

CPR: Cardiopulmonary Resuscitation

DA-CPR: Dispatcher assisted Cardiopulmonary Resuscitation

EMS: Emergency Medical Services

IHCA: In-Hospital Cardiac Arrest

IMD: Index of Multiple Deprivation

ILCOR: International Liaison Committee on Resuscitation

IQR: Inter Quartile Range

LSOA: Lower Super Output Area

no-BCPR:no bystander Cardiopulmonary Resuscitation

OHCA: Out-of-hospital cardiac arrest

OHCAO: Out of Hospital Cardiac Arrest Outcomes

ONS: Office of National Statistic

OR: Odd ratio

PAD: Public Access Defibrillator

PEA: Pulseless Electrical Activity

pOR: Pooled Odd Ratio

PRF: Patient Report Form

ROLE: Recognition of Life Extinct

ROSC: Return of Spontaneous Circulation

pVT: pulseless Ventricular Tachycardia

SES: Socioeconomic Status

UK: United Kingdom

VF: Ventricular Fibrillation

1 General Introduction

1.1 INTRODUCTION

Cardiac arrest (CA) is a fundamental healthcare concern in the medical profession and the community.[1] The therapeutic interventions required to address CA should be fast and efficient to save lives since a majority of incidences of CA often lead to death. In cases of CA, it usually occurs within a few minutes of occurrence unless necessary resuscitation measures are undertaken. Notwithstanding recent medical improvements, such as access to better defibrillation devices, the overall survival-to-discharge rate after an out-of-hospital cardiac arrest (OHCA) is minimal.[2, 3] Both paediatric patients and adults are potential candidates for CA; however, CA characteristics differ between the two groups. This thesis focuses on paediatric (OHCA). Several challenges arise from infant or child CA, including the emotional stress faced by family members, Emergency Medical Services (EMS) responders, and the emergency hospital team. The challenges continue during resuscitation, especially since CA in children is not as common as in adults and is considered unusual by EMS responders or laypeople. The child's unique cause of CA, pathophysiology, and event characteristics create a challenging environment for EMS responders. Therefore, this thesis looks deeply into the characteristics and incidence of paediatric OHCA and the effect of bystander cardiopulmonary resuscitation (BCPR) intervention on survival outcomes. Finally, it explores clinical and non-clinical factors that might influence the decision to perform BCPR.

This first chapter aims to introduce and define CA. A comparison is made between adult and child events, with more focus on the incidence and causes of CA in children, followed by a description of the impact of BCPR in paediatric OHCA and the survival outcomes. A discussion of the effect of SES factors on performing BCPR, which follows, is potentially helpful in identifying challenges and barriers that bystanders face. It also allows researchers to explore areas in which the BCPR rate can be improved.

1.2 DEFINITIONS OF CARDIAC ARREST

Constructive CA research should commence with a comprehensive and unifying definition of CA, understanding its severity and consequences among the adult and paediatric population, and determining appropriate medical intervention measures to address it. CA can be defined as the cessation of cardiac mechanical function, determined by the incapacity to palpate the central pulse, the cessation of respiration, and unresponsiveness.(4) The definition was proposed in 1995 in the Utstein paediatric guidelines, which created a consensus statement that encompassed a global resolution to improve knowledge in the realm of paediatric CA and instituted the beginning of a period of fundamental progress in the area.(5) Sudden cardiac death is also defined as natural death following cardiac diseases, including an unexpected loss of consciousness in under an hour following the onset of symptoms.(6) When the symptoms are unnoticed, sudden cardiac death occurs in a healthy person seen alive within the previous 24 hours. Hayashi et al.(7) define sudden cardiac death and sudden cardiac arrest as the rapid, unexpected death resulting from a cardiovascular cause that occurs more often outside a healthcare facility or in the emergency room. The epidemiological studies on sudden cardiac arrest and sudden cardiac death reveal that rapid death is due to ventricular arrhythmia underlying coronary heart conditions.(7) The above definitions of CA, sudden cardiac arrest and sudden cardiac death are essential to the analysis of the historical trend and prevalence of CA in adults and paediatric populations. CA is more common term in compared to sudden cardiac arrest and sudden cardiac death. It is a broader definition which can include cases where sudden cardiac death occurred. To explain sudden cardiac death usually used in the cases where the cause of arrest is due to cardiac disease, where CA can include cardiac and non-cardiac causes. Further, CA also used to specify the arrest location (in hospital, out of hospital). Therefore, through this thesis the term CA will be used to prevent confusion with other terms.

In CA cases, it has been recommended to perform chest compression or cardiopulmonary resuscitation (CPR).[8] CPR is an intervention that helps provide oxygenation and restore circulation during CA events.[4, 9] Generally, bystander CPR (BCPR) can be performed by a layperson without any medical equipment needed by starting chest compression only or ventilation with chest compression. A medical specialist can perform advanced CPR using medical equipment, including advanced airway management and medication administration.[4]

1.3 CARDIAC ARREST IN THE GENERAL POPULATION

Understanding the incidence and severity of a medical condition is essential to determine proper management. CA is a fundamental public health challenge. In the United States, CA claims approximately 300,000 lives yearly, with a yearly incidence of 350,000 out-of-hospital and 750,000 in-hospital-associated events among the adult and children population.[10] CA is responsible for approximately 20% of all cases of death in Europe, and the incidence of EMS-treated OHCA of presumed cardiac origin was 35 per 100,000 person-years.[11, 12] Compared to that, the incidence of treated OHCA-presumed cardiac origin is 28 in Asia and 44 per 100,000 person-years in Australia.[11] This variation can potentially be attributed to the definition of cases, different emergency medical services (EMS), the rate of bystander resuscitation, and data collection. Therefore, the reported incidence not only varied across continents but might not reflect the true incidence rate.

The vast majority of CA occurs in adults. In the United States, the annual incidence among adults suffering from OHCA ranges from 180,000 to 395,000[13, 14], and over 290,000 adults experience in-hospital cardiac arrest (IHCA) per year.[15] Further, over 98.0% of OHCA occurs in the adult population aged 18 years old or over.[16] The global incidence rate of EMS-treated adults suffering OHCA was 62 per 100,000 person-years.[11] The high incidence of CA among adults is mainly attributed to cardiac diseases.[7] Coronary artery disease is responsible for approximately 75% of the CA cases.[17] Further, the patient's age has also been linked to an increase in the incidence of CA.[2, 18] CA in adults, especially the elderly, often occurs at home, so they are less likely to be witnessed and receive BCPR.[19] Although factors such as age are irreversible, much work can be done by targeted CPR training to increase the BCPR rate, especially for families in which a member is suffering from cardiac diseases.[20, 21]

Despite significant steps taken during the past few decades to improve survival, the survival rate is extremely low. A systematic review of the adult population reported a pooled survival rate to hospital discharge of 7.1%.[18] Further, according to a report from the Cardiac Arrest Registry to Enhance Survival, the survival rate among OHCA patients ranged from 5.7% in 2005 to 8.3% in 2012.[22] The latter improvement in survival was due to increased BCPR and automated external defibrillator (AED) use for OHCA. Similar findings reported in a Swedish study included cases between 1992 and 2005, where the BCPR was associated with an increase in survival rate from 8.0% in 1992 to 8.8%, compared to survival rate of 2.3% in 1992 and 2.7% in 2005 when BCPR was not being performed.[23] In contrast, China's survival rate for adults after OHCA is only 1%, which may be partially explained by the lack of CPR training compared to developed countries.[24] Another study from Detroit in the US reported less than 1% survival to hospital discharge after OHCA.[25] The BCPR rate was approximately 27%;

however, 65% of the CA cases were unwitnessed. This might suggest that even in the cases where BCPR was performed, there was a prolonged time between the CA event and the time of BCPR initiation. Interestingly, in the latter study, most of the included CA patients were black and linked with a low BCPR and survival rate.

The above overview has captured the global trend of CA, which, although showing a variation in the incidence rate, shows a consistent low survival rate among patients suffering OHCA. These findings are attributed to several factors. The selected study population and sample size could potentially have an impact on reported survival rate. Clinical factors, such as the CA location, the status of the witnesses, and BCPR also affect the initial rhythm recorded and defibrillator use and eventually affect survival. Further, other factors, which might be related to SES, such as poverty and ethnicity, might also influence the survival rate.(26-29)

Infants, children, adolescents and adults are all candidates for CA, but these populations have essential differences. In the paediatric population, the cause of the CA, initial pathophysiology, and prehospital factors (e.g. the location of the CA, initial rhythm, and witness status) differ from the adult population. CA in the paediatric population is often a result of asphyxia (when ventilatory exchange of oxygen and carbon dioxide are inadequate or non-existent). In most cases, it can be caused by choking, drowning, electric shock, or poisoning.(5) Thus, Immediate ventilation is a crucial intervention for paediatric resuscitation.

In the United States, nearly 20,000 paediatric patients experience CA annually.(30) Infants (aged less than one year) constitute the most significant number of patients suffering from CA.(5) CA in the paediatric population is more common in hospital-based settings compared to OHCA. In the United States, over 15,000 paediatric CA events occurred in hospitals compared to 7000 cardiac arrests outside hospitals per year.[31, 32] However, survival to hospital discharge is higher in hospital settings than in OHCA.[30] According to a recent report from the American Heart Association: Heart Disease and Stroke Statistics, survival to hospital discharge after IHCA was 41.1%, compared to only 11.4% after OHCA.[30, 32] Several factors can influence survival outcomes, including CA cause, child age, the status of witnesses, the time before starting CPR or the duration of "no flow", the quality of the CPR, and post-resuscitation care.[30] Compared to OHCA, IHCA are more likely to be witnessed, the no-flow duration is shorter, and there is high-quality CPR by the hospital team and immediate post-resuscitation care. Although better survival outcomes are found in the IHCA compared to OHCA, CA remains a significant clinical event, with potential morbidity and mortality. Much work is needed to improve the survival outcome in both settings, but particularly in the out of hospital setting.

1.4 INCIDENCE AND OUTCOME OF PAEDIATRIC OHCA

The incidences of paediatric OHCA vary across nations. This can be attributed to the data sources, methods, definitions used, patients, population and health characteristics. Categorising the age of paediatric patients is an essential factor in understanding the variation of the incidence. For example, in a Japanese study focused on OHCA in infants less than one year old, the incidence was 65.9 per 100,000 person-years. The incidence was caused by different factors, including asphyxia, trauma, and drug intoxication. The one-month survival rate was 7.0%.[33] In a study of paediatric OHCA from birth to 19 years in North America, the incidence varied widely across the paediatric population age-range. The overall incidence of OHCA was low at 8 per 100,000 person-years, and the rate of survival to hospital discharge was 6%. The poor outcome after paediatric CA was attributed to patient, event, resuscitation, and post-resuscitation care factors.[34] For infants below one year of age, the incidence was

75.3 per 100,000 person-years. The incidence was 3.7 per 100,000 person-years for children, and for adolescents, the incidence was 6.3 per 100,000 person-years.[34] Concerning the outcome after OHCA, the overall survival to hospital discharge in medically addressed OHCA was 10.2%, ranging from 25.0% in perinatal (less than three days) to 17.3% in the adolescent age group.[34]

The incidences of paediatric OHCA in children caused by trauma varied widely and ranged between 2.6 per 100,000 person-years and 19.7 per 100,000 person-years annually.[35] The outcome of OHCA, especially that caused by trauma, is extremely low. The survivors often suffer serious neurological deficits. In over 3,000 paediatric trauma-associated OHCA, only 4% survived with an intact neurological system.[35] It is worth noting that traumatic CA is more common in older children than in infants.[35, 36] The results showed that the incidence and outcome of OHCA varied across age ranges—Table 1-1 highlights the variation in the survival rate among OHCA studies.

Table 1-1 The variation of the survival rate among OHCA studies

Study	Setting	Study design	Country	Age range	No. of paediatric cases	Survival to hospital discharge %
Nehme et al.(2018) [37]	Non-traumatic	Retrospective observational	Australia	≤16	948	8.1%
Law et al.(2018) [38]	All	Retrospective observational	HongKong	<18	53	20.8%
Inoue et al.(2017) [39]	All	Retrospective observational	Australia	<18	451	4.7%
Lee et al.(2017) [40]	All	Cross sectional prospective study based on national registry	Korea	<19	1013	6.4%
Naim et al.(2017) [41]	Non-traumatic	Secondary analysis of data registry	USA	≤18	3900	11%
Fink et al.(2016) [34]	Non-traumatic	Prospective observational	USA	0-19	1429	10.2%
Gerein et al.(2006) [42]	All	Retrospective observational	Canada	<18	503	2%
Young et al.(2004) [43]	All	Prospective observational	USA	≤12	594	9%
Kuisma et al.(1995) [44]	All	Retrospective observational	Finland	<16	34	15%

1.5 AETIOLOGY OF CARDIAC ARREST IN THE PAEDIATRIC POPULATION

Several studies have explored the aetiology of OHCA and highlighted the broad heterogeneity in the causes of paediatric CA. The most common cause of both IHCA and OHCA in the paediatric population is asphyxia.[43, 45] This is because most children suffer CA following a preceding respiratory illness or are compromised, leading to hypoxia and a reduction in myocardial oxygenation.[46] The CA occurs secondary to the primary hypoxic-ischaemic event. Other causes of CA in the paediatric population include cardiac trauma, drug overdose, and sudden infant death syndrome (SIDS). In a Swedish study, CA is caused by several factors, including cardiac cause, lung disease, suicide, drowning, suffocation, accidents, drug overdoses, and sudden infant death syndrome.[47] In this study, the causes are listed according to the patients' aetiology, and for the paediatric population, especially infants, the prominent aetiology was SIDS. SIDS was the most common aetiology, with 23% in a study involving 601 paediatric patients.[43] In this study, however, most paediatric population were infants less than one year old. Table 1-2 outlines the varying aetiology among paediatric patients suffering from OHCA. Among the aetiology and risk factors noted, SIDS is emphasised as the leading cause of CA in infants.

The variation of the upper age limits included within studies has an important impact on which aetiology is more common. In studies with a high upper age limit, the cardiac origin appears to be the common cause of CA. For example, two OHCA studies published in 2018 reported cardiac origin as the most common cause of paediatric CA.[37, 48] The first study was conducted in Victoria, Australia, and the incidence rate of cardiac origin in 0 to 16-year-olds was 40% (381/948). The other study was a multi-centre cohort study in Asia, and the incidence rate of cardiac causes in 0 to 17 years old was 34% (333/974). Therefore, careful evaluation of inclusion criteria in published studies is needed when comparing reported aetiology.

The variation in categorising the causes of CA also makes comparing studies difficult. For example, SIDS is a leading cause of death in infants.[49] SIDS is classified as cardiac or medical aetiology in some studies and in others as a separate aetiology. Similarly, drowning and suffocation are considered traumatic aetiology in some studies and respiratory aetiology in others. Therefore, establishing a clear definition that categorises the causes of CA is crucial in avoiding heterogeneity between studies and making more efficient comparisons.

Table 1-2 Presumed aetiology among paediatric OHCA

	Young et al. (2004)[43]	**Atkins et al. (2009)[49]**	**Tham et al. (2018)[48]**	**Nehme et al.(2018)[37]**
No. of patients	n= 521	n= 609	n=973	n= 948
Age range	0 to <13	0 to <20	0 to <17	0 to ≤ 16
Cardiac	48 (9.2)	nr	333 (34.2)	381 (40.2)
Trauma or accident	118 (22.6)	nr	246 (25.2)	nr
Respiratory	nr	nr	64 (6.6)	90 (9.5)
SIDS	136 (26.1)	38 (6.2)	nr	222(23.4)
Hanging	nr	34 (5.5)	nr	nr
Drowning	73 (14.0)	29 (4.7)	29 (3.0)	88 (9.3)
Suffocation	21 (4.0)	17 (2.7)	nr	57 (6.0)
Overdose	nr	17 (2.7)	nr	nr
Foreign body	12 (2.3)	4 (1.0)	nr	nr
Unknown	20 (4.0)	420 (69.0)	nr	nr
Other	93(17.8)	50 (8.2)	301 (31.0)	110 (11.6)

nr: not reported. Data expressed: number (percent)

1.6 MAJOR DIFFERENCES BETWEEN PAEDIATRIC AND ADULT CARDIAC ARREST

As described in the introduction, CA in children is different from that in adults. Differences between the two groups can be observed at different stages of CA. Table 1-3 highlight some of the major differences between paediatric OHCA and Adult OHCA.

Studies showed that the incidence of OHCA is higher among adults compared to the paediatric group. Although a similar incidence rate of OHCA has been reported in infants under one year of age and adults, the incidence rate in children over one year of age is significantly lower. The causes of OHCA are also different between adult and paediatric populations. In adults, CA is commonly due to heart disease.[50] However, paediatric CA is usually due to the lack of oxygen supply which initially affects the respiratory system and eventually leads to CA. Furthermore, the most common cause of CA in children might vary depending on the age group. SIDS is more common in infants under one year of age. Conversely, trauma, drowning, drug overdose, asphyxiation, and heart diseases are more common in older children.[37, 49] Causes of CA are reflected in various elements of the subsequent CA events, including the frequency of shockable initial rhythms (ventricular fibrillation (V-fib) and ventricular tachycardia (VT)). Since CA in adults is usually due to heart disease, more shockable rhythms are observed in adults compared to children, whereas asystole is more frequent in paediatric CA which is often due to the lack of oxygen supply and respiratory failure. Moreover, since chances of recording more shockable rhythms as the initial rhythm are more in adults, interventions, such as automated external defibrillator (AED) intervention are used more frequently in adults than in children. A recent study showed that AED intervention can significantly improve the survival outcome in adult patients. Although the use of AED is less common among children, a recent systematic review showed that AED intervention improves survival outcomes in children.[51] However, the evidence provided in the systematic review was insufficient, and data regarding the impact of AED intervention on infants under one year of age were limited. Therefore, further studies on the impact of AED intervention on children under one year who suffered from OHCA are needed. In a recent randomized control trial, it was found that epinephrine can improve 1-month survival in adults following OHCA.[52] However, there is no evidence of the impact of epinephrine on survival outcomes in children. Despite the limited evidence on the beneficial effects of epinephrine in patients who received extracorporeal cardiopulmonary resuscitation, its usefulness is more widely accepted in adults following OHCA. A recent systematic review showed that although the level of certainty is low, the survival outcome is better when extracorporeal cardiopulmonary resuscitation was performed rather than manual or mechanical CPR.[53] However, the authors did not find any study that compared the efficiency of extracorporeal cardiopulmonary resuscitation with that of manual or mechanical CPR in paediatric OHCA.

Injury to a developing brain OHCA can have a lifelong impact on child development due to the vulnerability for the developing brain and the impact on potential growth and recovery during infancy, childhood and adolescence.[54] OHCA can impact neurological development in children, which can significantly impact the child's academic and social skills. This type of impact and recovery trajectory will be different from the effects seen in adults as neurological majority will have been reached. Moreover, compromised neurological development can affect post-resuscitation care in children with OHCA since children usually require longer care, which in some circumstances continues for the rest of their life.

In summary, although the incidence, causes, interventions, and impact of OHCA are different in adult and paediatric populations, paediatric OHCA is under-studied, especially regarding interventions. Therefore, further studies focused on the paediatric population and establish trials are needed to examine the efficacy of various interventions that have already been established in the adult population.

Table 1-3 Similarities and differences between paediatric OHCA and adult OHCA

	Adult	**Paediatric**
Incidence rate	55 per 100000 years.[11]	<1 year 75.3 per 100000 person-years 1-11 years 3.7 per 100000 person-years 12-19 years 6.3 per 100000 person-years.[34]
Common cause of arrest	Cardiac diseases.[55]	Respiratory failure.[56] SIDS. [49]
Initial rhythm being shockable	40%.[18]	7.2%.[34]
Bystander CPR form	No difference between Conventional CPR and chest compression only except in cases where CA is secondary to asphyxia.[57, 58]	Conventional CPR is recommended over chest compression only.[59]
Extracorporeal cardiopulmonary resuscitation use	Recommended. [53]	Limited data to support the benefit of the ECPR in children
AED use/ effectiveness	More common than in children. Double survival outcome.[60]	Less common in children. Improve survival outcome, but little evidence—no data about its impact in an infant less than one year.[51, 61]
Impact development	Adults will have impact on the mature developed brain with different recovery patterns.	Children suffer in neurological, growth, social and cognitive development. Therefore require long life care after OHCA
ROSC rate	29.7%.[62]	<1 year= 6.5% 1-11 years=17.3% 12-19=27.0% <1-19=16.2.[34]
Survival to hospital discharge	8.8%%.[62]	<1 year= 3.2% 1-11 years=9.3% 12-19=12.7% <1-19=8.3%[34]
Survival to one month	10.7%.[62]	9.1%.[63]
Epinephrine effectiveness	Improve survival outcome [52]	Limited data about the impact of epinephrine on survival outcome

1.7 THE ROLE OF BYSTANDERS IN THE CHAIN OF SURVIVAL AND RESEARCH GAPS

Saving lives following CA depends on establishing the chain of survival. The American Heart Association (AHA) recommended the original chain of survival in early 1990, consisting of four elements to the chain of survival.[64] These include early access to emergency medical care, early cardiopulmonary resuscitation, early defibrillation, and early advanced cardiac life support.[65] In 2005, the European Resuscitation Council (ERC) Resuscitation Guidelines introduced prevention and post-resuscitation care as new links in the chain.[66] The updated chain of survival includes early recognition, prevention, and activation of an emergency medical response, performing high-quality basic cardiopulmonary resuscitation (CPR), applying defibrillation, and post-resuscitation care. However, the AHA recommended five links in the chain of survival and recently added a sixth link. The AHA-recommended chain of survival includes early access to emergency medical care, early cardiopulmonary resuscitation, advanced care, and recovery. Different chains of survival have been used for the past 20 years. This should be considered when comparing studies as the application of the chain of survival might differ, leading to different study findings. For example, studies when the original chain of survival came out may reflect the focuses on early recognition, early CPR, applying defibrillation and advance life support whereas new areas of improvement where highlighted later on the chain of survival such as prevention which might reflect on later studies.

The early access link, the first chain of survival, is an important element since the remaining chain of survival depends on it. It is very challenging for the bystander to recognise a CA event. Reports show that in some cases, people may confuse CA with seizure.[67, 68] Further, a study that used closed-circuit television recordings to capture BCPR behaviour during OHCA found that people hesitate to act when the patient has agonal breathing.[67] Those challenges in recognising CA could be attributed to bystanders not being trained in establishing basic life support (BLS); otherwise, a simple “look, listen and feel” approach could help recognise the CA event. Another factor could be the environment, and the heat of the moment in such cases might confuse the bystander emotionally. The problem extends to interrupting the activation of an emergency and calling for help. To explain, in such circumstances, the bystander may not be able to describe the CA event, and therefore the dispatcher-assisted team may fail to recognise the CA. However, in the ideal scenario, early recognition could prevent CA, especially in infants with SIDS, which is a common cause of CA. In this instance, the bystander should immediately call the dispatcher, who will help guide the bystander, and this will allow the EMS responders to arrive at the scene in a shorter time. This helps in initiating early CPR, which is the second link in the chain of survival

CPR during OHCA events can be performed by a bystander who is not part of the emergency team responding to the event or by an Emergency Medical Services (EMS) responder.[69] Performing any form of BCPR has been recommended over no-BCPR.[70, 71] However, there is inconsistency in reporting the impact of BCPR on survival outcomes.[18, 34, 41, 71] Donoghue et al.[72], in a systematic review of paediatric OHCA, reported a higher survival to discharge percentage of those who receive BCPR compared to no-BCPR (9.4% VS 4.7%). In the author's pooled analysis, the association between BCPR and survival to discharge became non-significant; however, there was heterogeneity between studies, which might affect the analysis result. Fink et al.[34], in a US study that included paediatric OHCA, found that BCPR was not associated with survival to hospital discharge (adjusted odds ratio (aOR) 1.33 (95% CI 0.80-

2.19)). However, Naim et al., in the multivariable analysis, found an increase in the odds of survival to hospital discharge when BCPR was performed compared to no-BCPR (discharge (adjusted OR 1.57; 95% CI 1.57-1.96)).[41] Similarly, a Korean study reported better survival to hospital discharge when BCPR was performed (adjusted OR 1.91 (95% CI 1.02-2.84)).[73] However, the latter also found that good neurological recovery was not associated with BCPR (adjusted OR 1.51 (95% CI 0.77-2.97)). This inconsistency in reporting the association between BCPR and survival outcomes is attributed to the heterogeneity among paediatric studies. The paediatric studies varied in the study design, sample size, patient characteristics (e.g. age, CA cause and location, witness status, initial rhythm, etc.) and EMS response time.

Dispatcher-assisted cardiopulmonary resuscitation (DA-CPR) is a concept that allows the dispatcher to give instructions via telephone to bystanders in OHCA. This will help initiate early CPR before the EMS responder arrives at the scene. It also helps increase the BCPR rate and ultimately improves survival outcomes.[74] Akahane et al.[75], in a study that included a paediatric population, identified an increase in BCPR with DA-CPR in delivery of chest compressions (27.8% to 69.0%) and mouth-to-mouth ventilation (18.4% to 43.8%). An adult study compared the BCPR rate before and after introducing the DA-CPR protocol and found that the BCPR rate doubled after introducing DA-CPR (5.7% to 12.4%).[76] However, in the latter study, DA-CPR was focused on the compression-only technique, which might explain the increased BCPR. Regarding survival, Goto et al.[77], in a paediatric OHCA study, found a higher survival rate at one month when DA-CPR was performed compared to no-BCPR (adjusted OR 1.81 (95% CI 1.24-2.67)). Using DA-CPR as a reference in multivariable logistic regression, there was a decrease in adjusted OR for one-month survival in the CPR without the DA group (adjusted OR 0.70 (95% CI 0.56-0.88)). However, there was no statistical difference between

DA-CPR and CPR without DA in one-month survival with Cerebral Performance Category 1 or 2.[77] Chang et al. found that good neurological recovery was associated with DA-CPR but not with BCPR without DA (adjusted OR 2.22 (95% CI 1.27-3.88) vs. 1.51 (0.77-2.97)). Yet, for survival to hospital discharge, both were associated with higher odds of survival compared to no-BCPR (adjusted OR 2.23 (1.47-3.38) vs. 1.91 (95% CI 1.02-2.84)).[73] The use of the DA-CPR protocol improved the BCPR rate, especially in the compression-only technique. There is a better survival outcome when DA-CPR is offered compared to no-BCPR; however, the impact of using DA-CPR vs. BCPR without DA does not differ significantly. This suggests that other factors related to DA-CPR quality, response time or patient characteristics might greatly influence survival outcomes.

EMS responders can be the personnel to deliver BCPR in the event of OHCA, although this usually happens when EMS responders witness the OHCA. Therefore, most studies compare OHCA witnessed by i) EMS responders, ii) bystanders, and iii) unwitnessed.[35, 78, 79] OHCA is more likely to be witnessed by a bystander than an EMS responder.[80] Further, the survival outcome is better when the OHCA is witnessed by an EMS responder or by a bystander than an unwitnessed CA.[78] Chia et al.[79] reported a higher return to spontaneous circulation at the scene (ROSC) for bystander and EMS-witnessed OHCA compared to unwitnessed OHCA (7.9% vs. 13.7% vs. 4.4%). Similarly, in the latter study, the survival to hospital discharge was also higher in the same groups compared to unwitnessed OHCA (5.3% vs 11.2% vs 1.3%). However, the survival outcome is better when the CA is witnessed by EMS responders compared to unwitnessed BCPR and OHCA witnessed by a bystander. Hostler et al.[78] found a decrease in the odds of survival in BCPR witnessed compared to that witnessed by EMS responders (adjusted OR 0.41(95% CI 0.36-0.46)), (adjusted OR 0.37 (95% CI 0.33 -0.43)). Similarly, Axelsson et al.[80] reported a better survival to one month for the EMS-witnessed group (EMS witnessed survival of 16.0% vs. witnessed BCPR survival of 9.5%). These findings may be explained by the better quality of CPR performed by the EMS responder and the rapid access and use of a defibrillator in cases where shockable rhythm is found. Further, the shorter response time might also be a major factor when EMS personnel witness the CA. To summarise, CPR by a bystander or EMS responder can lead to a better survival outcome; however, CA witnessed by EMS responders is more favourable to survival compared to witnessed BCPR. Therefore, there may be room for improvement to increase the quality and impact of CPR performed by bystanders.

BCPR can occur in the form of conventional CPR (chest compression and rescue breathing) or compression-only. Since paediatric CA commonly occurs secondary to respiratory failure [56], it has been thought that conventional CPR is more effective than compression-only. However, data is limited regarding which technique is more suitable for children. A systematic review comparing conventional CPR and compression-only found a better outcome for children receiving conventional CPR.[59] However, the review included only five studies, and four of the five studies were conducted within a single nation (Japan). Conventional CPR had higher odds of 30-day survival and favourable neurological outcomes in 30-day survival (OR 1.49 (95% CI 1.27-1.74); 1.63 (95% CI 1.30-2.04), respectively). Further, based on the cause of the CA, 30-day survival was higher in the non-cardiac cause groups when conventional CPR was performed. Still, there was no statistical difference in 30-day survival for cardiac causes of CA. This is probably due to the nature of CA in children, where asphyxia is more common, so ventilation and oxygenation are essential. Although this review showed a better outcome when conventional CPR was performed, the evidence is still limited as only five studies were included. Further, four of the five studies were from one country, and therefore, the patients' characteristics, the BCPR training and the EMS system might differ from other countries. Further research is needed to draw a solid conclusion about the favourable CPR technique for paediatric OHCA. Finally, in these studies, performing any form of BCPR appears better than no-BCPR.

The rate of resuscitation attempted by bystanders varies across paediatric studies, and several factors can cause this variation. Factors related to the patient's characteristics differ between studies and affect the rate of BCPR. For example, studies that exclude traumatic causes report a higher BCPR rate. A study that included only non-traumatic OHCA reported a BCPR rate of 46% (1814/3900), whereas a study that included only traumatic OHCA found that only 17% (20/123) of the cases received BCPR.[35, 41] It is worth noting that there was a large difference in study size, another cause of variation in paediatric OHCA reported outcomes.[44, 77, 81] The location of the CA is another factor that affects the BCPR rate. The rate of BCPR in a school settings study was 86% [28], compared to studies that included CA at home, where BCPR was less than 50%.[37, 41, 73] People who are less educated and have a low income have a lower chance of being trained to perform BCPR; therefore, the BCPR rate is lower in deprived areas.[77, 82] As mentioned previously, the presence of DA-CPR can increase the BCPR rate. Studies identified an improved BCPR rate with DA-CPR.[73, 77] Although the Utstein guideline minimises the variation in defining the OHCA resuscitation, the variability is still observed and affects reporting of the BCPR rate across paediatric OHCA studies. BCPR is a key intervention to improve outcomes, and much work is needed to describe it and its impact on survival. Without following a constituent guideline, comparing the BCPR rate across paediatric OHCA will be challenging.

Early defibrillation is another critical element of the chain of survival in which bystanders play a significant role. Early defibrillation helps re-establish the normal electrical rhythm of the heart in cases of cardiac dysrhythmia (e.g. ventricular tachycardia or fibrillation).[64] The EMS systems have encouraged communities to use automated external defibrillators (AEDs) using innovative training programmes and to make their use accessible to the public. Among the adult population, it has been shown that early defibrillation improves the survival of the hospital discharge rate.[83] Similarly, in children, the one-month survival rate increases when AEDs are applied (aOR 2.09 (95% CI 1.33-3.33)).[84] A favourable neurological outcome in one-month survival was also better when AED used (aOR 2.63 (95% CI 1.23-5.62)).[85] Further, in a recent systematic review, the use of AED was associated with better neurological outcome (Cerebral Performance Category 1 or 2 (CPC)) at one month survival and higher survival to hospital discharge among children aged 1-18 years.[51]

Despite the effort to increase the availability and training to use the AED, some studies reported that the AED was used in less than 5% of cases. In a Japanese study, Kitamura et al.[64] included only witnessed cases with a higher possibility of applying a defibrillator, which found that AED was used in 3.3% of the total paediatric OHCA cases. A Korean study reported that less than 0.7% of paediatric OHCA have AED.[73] However, a higher percentage of the AED used was reported in a study from the US (17.4%).[41] Several factors could affect the use of AED in children. Most occur at home, limiting access to the AED.[34, 41, 85] Further, in paediatric OHCA, the shockable rhythm is low compared to adults, in which the need to use AED is minimal.[86] The availability of the programme to teach the public how to access and use public access defibrillation (PAD) is a crucial factor in increasing the use of AED. Reports showed a higher percentage of PAD use in educational places.[28] Factors such as the CA being witnessed and the level of BCPR training might also affect the presence of shockable rhythm in which AED can be used.

1.8 DIFFERENCES BETWEEN HEALTH CARE SYSTEMS

The structure of the EMS system differs between countries. This includes the number of organisations providing EMS in a country and the quality of care provided by various EMS. Other questions that can be asked include: What are the skills of the paramedic who responded to OHCA? Are there other healthcare providers, such as physicians responding to OHCA cases along with paramedics? Does the system allow the paramedic responder to perform advanced life support on the scene? How does the dispatcher system work for OHCA events? What is the EMS response time? Understanding how the EMS functions is important for identifying variations in the care provided that might impact the study outcomes.

Each state of the United States of America has its own EMS and standard of care that might differ from those in other states.[87] In some states, more than one agency regulates ambulance services. EMS can be provided by the government, fire services, or private agencies.[88] Although the National Highway Traffic Safety Administration has prescribed a minimum standard needed to be achieved by the EMS in the country, due to variations in the standard care provided by different states and agencies, the performance of EMS varies across the US, which makes the comparison between EMS systems of the US and other countries very challenging. One unique feature of EMS in some states of the US is that the fire services can also be dispatched to the scene as a first responder in some cases.[88] The dispatcher receives calls when someone dials 911 and then assigns the incident to the proper EMS responder. The level of training and skills of the ambulance services might differ. Two EMS personnel usually attend the scene; one has the skills to provide basic life support (BLS) care while the other is a paramedic who can provide advanced life support (ALS) care, including advanced airway management and intubation.[89, 90] However, insurance is necessary to receive ambulance care services. If the patient is supposed to pay for the ambulance services in cases without insurance, the cost depends on the type of service provided and the service provider (private or government).[91, 92]

In Japan, the Fire and Disaster Management Agency (FDMA) regulates the EMS and provides emergency medical care. The local government regulates the fire department and dispatches the EMS care provider to needy patients.[63] EMS can be received by calling 119, and there are no charges for patient transportation to the hospital.[93] Based on the level of urgency, the fire department sends EMS personnel. There are different levels and skills of the EMS provider. These can be categorised as basic and intermediate levels, which can provide the BLS, and the advanced level consists of a lifesaving technician.[93] However, the paramedic or the lifesaving technician is not allowed to administer drugs to the patients on the scene or use endotracheal intubation without online instructions from a physician.[94]

In England, ambulance services are provided by the National Health Service (NHS) and are based in 11 different regions. They respond to both urgent and non-urgent calls. The calls can be made by dialling 999 or 112 for emergency and 111 for non-emergency cases.[95] The ambulance call centre categorises calls as Red 1 for CA cases, Red 2 for cases including stroke, or Green calls for non-life-threatening cases.[95] Based on the nature of the call, the dispatcher can solve the problem on the phone or send the appropriate ambulance crew to attend to the case. Since Red 1 calls for CA are considered to be the highest priority calls, the ambulance crew for these cases are capable of delivering defibrillation in at least 75% of cases within 8 min.[95] Dispatcher lead CPR with instructions given to bystanders is given in the English EMS system.[96]

The ambulance service team includes paramedics and emergency medical technicians. Both are qualified to provide BLS, including CPR and defibrillation. The paramedics are also qualified to perform ALS interventions, including advanced airway management and drug administration. In CA cases, the EMS team is expected to resuscitate all patients; however, in cases where signs of death are obvious (including putrefaction, rigor mortis, incineration, and hypostasis), resuscitation might be terminated. For patients who have a do not attempt resuscitation order, resuscitation should be withheld.[97]

1.9 SOCIOECONOMIC ASSESSMENT AND IMPACT ON OHCA

It has been well established that SES factors generally affect health outcomes.[98] Since OHCA is a major health concern, studies have shown that SES factors could affect the clinical factors (e.g. CA cause, witness status, BCPR and initial cardiac rhythm) and survival outcomes.[82, 99] To explain, people living in deprived areas have a low income, low education levels, low or no work, and limited access to health care systems. A lower level of education may lead to lack of training in resuscitation skills (because of inadequate numbers or access to training courses) which therefore may reduce the chance of the public performing BCPR.[100] A UK study on adults found that the BCPR rate decreased with increasing levels of deprivation.[101] Naim et al., in a paediatric study, reported a low rate of BCPR in low-income and unemployment groups.[82] In addition, minority groups living in deprived areas may find it difficult to communicate with dispatchers due to language barriers, or they may be afraid of being asked for identification.[99, 102] For example, in an adult study in the US, CA in Hispanic minority neighbourhoods were less likely to receive BCPR and survive.[102] Similarly, in paediatric populations, compared to White ethnicity, Black, Hispanic and other ethnicities were less likely to receive BCPR.[82] Although studies described the association of SES factors with BCPR and survival, there is limited evidence regarding the impact on paediatric OHCA. Further research is needed to identify the barriers and SES factors that might affect the BCPR.

1.10 THE ROLE OF REGISTRIES OF OHCA

Database registries are an important way to understand important health care conditions such as OHCA. According to the National Institutes of Health, a registry is "a collection of information about individuals, usually focused around a specific diagnosis or condition".[103] The registry aims to understand the specific condition and population better and ultimately improve the outcomes. Data registries help capture the data of many patients and explore any geographical differences in factors and outcomes among the same population. Further, a registry is less costly than the more expensive prospective clinical trials which may require additional governance and oversight (e.g. randomised controlled trials run by clinical trial unit) .[104] There are several ways to obtain registry data, including patients' medical records and health care providers. However, using registry data has some limitations. Registry data is pre-collected hence not all potential confounders would have been recorded, which raises the risk of bias.[105, 106] Further, Loss of follow-up is a significant issue for a data registry, where individuals or organisations might withdraw from the registry, affecting the findings' generalisability.[105]

OHCA registry data is the source of data for the incidence, epidemiological and demographic information, patient characteristics, and survival outcomes in both adult and paediatric OHCA populations. The OHCA registries have been used in several countries and have offered an opportunity to compare data globally.[41, 107-109] In the UK, the University of Warwick, in collaboration with the National Ambulance Service, established the OHCAO registry in 2012. The data were collected from 10 EMS covering the majority of the England regions. The goal of establishing a data registry is to improve outcomes by identifying the quality and strategies needed for interventions, the challenges the EMS systems face, and regional differences. EMS dispatch, providers, and hospital records usually obtain data for the OHCA registry. Usually, there is a standard protocol that data collectors should follow to avoid any conflict when submitting data. However, since OHCA is a highly stressful clinical event, there is a possibility for recall bias by a bystander or emergency responder, which should be considered when using registries.

1.11 SUMMARY

OHCA is a life-threatening health condition in the paediatric population, and the survival and neurological outcomes are poor. The chain of survival has identified sequences of interventions that help improve survival. Bystanders play a major role in recognising CA, activating an emergency call, performing CPR, and using a defibrillator. However, one of the research gaps in paediatric OHCA is that the current knowledge of BCPR is poor and varied across studies. Indeed, no systematic assessment of the role of bystander CPR in the paediatric population has been conducted. In the UK, there is limited data on the epidemiology of paediatric OHCA to allow the exploration of factors associated with survival and neurological outcomes after CA. Understanding the UK paediatric OHCA landscape and any variation in EMS systems may identify important geographical or patient characteristics associated with improved outcomes. Understanding the potentially modifiable factors in paediatric OHCA survival, including the role of bystander CPR, SES and deprivation, may allow future research to direct the effort toward areas in need. Finally, strong evidence to support the BCPR benefits may be helpful to health policy-makers and funders wishing to introduce training for the general population in regions where bystander-training rates in CPR are low and thus, provision of bystander CPR is low.

2 Study Aims and Outline of the Thesis

2.1 **STUDY AIMS**

2.1.1 Thesis Objective

The overarching objective of this thesis is to "understand the impact of bystander cardiopulmonary resuscitation and emergency medical services on the survival outcome of paediatric OHCA".

To achieve this, we aim to answer the following research questions with associated aims:

2.1.2 Research Questions

1. **Does bystander CPR during paediatric OHCA improve the rate of return to spontaneous circulation (ROSC), survival, or survival with a favourable neurological outcome?**

    1.1. Evaluate the literature reporting bystander CPR during paediatric OHCA and assess the impact of bystander CPR on clinically important outcomes. (Chapter 3)

    1.2. Explore the risk of bias in the reported literature. (Chapter 3)

2. **What is the incidence rate and the epidemiology of paediatric OHCA in England?**

    2.1. Describe the epidemiology of paediatric OHCA in England using a national registry database. (Chapter 4)

3. **Is there regional variation across Emergency Medical Services (EMS) in England in the incidence and outcome of paediatric OHCA patients?**

    3.1. Explore the incidence rate of OHCA across the EMS regions in England. (Chapter 4)

3.2. Assess the variation in ROSC and survival across EMS regions. (Chapter 4)

4. **Are patient demographics and prehospital resuscitation factors associated with rate of bystander CPR in paediatric OHCA in England?**

4.1. Evaluate the relationship between patient demographics and the prehospital factors with the delivery of BCPR. (Chapter 5)

5. **Does bystander CPR improve ROSC and survival after paediatric OHCA?**

5.1. Describe the association of bystander CPR and clinically important outcomes. (Chapter 5).

6. **Does the rate of bystander CPR during paediatric OHCA vary across England?**

6.1. Describe the bystander CPR rate across EMS regions in England (Chapter 5)

7. **Do socioeconomic status factors impact the rate of bystander CPR delivery?**

7.1. Examine the relationship of socioeconomic status factors and the rate of bystander CPR in paediatric OHCA. (Chapter 6)

3 Bystander versus no Bystander Cardiopulmonary Resuscitation for Paediatric Out-of-Hospital Cardiac Arrest: A Systematic Review

Part of this chapter has been presented at a conference:

H.S.Albargi , W.Tremlett , A.Sitch , S.Mallett , B.R.Scholefield
Bystander versus No Bystander Cardiopulmonary Resuscitation for Paediatric OHCA:
A Systematic Review. Presented at Resuscitation Council (UK) Conference, December 2019.
(Abstract).(see Appendix 8-1, p207)

3.1 ABSTRACT

Background: The survival rate after paediatric out-of-hospital cardiac arrest remains low. There is a paucity of data describing the impact of bystander cardiopulmonary resuscitation (BCPR) in paediatric OHCA. We aimed to systematically review the literature, comparing the effect of bystander CPR versus no-bystander CPR on important clinical outcomes for paediatric OHCA patients.

Method: Systematic search of randomized and non-randomized control trials (RCTs) and observational studies in PubMed, MEDLINE, Embase, and Cochrane Library (searched Feb 2019). Study inclusion: OHCA studies, including children (age<18yrs), reported an association between BCPR intervention and outcome. Excluded: adult, animal and simulation studies. The primary outcome was favourable neurological outcome (Cerebral Performance Category (CPC) 1 or 2) at one month. The secondary outcome of return to spontaneous circulation (ROSC) and survival to discharge or at one month. Two reviewers (HA, WT) independently assessed data extraction and the risk of bias.

Result: 3,144 records were identified, 381 underwent full text assessment. We included 22 observational cohort studies (no RCTs). Nine out of 22 reported the primary outcome (CPC 1 or 2) at one month and showed benefit of bystander CPR; pooled meta-analysis was not possible due to overlapping data-series. The largest of the nine studies reported an increased odds of good neurological outcome (CPC 1 or2) with BPCR (Odds Ratio (OR) 1.58 [95%CI 1.26 to 1.99]). ROSC outcome was reported in three studies, with meta-analysis showing higher pooled odds of achieving ROSC with BCPR compared to no-BCPR (pOR: [95%CI] 2.30 [1.17-4.52]). The pooled odds of survival to discharge (six studies) and survival at one month (four

studies) were also higher for BCPR compared to no-BCPR: pOR 2.30 [1.41 to 3.75] and pOR 1.43 [1.27 to 1.60], respectively. Overall assessed risk of bias was low.

Conclusion: Children receiving bystander CPR after OHCA have a significantly higher chance of achieving ROSC, survive to hospital discharge and survival at one month. Improved one month favourable neurological outcome was also found, but we identified limited reporting from only one cohort of patients (Japan). Understanding the role of BCPR in the UK population and the difference in BCPR rates and impact may support ongoing public campaigns to improve BCPR.

3.2 INTRODUCTION

Bystander cardiopulmonary resuscitation (BCPR) is a key factor in improving the survival rate. As described in chapter one, BCPR is “a CPR performed by a person who is not responding as part of an organized emergency response system to a cardiac arrest”.[69] Studies in adults showed that BCPR improves the survival rate compared to patients who do not receive resuscitation.[18] However, in paediatric OHCA, as few as a third may receive BCPR, and the impact on survival is unclear.[49] Unlike adults, where cardiac diseases are common, most cases of CA in paediatric cases are due to primary respiratory aetiology. Thus, the American Heart Association (AHA) recommends performing conventional CPR in paediatric OHCA (e.g. rescue breathing in addition to chest compressions). Compression-only CPR is recommended over no bystander CPR if a bystander is unwilling to perform conventional CPR.[110] A systematic appraisal of the evidence supporting these recommendations has not been completed. This systematic review, therefore, aims to review the literature to identify studies which compare the effect of BCPR versus no-BCPR on important clinical outcomes for paediatric OHCA patients.

3.3 METHODOLOGY

3.3.1 Search strategy and selection criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(see Appendix 8-2, p208) The Prospero registration number for the systematic review protocol is CRD42019129304.

The literature search was developed in consultation with information specialist and with discussion with expert in the topic area to examine the search terms to assure that there was a balance between being specific and trying to get broader cover. The literature search conducted up to February 26th, 2019, in the following publication databases: Excerpta Medica dataBASE (Embase), Medical Literature Analysis and Retrieval System Online or MEDLARS Online (Medline), the Cochrane Library database and Pubmed. Search for grey literature was undertaken for ongoing/unpublished studies from Zetoc. We searched both PubMed and Medline to assess the assumption that the databases report identical outputs. The Prospero database was searched for ongoing and recently completed systematic reviews. In addition, we manually searched through the references of the included studies for any other relevant studies. To avoid any bias, no language or publication period restrictions were applied.

Search terms were: “cardiac arrest”; or “heart arrest”; or “heart collapse”; or “cardiorespiratory arrest”; or “cardiopulmonary arrest.ti,ab”; and “resuscitation”; or “cardiopulmonary resuscitation”; or “heart massage.ti,ab”; and : “bystander*”; or “lay-person”; or “lay person”; or “witness”; or “rescue breath*.ti,ab”. The paediatric terms were removed from the final search strategy because they minimised the chance of capturing all relevant studies. A full description of different search strategies and terms used in this systematic review are in Appendix 8-3,p212 .

3.3.2 Research question

Among children who have an out-hospital cardiac arrest , does bystander CPR compare to no bystander CPR improve the rate of return to spontaneous circulation (ROSC), survival to hospital admission, 30 days or 1 year survival and survival with a favourable neurological outcome at hospital discharge, 30 days or 1 year?

The review question was created to follow the Population, Intervention, Comparison, and Outcome (PICO) model:

Population: Infants and children, from birth to less than 18 years, who have an out-of-hospital cardiac arrest from any aetiology

Intervention: Patient received bystander cardiopulmonary resuscitation

Comparator: Patient did not receive bystander cardiopulmonary resuscitation

Outcome: Primary outcome is survival with favourable neurological outcome CPC 1 OR 2 at one month.

Additional outcomes including: return to spontaneous circulation, survival to hospital admission, or survival with a favourable neurological outcome at hospital discharge, one year. The final included outcomes were based on the available data.

3.3.3 Inclusion Criteria

3.3.3.1 *Type of study*

We planned to include randomized, nonrandomized control trials and observational studies (cohort studies, case control, cross sectional) in this review. For a study to be eligible, the author needed to report the association between BCPR intervention and at least one outcome of interest. Studies including animal simulation and manikins were excluded. In addition, conference abstracts, non-full-text articles, case reports, comments, editorials, and case series with less than ten patients were excluded.

3.3.3.2 *Type of participants:*

Infants and children from birth to less than 18 years old who experienced an OHCA. Studies in adult population were excluded. In studies that cover both populations, further assessments were done to ascertain the possibility of extracting the paediatric data. If the study abstract did not clarify the type of population or did not include any information about the paediatric population, the study was excluded.

3.3.4 Intervention

We included studies showing the association between the BCPR and at least one outcome of interest. Studies where BCPR was performed by an EMS provider only were excluded and if study included both BCPR by a lay person and EMS, we aimed to extract data of lay person BPCR if feasible.

3.3.5 Outcome measures

3.3.5.1 *Primary Outcome*

The primary outcome of interest was favourable neurological outcome CPC 1 OR 2 at one month. The Glasgow-Pittsburgh Cerebral Performance Category is a score from 1 to 5 (1=good cerebral performance: patients is conscious and alert, 2= Moderate Cerebral Disability: patient is conscious, disabled but independent, 3=Severe cerebral disability: patient is conscious but disabled and dependent, 4=coma/Vegetative state: the patient is unconscious and 5= Brain death: patient is certified brain dead). Favourable neurological classified as CPC 1 or 2, and unfavourable neurological function as 3 to 5.[111]

3.3.5.2 *Secondary outcomes*

I. Favourable neurological outcome at 6 months,1 year, 5 years

II. Return of spontaneous circulation

III. Survival to hospital admission

IV. Survival to hospital discharge with or without favourable neurological outcome

V. One-month survival with or without favourable neurological outcome

VI. Six months, one year and five years survival

VII. A post-hoc analysis combining survival to hospital and one-month survival.

3.3.6 Data management Plan

After completing the literature search, all results were transferred to EndNote software to remove the duplicates.[112] To complete screening title, abstract and study selection, Rayyan software was used.[113] We also manually searched for duplicates to avoid software errors.

3.3.7 Selection Process

Two reviewers (Hussin Albargi (HA) and William Tremlett (WT) screened the title and abstract separately. Studies meeting the inclusion criteria were transferred to the stage of full text assessment. Independently, the reviewers made their list of potential studies to be included in the review. Full text studies were evaluated and assessed separately, based on the intervention and the outcome. Discrepancies between authors were resolved by a discussion and third reviewer consultation (Barnaby Scholefield (BS)).

3.3.8 Data Collection Process

Both reviewers extracted the data independently. A data extraction form was created. The data extraction form was modified after piloting. In the presence of disagreement between reviewers, a third member of the team was consulted (BS). Extracted data included the following: first author name, year of publication, source of funding, country of study, study design, inclusion and exclusion criteria, participants, demographics of participants (age, gender, race, other), location of OHCA (home, public), witnessed status, cause of arrest (cardiac, traumatic, other), initial rhythm (ventricular fibrillation, ventricular tachycardia, pulseless electrical activity, asystole, other), BCPR rate, type of bystander (family, non-family), main/additional outcomes, result.

3.3.9 Risk of Bias Assessment

Two authors independently assessed the risk of bias. The Newcastle Ottawa Scale was used to assess the methodology and quality of the observational studies.[114] One of the main advantages of using the Newcastle Ottawa Scale is that the scale is easy to be applied and interpret and it is commonly used in assessing observational studies.[114] Further the scale is comprehensive and cover the important element of the study. The scale consists of three domains: selection, comparability, and outcome. The highest score is 9, and the lowest is zero. The awarded score is 4 for selection, 2 for comparability, and 3 for the outcome. a sample of the Newcastle Ottawa score in Appendix 8-4,p217 . Both reviewers performed the risk-of-bias assessment. A third reviewer was consulted if there was any discrepancy.

3.3.10 Data synthesis

All data were synthesized and reported in accordance with the PRISMA guidelines. Quantitative analyses using unadjusted odds ratio were performed using Stata 15 to generate a forest plot to assess the association between BCPR and paediatric OHCA survival. Pooled odds ratio (pOR) and 95% CI were calculated from extracted raw data or backward calculated from the presented odds ratio.[115] DerSimonian & Laird's random effects method was used, with Mantel-Haenszel's heterogeneity estimates. Studies were assessed for clinical, methodological and statistical heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic (I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; and I^2 = 75–100%, extreme heterogeneity). A narrative synthesis was conducted if clinical, methodological, and statistical heterogeneity were deemed too substantial across studies to allow for meaningful meta-analyses. If there were sufficient studies, the factors affecting heterogeneity (e.g. age, sex, cause of CA, the status of witnesses, initial rhythm) were analysed using Meta-Regression Analysis. Where studies were found to include overlapping patient data, a risk-of-bias tool was used to select the studies to be used in meta-analysis. Studies with the lowest risk of bias were selected, or the largest sample size was included if the risk of bias was similar.

3.4 RESULTS

Initially, 6,296 studies were considered eligible. After removing the duplicates, 3,144 titles and abstracts were included. 2,763 studies were excluded after screening the title and abstract. 381 studies were eligible for assessing the full text. After reading their full text, 358 studies were excluded for the following reasons: study design (80 studies), data cannot be extracted (89 studies), literature, systematic reviews or guidelines (122 reviews), conference abstracts (64 abstracts) and non-full text papers (3 studies) (see Figure 3-1 for PRISMA diagram). Screening references revealed one relevant study. 22 studies met the inclusion criteria for this systematic review. However, seven studies were excluded from the meta-analysis due to data overlapping.

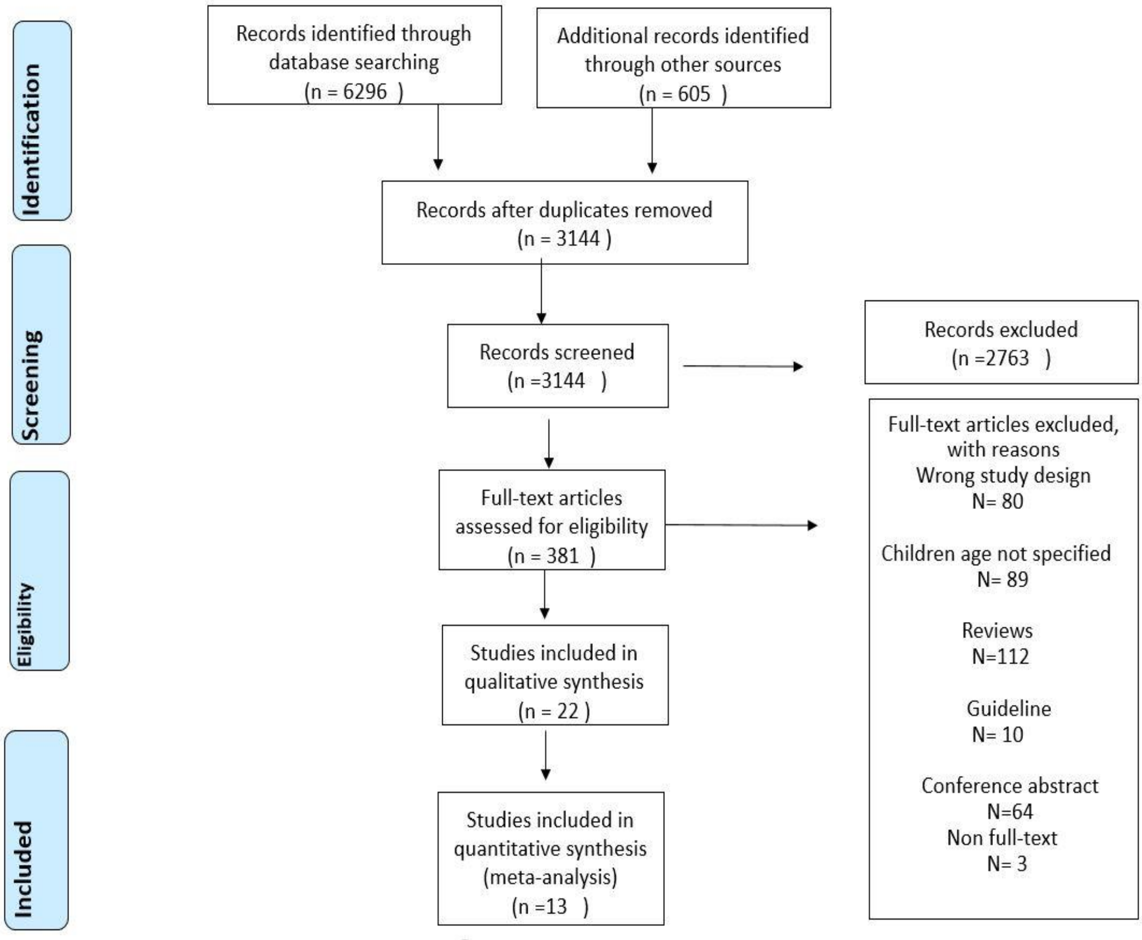

Figure 3-1 The PRISMA flow diagram of the study selection

3.4.1 Description of the studies

A description of 22 cohort studies is shown in Table 3-1. All studies included in this systematic review were observational studies. Ten studies were conducted in Japan[3, 28, 33, 63, 71, 75, 77, 84, 116, 117], four in Korea[40, 73, 118, 119], two in Sweden[47, 120], and one each in the following countries: United States[41], Finland[44] Denmark,[29], Hong Kong[81], Australia[121], and United States /Canada[122]. The number of participants ranged from 40 to 12,877. Five studies have participants aged over 18 [29, 40, 73, 75, 120], but there was a possibility to extract paediatric data from all studies. All studies were published between 1995 and 2018. All studies included in this review have tested the association of BCPR and at least one of the outcomes of interest.

Table 3-1 Studies included in review

Author/ Year	Country	Type of Study	Number of Patients	Male(%)	Age of Patients	Time point	Clinical Outcomes
Kitamura 2010[3]	Japan	Prospective observational study (national population-based)	5,170	61.1	≤ 17 yrs	1 month	CPC 1 or 2, Survival, ROSC
Abe 2012[33]	Japan	Prospective observational study (national population-based)	3,189	58	< 1 year	1 month	Survival
Akahane 2012[75]	Japan	Prospective observational study (national population-based)	1,723	67.8	≤20 yrs	1 month	CPC 1 or 2, Survival
Akahane, 2013[117]	Japan	Prospective observational study (national population-based)	7,624	62	≤ 18 yrs.	1 month	CPC 1 or 2, Survival
Kitamura 2014[84]	Japan	Prospective observational study (national population-based)	3,278	62.6	<18 yrs	1 month	CPC 1 or 2, Survival, ROSC
Goto, 2014[77]	Japan	Prospective observational study (national population-based)	5,009	60.6	<18 yrs	1 month	CPC 1 or 2, Survival
Goto 2015[116]	Japan	Prospective observational study (national population-based)	7,332	60.7	<18 yrs	1 month	CPC 1 or 2, Survival
Goto 2016[63]	Japan	Prospective observational study (national population-based)	12,877	61	< 18 yrs	1 month	CPC 1 or
Fukuda 2016[71]	Japan	Prospective observational study (national population-based)	2,157	62.4	1 to <18 yrs	1 month	CPC 1 or 2, Survival, ROSC
Kiyohara 2018[28]	Japan	Prospective observational study (national population-based)	232	75.4	School age*	1 month	CPC 1 or 2, Survival, ROSC
Naim 2017[41]	US	(secondary analysis of data registry)	3,900	40	≤18 yrs	HD	CPC 1 or 2, Survival
Topjian 2018[122]	US and Canada	Secondary analysis of data registry	292	66.4	> 48 hrs <18yrs	HD	Survival
Herlitz 2005[47]	Sweden	National data registry	457	62	< 18 yrs	1 month	Survival
Gelberg2015[120]	Sweden	Prospective observational study based on national registry data	2,864	N/A	≤35 years	1 month	Survival
Ro 2016[118]	Korea	Cross sectional prospective study based on national registry	1,529	66.1	≤18 yrs	HD	CPC 1 or 2, Survival, ROSC
Lee 2017[40]	Korea	Cross sectional prospective study based on national registry	1,013	64.3	< 19 yrs	HD	CPC 1 or 2, Survival, ROSC
Chang 2018[119]	Korea	Cross sectional prospective study based on national registry	2,020	66.3	≤18 yrs	HD	CPC 1 or 2, Survival, ROSC

Author/ Year	Country	Type of Study	Number of Patients	Male(%)	Age of Patients	Time point	Clinical Outcomes
Chang 2018[73]	Korea	Cross sectional prospective study based on national registry	1,953	68.7	> 1yr < 19 yrs.	HD	CPC 1 or 2, Survival, ROSC
Deasy 2011[121]	Australia	Case series observational study based on registry data	53	58.5	<18 yrs	HD	PCPC, Survival, ROSC
Rajan 2014[29]	Denmark	Prospective observational study based on registry data	459	67.1	≤21 yrs	1 month	Survival
Kuisma 1995[44]	Finland	Retrospective observational study	79	53.2	≤16 yrs	HD & 1 yr	Survival
Ho 2016[81]	Hong Kong	Retrospective case series study	40	60	≤17 yrs old	HD	Survival, ROSC

*Non-traumatic OHCA patients from elementary school, junior high school, and high school/technical college. HD: Hospital discharge. CPC Cerebral Performance Category, PCPC: paediatric cerebral performance category

3.4.2 Sex

All the studies except for one had a higher number of male patients than females; the total number was 36,610 males out of 60,386 patients (60%) (Table 3-2). There was a slight variation in the percentage in each study, ranging from 40% to 68%. The only study where female patients exceeded males was in the United States, with a total percentage of 60% female.[41] Furthermore, there was one study from Sweden where we could not extract the percentage for each sex due to missing data.[120]

3.4.3 Age Differences

Eighteen studies included infant and paediatric patients, with ages ranging from less than one to 21 years. Four studies did not include the infant population.[28, 71, 73, 121] One study did not include children aged over one year.[33] Two studies reported the median age of two years and 23 months.[47, 122] Sixteen studies allowed analysis of age groups and overall was 24,458 (40%) patients were less than one year and 36,536 (60%) patients were older than one year (Table 3-2).

3.4.4 Aetiology

Twenty-one studies reported adequate data about the cause of CA. Based on the classification we have used, which is cardiac vs non-cardiac origin, nineteen studies included both causes. Of the two remaining studies, one study included only cases caused by cardiac, and the other included OHCA due to hanging.[41, 121] The majority of cases were due to non-cardiac origin, with a total number of 36,456 (62%) cases, compared to 22,022 (38%) cases caused by cardiac origin.

3.4.5 Initial Rhythm

The type of rhythm recorded in CA was reported in 21 studies. The rate of shockable rhythm was lower compared to non-shockable. Overall, the proportion with a shockable rhythm was 11% (4,744/ 41491). However, this ranged from 0 to 96% due to trial inclusion criteria.(40, 81) Asystole was reported in ten studies and was the most common rhythm recorded, with 24,191 cases.

3.4.6 Witness status of CA/ Location of CA

Twenty-two studies included in this review reported the status of the patient being witnessed. Two studies included only witnessed cases.(75, 84) After excluding those two studies, the average percentage of the OHCA patient being witnessed was 30%. The witness status percentage in the largest study was 29%.(63) The lowest witness status recorded was 6%, whereas the highest was 86%.(28, 121) Regarding the location of CA, eleven out of these twenty-two studies included sufficient data about the location of CA. We found that most OHCA occurred at home (64%).

3.4.7 Bystander CPR rate

Twenty-one studies reported the rate of BCPR. For the BCPR rate, 51% (27,640/53,945) of patients received bystander CPR. The lowest bystander rate was 20%, and the highest was 85%.(28, 81) Seven studies reported the type of bystander CPR (conventional, compression only or rescue breathing).(3, 33, 41, 63, 71, 75, 77) (see Appendix 8-5, p219) Dividing results based on the largest study conducted in each continent, the largest study in Asia, North America, and Europe had 52%, 47% and 75% of patients receiving bystander CPR respectively.(41, 63, 120) (Table 3-3)

Table 3-2 Patient Characteristics

Characteristics of participant n (%)	Total n (%)
Male	36,610/60,386 (60%)
< 1 year of age	24,458/60,994 (40%)
Cardiac origin	22,022/58,478 (37.5%)
Shockable	4,744/41,491 (11%)
Witnessed	17,287/56,553 (30%)
Home	8,249/11,394 (72%)
Bystander CPR performed	27,640/53,945 (51%)

Table 3-3 Bystander rate in the largest studies in each continent

Author	year	Country	Total pediatric participants n	Bystander CPR n	(%)
Gelberg[(120)]	2015	Sweden	1,321	950	(75)
Goto[(63)]	2016	Japan	12,877	6,722	(52)
Naim[(41)]	2017	US	3,900	1,814	(46)

3.4.8 Favourable neurological outcome CPC 1 OR 2 at one month

Although nine out of 22 reported the primary outcome of good neurological outcome (CPC1 or 2) at one month, all nine studies were from the same Japanese national registry and included overlapping data series, so pooled analysis was not possible.[(3, 28, 63, 71, 75, 77, 84, 116, 117)] The largest of these studies was by Goto et al. in 2015[(116)], which identified a statistically significant association between BCPR and good neurological outcomes at one month. The odds of a favourable neurological outcome was 58% higher upon receiving BCPR compared to no-BCPR (Odds Ratio (OR) 1.58 [95%CI 1.26 to 1.99]). Eight studies showed a higher odds of a favourable neurological outcome at one month when BCPR was performed. In contrast, one study [(116)] showed a non-significant association when the BCPR performed was compared to no-BCPR (Odds Ratio (OR) 1.60 [95%CI 0.99 to 2.61]).

3.4.9 Return of Spontaneous Circulation

Eight studies reported data on the association of bystander CPR and ROSC outcome. Due to overlapping data, only three studies were included in the meta-analysis, and pooled odds ratio showed that the odds of achieving ROSC was 130% higher in those receiving BCPR compared to those who did not (pOR: [95%CI]) was 2.30 [1.17-4.52]. These three studies were in Asia and reported the outcome for 7,218 cases. ROSC rate in the largest study was 6.7%, with an odds ratio of 1.50 (95%CI, 1.20-1.90). (Figure 3-2)

3.4.10 Survival to Hospital Discharge

Survival to hospital discharge was reported in eight studies. The majority of studies were in Asia (five studies), two in North America and one in Europe. Two studies were excluded from the meta-analysis because of data overlapping. The overall number of cases was 11,354, and pooled odds ratio showed improvement in survival to hospital discharge in those receiving BCPR compared to those who did not (pOR: [95%CI]) was pOR 2.30 [1.41 to 3.75]. (Figure 3-3)

3.4.11 Survival to One Month

Of the twenty-two studies included in this review, thirteen reported survival to one month. Ten studies were conducted in Japan and three studies in Europe. For the meta-analysis, only four studies, including 14,970 patients, were included due to data overlapping. The meta-analysis showed that the odds of one-month survival was significantly higher with BCPR vs no-BCPR; pOR 1.43 [95% CI 1.27 to 1.60]. (Figure 3-4)

3.4.12 Survival to hospital discharge and survival to one month

We performed a post-hoc analysis using the combined outcomes of survival to hospital discharge and survival to one month. Six studies reported survival to hospital discharge and four reported survival to one month. The meta-analysis showed that the odds for both survival was significantly higher with BCPR compared to no BCPR; pOR 1.84 [95% CI 1.39 to 2.43].(Appendix 8-5, p220)

Author	Country	Year	BCPR	No BCPR	BCPR with ROSC	No BCPR with ROSC	OR (95% CI)	% Weight
Kitamura	Japan	2010	2439	2719	165	122	1.50 (1.20, 1.90)	49.16
Ho	Hong Kong	2016	8	32	7	6	30.30 (3.10, 295.00)	7.49
Chang	Korea	2018	1040	980	78	32	2.40 (1.58, 3.66)	43.35
Overall, DL (I^2 = 79.7%, p = 0.007)							2.30 (1.17, 4.52)	100.00

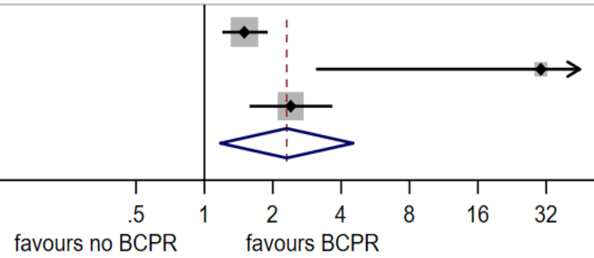

Figure 3-2 Pooled analysis of odds of return of spontaneous circulation by BCPR status.

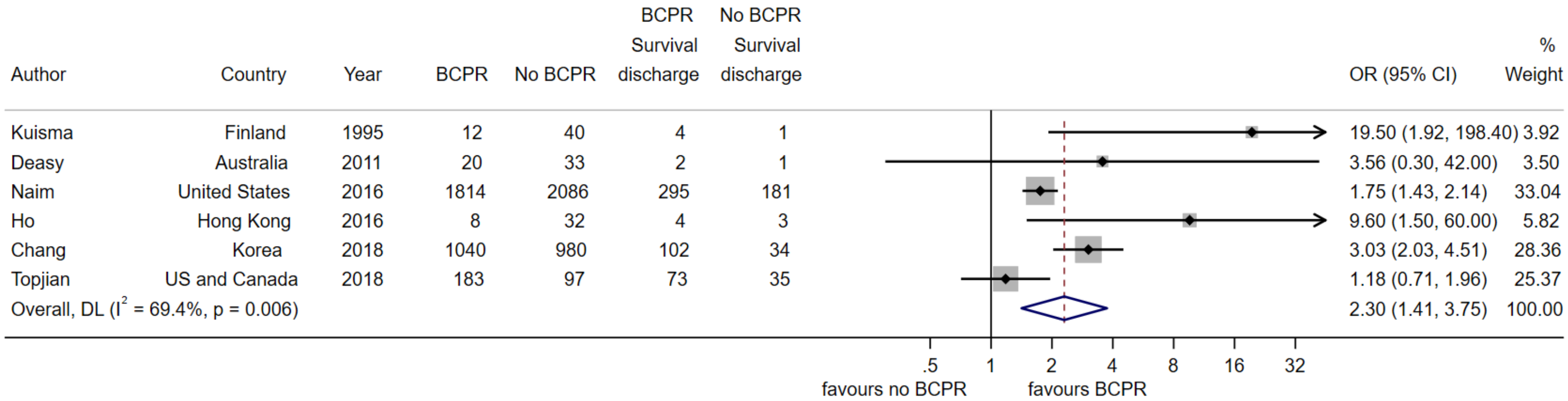

Figure 3-3 Pooled analysis of odds of survival to hospital discharge by BCPR status

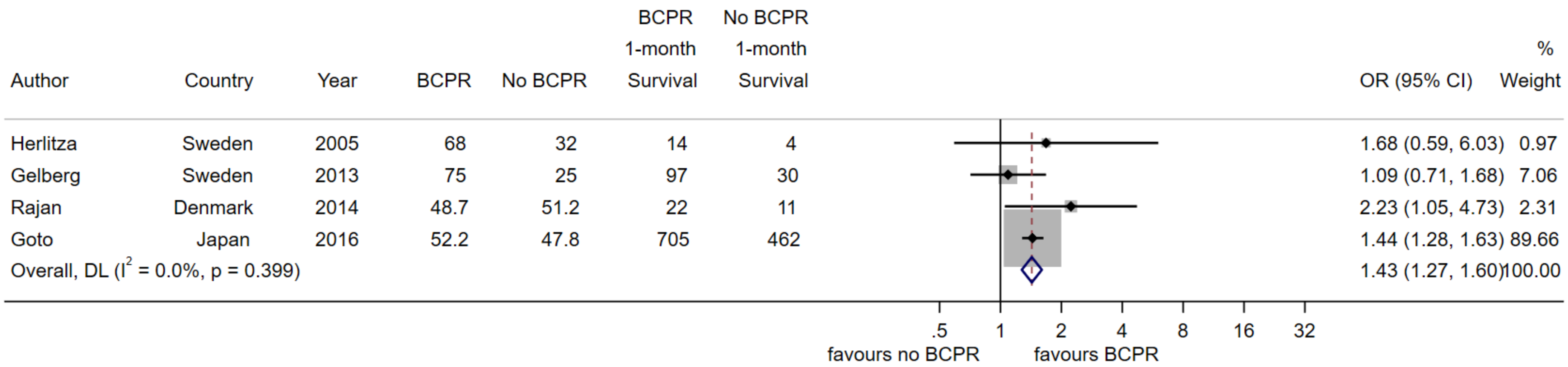

Figure 3-4 Pooled analysis of odds of survival to one month by BCPR status

3.4.13 Quality of the included studies

The overall risk of bias was low, as assessed by the Newcastle Ottawa Score (NOS) (Table 3-4). All studies scored higher than 6 in the NOS. Yet, most studies failed in comparability due to heterogeneity within studies and the significant difference in characteristics of the underlying cohorts. The adjustment for bystander resuscitation, compared to no bystander resuscitation, was only available in three studies.

Table 3-4 Quality assessment for included studies

Study, Year (Reference)	Selection				Comparability	Outcome			Aggregate score
	Representativeness of the exposed cohort (maximum:*)	Selection of the non-exposed cohort (maximum:*)	Ascertainment of exposure (maximum:*)	Demonstration that outcome of interest was not present at start of study (maximum:*)	Comparability of cohorts on the basis of the design or analysis (maximum:**)	Assessment of outcome (maximum:*)	Was follow up long enough for outcomes to occur (maximum:*)	Adequacy of follow up of cohorts (maximum:*)	
Kitamura 2010	*(b)[a]	*	*(a)[d]	*	/	*(b)[e]	*	*(b)[g]	(7)
Abe et al 2012	*(b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Akahane 2012	*(b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Akahane 2013	*(a)[b]	*	*(a)	*	/	*(a)	*	*(a)	(7)
Kitamura 2014	*(b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Goto 2014	*(a)	*	*(a)	*	/	*(b)	*	*(a)[h]	(7)
Goto 2015	* (b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Goto 2016	*(a)	*	*(a)	*	/	*(b)	*	*(a)	(7)
Fukuda 2016	*(b)	*	*(a)	*	*	*(b)	*	*(a)	(8)
Kiyohara 2018	(C)[c]	*	*(a)	*	/	*(b)	*	*(a)	(7)
Naim 2017	* (b)	*	*(a)	*	*	*(b)	*	*(b)	(8)
Topjian 2018	* (b)	*	*(a)	*	/	*(a)[f]	*	*(b)	(7)
Herlitz 2005	* (b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Gelberg 2015	* (b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Ro 2016	*(a)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Lee 2017	* (b)	*	*(a)	*	*	*(b)	*	*(a)	(8)
Chang 2018	*(a)	*	*(a)	*	*	*(b)	*	*(b)	(8)
Chang 2018	* (b)	*	*(a)	*	*	*(b)	*	*(b)	(8)
Deasy 2011	*(b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Rajan 2014	*(b)	*	*(a)	*	/	*(b)	*	*(b)	(7)
Kuisma 1995	*(b)	*	*(a)	*	/	*(b)	*	*(a)	(7)
Ho 2016	*(b)	*	*(a)	*	*	*(b)	*	*(a)	(8)

Legend for table 3-4 :
NOS: selection, comparability and ascertainment asterisks (*) of a maximum score of 4, 2, and 3 respectively. The highest score is 9 and the lowest is zero.
[a] truly representative
[b] somewhat representative
[c] selected group of users e.g. student
[d] secure record e.g. data registry
[e] record linkage
[f] Independent blind assessment
[g] subjects lost to follow up unlikely to introduce bias (small percentage)
[h] complete follow up - all subjects accounted for

3.5 DISCUSSION

In this systematic review, we identified that bystander CPR significantly increases the chance of achieving good neurological outcomes (CPC 1 or 2) at one month, although this was only available from studies reporting from the Japanese registry, and only one study could be included in our analysis. In addition, BCPR significantly increased the chances of ROSC, survival to hospital discharge and survival at one month among paediatric patients who suffer OHCA.

In comparison, a systematic review published a decade ago showed no clear link between bystander CPR and survival.[72] The authors ascribed that to the heterogeneity which existed among studies. However, despite the variation found between studies, our pooled analysis suggested that bystander CPR is associated with better survival outcomes. It is worth mentioning that the unadjusted, rather than the adjusted odds ratios, were pooled as all the included studies used different variables for adjustment within their logistic regression analysis. Pooling the adjusted odds ratio was therefore not possible and would have added significant statistical heterogeneity.

We undertook meta-analysis having considered clinical and statistical heterogeneity of our data. Although there was an inherent risk of heterogeneity due to missing data in the registries and variability in the studies design, we felt that as the population studied and the exposure of interest (eg BCPR by a lay person) were consistent, and the outcomes were clearly reported, that it was appropriate to proceed to perform meta-analysis.

When examining the association of bystander CPR and survival to hospital discharge, we found that these children have a higher chance of surviving until discharge. This is similar to the adult population, where bystander CPR is considered a major factor to positively affect survival to hospital discharge.[18] Further, our meta-analysis refutes the conclusion in a previous review, where the association of bystander CPR with survival to hospital discharge was not statistically significant.[72] Yet, we agree with the author that heterogeneity is a major issue in paediatric studies that might lead to inaccurate results.

In paediatrics, the overall survival rate at one month is low, with an approximate rate of 9%.[63, 120] When limiting the data to the association of bystander CPR and one-month survival, we found that 70% of patients who survived to one month had bystander CPR.[29, 47, 63, 75, 120] These data are similar to report from The American Heart Resuscitation (AHA).[110] Our meta-analysis confirmed that bystander CPR increases the chance of survival to one month, compared to paediatric patients who do not receive bystander CPR.

In our a-priori analysis plan, we kept the survival to hospital discharge and survival to one month outcomes separate. There are several reasons for this decision. One of the main reasons is that due to the heterogeneity that was observed in the paediatric studies included in this review, combining both outcomes may have added additional heterogeneity. This may have resulted because the length of stay at hospital was not reported in the studies that reported the survival to hospital discharge. In the cases of paediatric CA, some of them may have stayed at the hospital for a longer period since they required longer time for post resuscitation care and recovery. Further, there was also a potential issue with overlapping data as a number of studies came from the same international registry.

Regarding the one-month favourable neurological outcome CPC1 or 2, which is the main outcome we were aiming to assess, the data were limited to one national data set. Thus, the pooled analysis was unobtainable. However, the existing data suggest that the rate of favourable neurological outcome CPC1 or 2 at one month improved when a bystander performed resuscitation.[63, 116] One month timescale remains short-term, and therefore there is a need to increase the long-term outcome measurement, as described in the Pediatric Core Outcome Set after Cardiac Arrest [123] to create a clear image about the longer-term effect of bystander CPR in paediatric OHCA.

In this review, the average percentage of BCPR was 51%. However, similar to studies including adults only, there was a wide variation in the rate of bystanders performing CPR, where the highest rate was 85% in Japan, and the lowest was 20% in Hong Kong.[28, 81] In the Japanese study that reported the highest BCPR rate, cases of OHCA were limited to non-traumatic CA on school campuses. Furthermore, 87% of cases were witnessed, which has the opportunity to increase the rate of BCPR. Additional reasons in these health care settings could influence the bystander CPR rate, such as the existence of dispatcher-assisted EMS system, the community willingness to perform CPR, their education level, and the establishment of community CPR training programmes. In the Hong Kong study, despite the small study size, the BCPR rate was only 11% in the cases occurring at home. This suggested that there was potentially a difficulty in recognizing CA and people not being educated to perform resuscitation.

Our result showed that boys were more likely to suffer OHCA compared to girls. The epidemiological findings were consistent in all studies, except one study from the United States.[41] The result is similar to the findings in the adult population.[124, 125] This association between sex and OHCA is not well addressed. Further, the result showed that children aged less than one year formed about 40% of the total cases included in this review. This is in contrast with other studies, where the incidence of OHCA is higher in infants compared to other age groups.[34] One possible factor that could justify our result is that infants were excluded in four of the studies included in this review.

Previous studies in paediatric OHCA demonstrated that asphyxia is a major cause of CA.[33, 42] Our results emphasise that non-cardiac origin is the most common cause of CA, compared to cardiac origin among paediatric cases in this review. Because of the variability in describing aetiology, where some studies include asphyxia under the category of non-cardiac causes and other studies have asphyxia as a separate category, we could not have further details to describe the cause of CA. To summarise, unlike adults, children tend to have OHCA due to non-cardiac origin.[16]

In a previous systematic review by Donoghue et al., the overall percentage of paediatric patients who were witnessed by a bystander was 30%, and 13% of them survived to discharge.[72] Similarly, our result showed the total percentage of patients being witnessed by a bystander was 30%. We were not able to assess the association of witness status and survival. Further, our finding regarding the location of CA was similar to previous studies, where most cases occur at home.[1, 73, 120] Previous studies suggested that CA occurring at home had less chance of being witnessed. However, we could not find a link between CA's location and witness status.

Our result emphasises the importance of BCPR in Paediatric OHCA. BCPR is clearly a critical element of the chain of survival and is associated with the chance of good neurological survival. The results also showed a variation in the rates of BCPR between communities. Establishing training programmes and building up strategies to raise awareness about the importance of BCPR is a crucial step: targeting the family at home, encouraging them to learn basic life support, and discussing reasons that could stop them from performing resuscitation. In addition, establishing courses that target pupils at school is important. The highest BCPR rate in this review was in a Japanese study focused only on OHCA on the school campus. Thus, establishing first aid courses that target students at school is important.

3.6 STRENGTH AND LIMITATIONS

This systematic review has several limitations. Firstly, all studies included in this review were observational studies. Secondly, heterogeneity was observed between studies. In two of the pooled analyses we identified a high I-squared value (68.9%, 79.7%) indicating a high percentage of variability due to between-study heterogeneity. We also found differences in EMS systems in each country, how data were collected, and the skill of the EMS providers. In addition, categorising the paediatric age differed between studies. Further, we have included five studies where the upper age limit was over 18 years. However, the majority used 21 years as the upper age cut off and the number of patients between 18 and 21 was small. This may have altered our result as two studies with a few children over 18 were included in the meta-analysis. However, this is unlikely to have affected our conclusion. Thirdly, we could not assess for possible confounding factors that might have affected survival. Fourth, there were limited data showing the association between BCPR and one-month favourable neurological outcome CPC1 or 2 which was the primary outcome.

3.7 CONCLUSION

Children receiving BCPR after OHCA have a significantly higher chance of achieving ROSC, survival to hospital discharge and survival at one month. Improved one-month favourable neurological outcome was also found, but we identified limited reporting from only one cohort of patients. Data describing the impact of BCPR on survival outcomes is limited. Therefore, further research is needed to examine the association of BCPR and survival outcomes. Also, it is important to describe the epidemiological and clinical factors that might have an impact on BCPR rate and quality. Finally, global initiatives to increase BCPR should be encouraged to improve important clinical outcomes for children. This review of the evidence should encourage emergency care providers to raise awareness among the population about the importance of bystander intervention.

3.8 ACKNOWLEDGEMENT

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4 The Epidemiology and Outcome of Paediatric OHCA in England.

4.1 ABSTRACT

Background: Little is known about the epidemiology of paediatric OHCA in England. Factors including CA characteristics, prehospital factors and emergency medical services (EMS) procedures may affect patients' outcomes. Therefore, exploring the epidemiology of paediatric OHCA in England may identify factors associated with improved survival outcomes and be potential targets for quality improvement strategies.

Objective: To describe the incidence rate and the epidemiology of paediatric OHCA across EMS regions in England and explore variation in patient and EMS factors associated with a return of spontaneous circulation (ROSC) and survival.

Method: An analysis of paediatric (<18 years of age) OHCA in England from the national OHCA registry. Data on OHCA location, patient demographics, resuscitation management and EMS activity have been prospectively collected from January 2014 to November 2018. The study's primary outcome was the rate of EMS-treated paediatric OHCA. The primary endpoint was survival to hospital discharge, and secondary endpoints were ROSC at any time and at hospital admission.

Result: A total of 2,865 paediatric OHCA cases were treated by EMS across 5 years. The median age was 3.3 years (IQR 0.5 to 11.8 years) and 59.0% were male. An EMS practitioner or a member of the public witnessed 40.6%, bystander CPR was performed in 65.8% and an Automated External Defibrillator (AED) was used in 2.2% of OHCA cases. The most common aetiology was an assumed medical cause (70.9%). Asystole was recorded as the initial rhythm in 78.2% and a shockable rhythm in 7.3%. The overall incidence rate was 5.3 per 100,000 person-years and was five times higher in children less than one year. ROSC was achieved at

any time point in 25% and at hospital handover in 20%. The overall rate of survival to hospital discharge was 11%, although varied by EMS region from 6.5 to 21.7%.

Conclusion: The incidence rate of paediatric OHCA is low compared to adults, although highest in children under one year. Although one in four cases achieved ROSC, survival to hospital discharge was only 11%. Variation in ROSC and survival rates across the English EMS regions may allow opportunity to identify modifiable factors and target quality improvement measures to improve resuscitation outcomes.

4.2 INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) in children is rare compared to adults.[11, 126] Similar to reported outcomes for adults after OHCA [62], the survival rate in children is low, ranging from 2 to 11%.[34, 37, 41, 42, 49] The variability in the reported survival rate may be due to heterogeneity among paediatric studies which was describe in chapter one. The factors associated with improved rates of survival include event characteristics (e.g. witnessed CA[34, 37, 41, 43, 72], shockable rhythm [34, 37, 127]), and community interventions (e.g. BCPR and public access defibrillation (PAD) use).[28, 41, 64, 128] Such interventions may be dependent on government or charity financial support to establish training, courses and increase the availability of PADs which in turn may raise public awareness and improve their skills in managing OHCA cases. Understanding the role of these factors in paediatric OHCA is important for health care policy makers to promote and support community health training initiatives.

To accurately understand the epidemiology of paediatric CA, its incidence across different age ranges, aetiologies and eventual outcomes, establishing a prospective data registry is a crucial step. Data registries allow to prospectively define the patient demographics of interest, event characteristics to be collected and standardise data collection nationwide. Furthermore, it allows for a comparison of systems of care within one country with other international data registries. In England, the Out of Hospital Cardiac Arrest Outcome Registry (OHCAO) was established for this purpose in 2012, aiming to provide data on patient demographics and clinical outcomes across the English regions. It also enables the observation of regional differences across the country.[2]

Data from the OHCAO registry has been used to report the epidemiology of adult OHCA in the English population [(2)]; however, the current epidemiology and outcomes of paediatric cases in the OHCAO registry have not been described. Therefore, we aim to use the OHCAO registry to:

1) Calculate the incidence rate of paediatric OHCA across England and individual emergency medical services (EMS) regions.

2) Examine the association between CA characteristics, prehospital factors, and clinical outcomes in paediatric OHCA cases.

4.3 METHODOLOGY

4.3.1 Setting and population

This is a retrospective analysis of prospective data for OHCA occurring in children younger than 18 years who were resuscitated by EMS from January 2014 to November 2018. The data were collected by 11 English ambulance services in different regions of England (the Isle of Wight submitted data for 2018 only) and submitted to the OHCAO registry. Cases with a 'Do not Attempt Resuscitation' (DNAR) notice or whose arrest occurred during inter-hospital transfer were excluded. The incidence rates for the paediatric OHCA age group were calculated using data from the Office for National Statistics for Great Britain's mid-year estimate from 2014-2018.

4.3.2 Why registry data

As previously mentioned in the introduction, using a data registry has its advantages and disadvantages. On the one hand, a data registry can provide real-life data and a large sample size, making it more representative of the true population. However, the purpose of the data registry may influence the number of data items, the definitions and the quality of the data being collected. It is collected prospectively, however registries often do not have the additional resources required for data monitoring, data verification, and missing data completion.(129, 130) Therefore preforming a secondary analysis on registry has its limitation. Another approach considered when designing this study was a prospective cohort study. Unlike a data registry, a prospective cohort study specifies variables prior to the start of the study, giving it better control over confounders and selecting variables.(131) However, a prospective cohort study is time-consuming, and data collection and follow-up can last for years.[132] Despite the advantages and disadvantages of each approach, we chose to use a data registry in our study due to its suitability for our specific research needs.

4.3.3 Description of EMS

The description of the EMS in England was described elsewhere.(Section 1.8)

4.3.4 Variable definitions

According to OHCA registry protocol, age is calculated based on date of birth and the EMS' estimated age if the date of birth is missing.[2] Using Utstein Style[4], children were divided into five age groups: infants (≤1 year), pre-school children (>1-4 years), schoolchildren (>4-8 years), older school children (>8-12) and adolescents (>12-18 years). CA cause was categorised as medical (presumed cardiac origin), trauma, drowning, drug overdose, asphyxia and non-cardiac cause. Shockable rhythm included ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT), and non-shockable rhythm included asystole and pulseless electrical activity. Bystander CPR has been defined as CPR performed by a public member. Witnessed was defined as CA witnessed by a bystander, an EMS provider or either.

4.3.5 Primary outcome and endpoints.

The primary outcome was survival to discharge, which was calculated based on the number of patients surviving to hospital discharge compared to all patients with attempted resuscitation during the study time period. The secondary outcome was ROSC which included: ROSC at hospital handover, including cases where patients arrived at the hospital with ROSC; ROSC at anytime, including ROSC at hospital handover and prehospital ROSC, where ROSC was noted on the arrival of the EMS and cases where ROSC was achieved during transportation.

4.3.6 Database handling, testing and cleaning

Data were documented as Microsoft excel spreadsheets (Microsoft, Seattle, WA). The data cleaning process started by removing OHCA cases for patients aged 18 or over and any repetitive cases. A sample of 5% of the data was used to test the data. We then created a table of definitions, which included each variable of interest. The table also included how each variable should be treated (e.g. continuous, categorical or both continuous and categorical). Some of the variables were grouped into fewer categories. The percentage of missing data was calculated for each variable of interest. An additional statistical plan was created to describe how the data were presented and analysed for this study.(Appendix 8-7, p221)

4.3.7 Handling missing data

We anticipated missing data in the registry. We therefore considered different approaches to handling missing data in the descriptive analysis and logistic regression modelling.

For descriptive analysis we planned to report amount of missing data per variable. We included maximum available data and did not exclude variables with missing data as this could lead to bias and information loss especially when sample sizes are small.

Where the outcome data was missing, our approach to dealing with missing data included a sensitivity analysis where we assumed all missing outcome data of survival to hospital discharge, either survived or did not survive. This method provides a range for a particular variable; however, it is may not be an accurate method to handle missing data as it will report extremes of outcome potential.

Multiple imputation[133] was another approach we considered for handling missing data.[134] In this method, multiple copies of the dataset are generated with imputed values replacing the missing values each time. The imputed datasets are then analysed, and their results appropriately combined. However, there are several challenges to this approach. First, the vast majority of the variables included in this study were binary and categorical variables, and this increases the likelihood of failure in the imputation process due to perfect prediction.[135, 136] This occurs when an explanatory categorical variable (or a combination of) perfectly discriminates the outcome, leading to biased results. Second, the underlying cause of missingness can be challenging to identify. Multiple imputation relies on the assumption that the data is missing completely at random (or at worst, missing at random) and violations to this assumption could lead to biased results.[137, 138] Therefore we did not plan to perform multiple imputation on the available data.

To summarise, there are different methods to handle missing data and we have chosen to include all cases and report the percent of the missing data and do some sensitivity analysis for the key outcomes that were missing to see what effect that would have on the data and we chose not to use imputation.

4.3.8 Statistical analysis

The demographic and clinical characteristics of OHCA patients were described as numbers and percentages for categorical variables and median and interquartile ranges for continuous variables. The Chi-square test was used for comparisons between categorical variables (or Fisher's Exact test if the sample size was small). The Mann-Whitney test was used to compare continuous variables. The incidence rate of OHCA was defined as the total cases of OHCA who received EMS resuscitations per 100,000 population. The overall incidence rate among the English population was estimated by calculating the average of the 2014-2018 mid-year estimate based on the UK Office of National Statistics (ONS).[139] The rates and the 95%

confidence interval were calculated for the incidence of OHCA by year, the incidence by age group (≤1 year, >1-4 years, >4-8 years, >8-12, >12-18 years) and the EMS regions. The analysis of the incidence rate was carried out using Microsoft Excel. The patients' characteristics were described by age group, EMS region and OHCA cases by EMS and year. We performed a sensitivity analysis of the outcomes: survival to hospital discharge, ROSC at any time and hospital ROSC, for each of the EMS regions as we identified variation in the missingness of data. Two groups were compared where the missing data in the first group were assumed to be positive (e.g. all missing outcomes for EMS1 were categorised as "survived to hospital discharge"), and in the second group, all the missing data were assumed to be negative (e.g. all missing outcomes for EMS1 categorised as "died" or did not survival to hospital discharge).Stata 15.0 was used for data management and analysing demographic and prehospital characteristics. Statistical significance was set at P < .05

4.3.9 Ethics and database application

The University of Warwick hosts the OHCAO project, which has approval from the National Research Ethics Service (13/SC/0361). Details of the registry have been previously summarised.[15] This study was additionally approved by the University of Birmingham Internal Review Board (RG 17-246. 14.11.2018).

4.4 RESULTS

4.4.1 Demographics

After the exclusion of patients 18 years or older (n=308), there were 2,865 paediatric OHCA patients from January 2014 to November 2018, as shown in Figure 4-1 . The median age was 3.3 years (IQR = 6 months - 11.8 years), and 59.0% (1648/2790) were male. CA cases were witnessed by EMS or bystanders in 40.6 % (1061/2608) of cases, and BCPR was performed in

65.8 % (1716/2608). The leading cause of CA was medical at 70.9% (1904/2682), and asystole was the most common initial rhythm recorded in 78.2% (1899/2428) of cases. Shockable rhythm was found in only 7.3% (179/2428) of cases, and AED was used in 2.2% (36/1571). Overall, ROSC at any time was achieved in 25.1% (648/2591) of cases, ROSC at hospital handover in 20.0% (514/2581) of cases, and 11.0% (261/2375) of cases survived to hospital discharge.

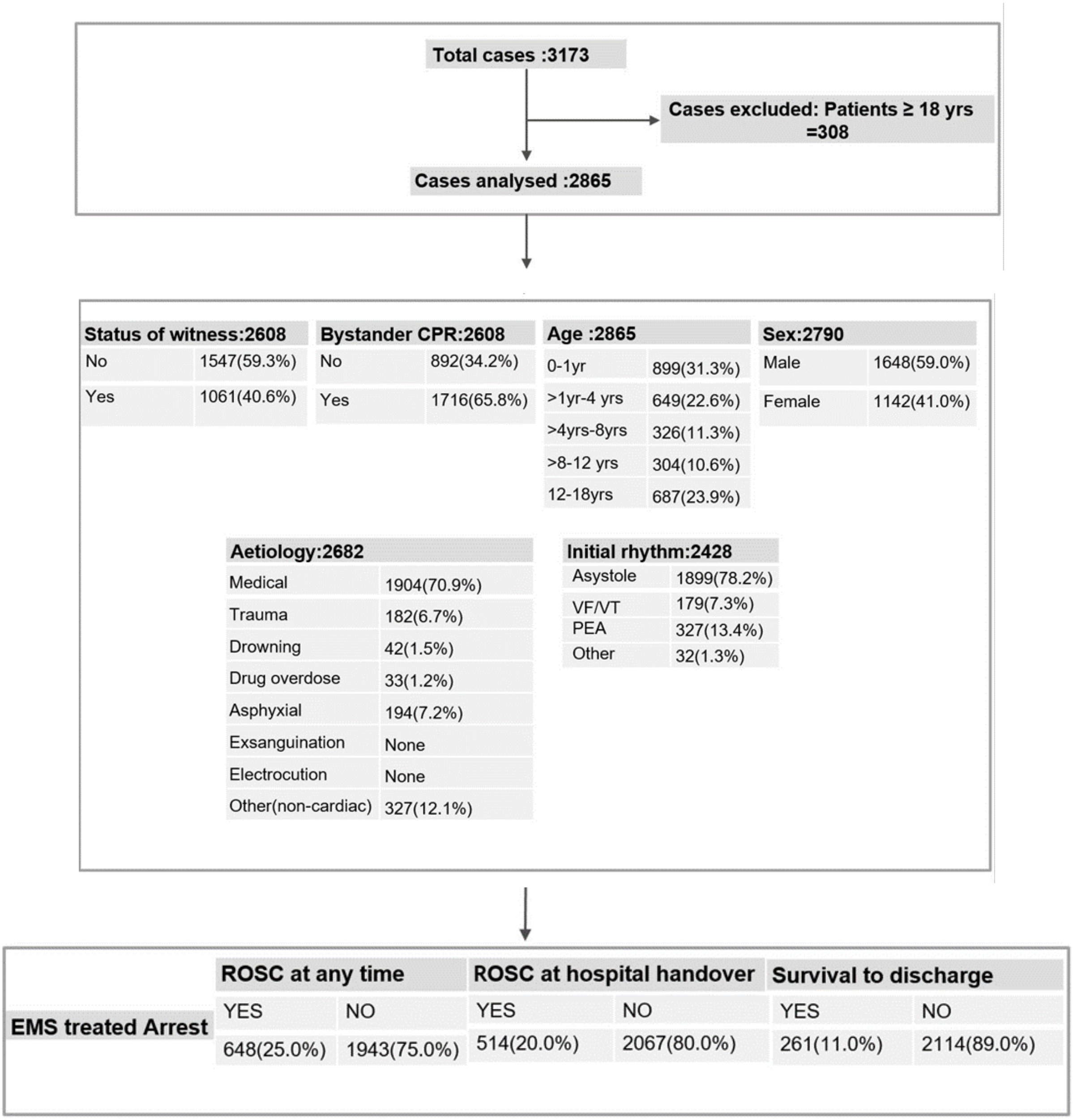

Figure 4-1 Flow chart using Utstein Style

4.4.2 Resuscitation factors analysed by age group

The age distribution of cases was skewed towards infants less than 1 year (Figure 4-2). Approximately one-third of all cases included were infants, which counted as the largest age group, followed by children aged 12 to 18 years (23.9%) based on the Utstein age grouping.

Table 4-1 presents the demographic data by age group. There were more males than females across all age groups, although a larger difference was observed in the 12 to 18 years old cohort (male 63.6% vs female 36.3%) (p=0.02). There was an association between age and the cause of CA. The Proportion of CA secondary to a medical cause decreased as age increased(≤1yr=85.8%),(>1-4yrs=77.5%),(>4-8yrs=67.3%),(>8-12yrs=63.3%),(>12-18yrs=50.8%)(p <0.0001). Trauma and asphyxia aetiology were more common in the 12 to 18 age group (15.0% and 15.8%, respectively).

Infants (< 1 year) and children aged 1-4 years were the least likely age groups to have their OHCA witnessed (31.3% & 38.9%, respectively); however, there was no difference in the BCPR rate across age groups (p=0.815). The proportion with an initial shockable rhythm was higher in older schoolchildren and adolescents compared to younger children.

The rate of survival to hospital discharge ranged from 8.4% in infants ≤1 year to 11.0% in children aged >12 to 18 years old, although this difference was not statistically significant (p=0.633); however, ROSC at any time showed improvement as the age increased (≤1yr=17.0% up to >12-18=36.5%), (p<0.0001).Similar relationship was also found for ROSC at hospital handover, as it increases as age increases (≤1yr=15.0% up to >12-18=28.7%) (p<0.0001).(Table 4-1)

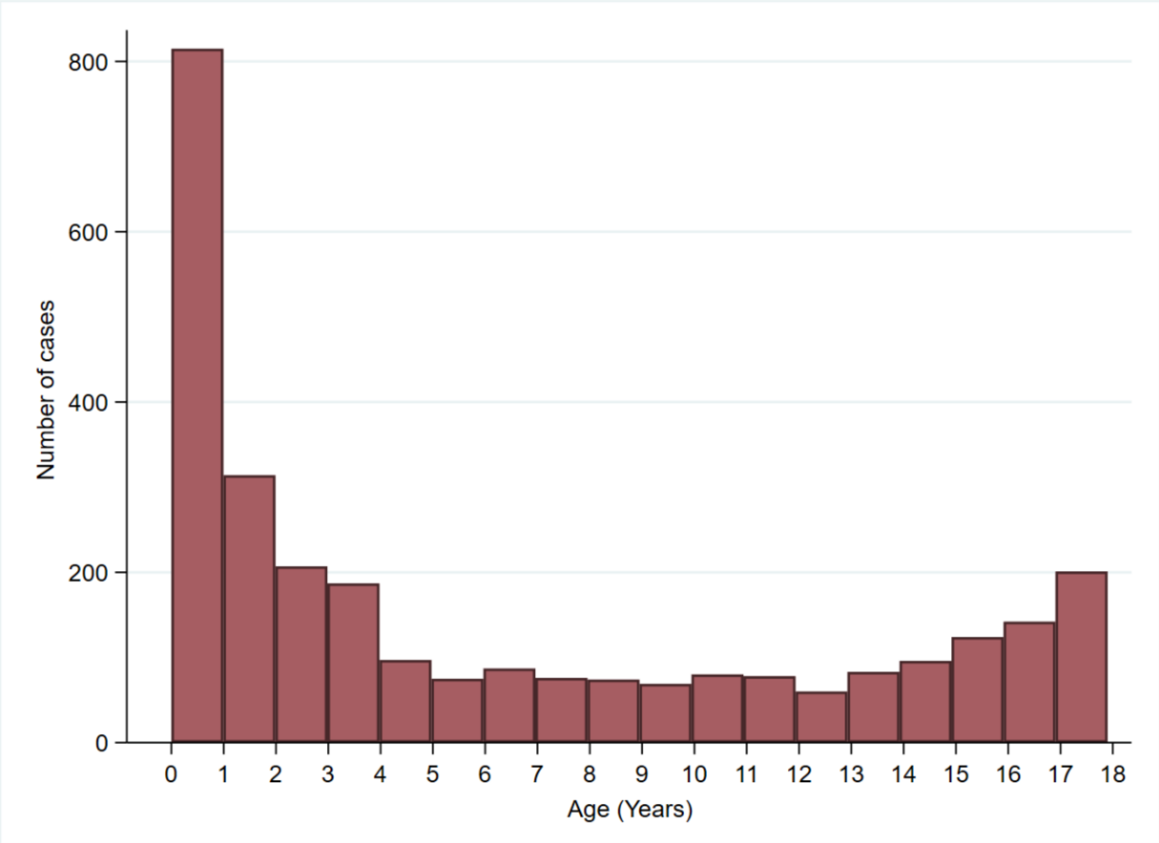

Figure 4-2 Age distribution for OHCA patient

Table 4-1 Event characteristics according to age group

	Total n(%)	≤1yr	>1 to4yrs	>4 to 8yrs	>8 to 12yrs	>12 to <18yrs	P value[b]
Overall [a]	n=2865 (100)	n=899 (31.3)	n=649 (22.6)	n=326 (11.3)	n=304 (10.6)	n=687 (23.9)	
Sex	n=2790 (97.3)	n=876 (97.4)	n=632 (97.3)	n=291 (89.2)	n=291 (95.7)	n=674 (98.1)	
Male	1648 (59.0)	491 (56.0)	379 (59.9)	188 (59.3)	161 (55.3)	429 (63.6)	
Female	1142 (41.0)	385 (43.9)	253 (40.0)	129 (40.6)	130 (44.6)	245 (36.3)	0.02
Aetiology	n=2682 (93.6)	n=829 (92.2)	n=606 (93.3)	n=312 (95.7)	n=292 (96.0)	n=643 (93.5)	
Medical	1904 (70.9)	712 (85.8)	470 (77.5)	210 (67.3)	185 (63.3)	327 (50.8)	
Trauma	182 (6.7)	9 (1.0)	32 (5.2)	23 (7.3)	21 (7.2)	97 (15.0)	
Drowning	42 (1.5)	6 (0.2)	14 (2.3)	6 (1.9)	6 (2.0)	10 (1.5)	
Drug overdose	33 (1.2)	0 (0.0)	2 (0.3)	1 (0.3)	3 (1.0)	27 (4.2)	
Asphyxia	194 (7.2)	26 (3.1)	24 (3.9)	24 (7.6)	18 (6.1)	102 (15.8)	<0.0001
Other (non-cardiac)	327 (12.1)	76 (9.1)	64 (10.5)	48 (15.3)	59 (20.2)	80 (12.4)	
Witness status	n=2608 (91.0)	n=840 (93.4)	n=563 (86.7)	n=291 (89.2)	n=272 (89.4)	n=642 (93.4)	
Yes	1061 (40.6)	263 (31.3)	219 (38.9)	124 (42.6)	143 (52.5)	312 (48.6)	<0.0001
No	1547 (59.3)	577 (68.6)	344 (61.1)	167 (57.3)	129 (47.4)	330 (51.4)	
Bystander CPR	n=2608 (91.0)	n=855 (95.1)	n=547 (84.2)	n=298 (91.4)	n=269 (88.4)	n=639 (93.0)	
Yes	1716 (65.8)	561 (65.6)	354 (64.7)	203 (68.1)	182 (67.6)	416 (65.1)	0.815
No	892 (34.2)	294 (34.3)	193 (35.2)	95 (31.8)	87 (32.3)	223 (34.9)	
Shockable rhythm	n=2428 (84.7)	n=769 (85.5)	n=515 (79.3)	n=265 (81.2)	n=256 (84.2)	n=623 (90.6)	
Yes	179 (7.3)	28 (3.6)	20 (3.8)	8 (3.0)	26 (10.1)	97 (15.2)	<0.0001
No	2226 (91.6)	732 (95.1)	488 (94.7)	257 (96.9)	225 (87.8)	524 (84.1)	
Other	23 (0.95)	9 (1.1)	7 (1.3)	0 (0.0)	5 (1.9)	2 (0.3)	
survival to discharge	n=2375 (82.8)	n=851 (35.8)	n=550 (23.1)	n=284 (11.9)	n=271 (11.4)	n=635 (26.7)	
Yes	261 (11.0)	72 (8.4)	61 (11.0)	31 (10.9)	27 (9.9)	70 (11.0)	0.633
No	2114 (89.0)	779 (91.6)	489 (89.0)	253 (89.1)	244 (91.1)	565 (89.0)	
ROSC at anytime	n=2591 (90.4)	n=851 (32.8)	n=550 (21.2)	n=284 (10.9)	n=271 (10.4)	n=635 (24.5)	
Yes	648 (25.0)	145 (17.0)	122 (22.1)	74 (26.0)	75 (28.6)	232 (36.5)	<0.0001
No	1943 (75)	706 (83.0)	428 (77.9)	210 (74.0)	196 (71.4)	403 (63.5)	
Hospital ROSC	n=2581 (90.0)	n=850 (32.9)	n=543 (21.0)	n=282 (10.9)	n=269 (10.4)	n=637 (24.6)	
Yes	514 (19.9)	133 (15.6)	87 (16.0)	52 (18.2)	59 (21.9)	183 (28.7)	<0.0001
No	2067 (80.1)	717 (84.4)	456 (84.0)	230 (81.8)	210 (78.1)	454 (71.3)	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable

4.4.3 Incidence rate overall

In total, there were 2862 paediatric OHCA cases in England across the study duration (range 514 to 650 per year).(Table 4-2) Using ONS data, the overall, yearly average paediatric population in England, between 2014 and 2018, was 11.7 million.[24] Therefore, the yearly, average incidence rate of all paediatric OHCA cases, during the study period, was 5.3 per 100,000 person-years (95% CI: 4.9-5.7).

4.4.4 Incidence rate by age

The incidence rate for infants ≤1 year was highest at 29.9 per 100,000 person-years (95% CI: 25.5-34.2), with the highest rate occurring in 2014 at 37.9 per 100,000 person-years (33.2-42.6). Children aged >1-4 years had the second highest incidence rate at 6.9 per 100,000 person-years (5.7-8.1) across the study period. Similar overall incidence rates were observed for the >4-8 years age group (2.6 (95%CI: 1.9-3.2)) and >8-12 years group (2.5 (95%CI: 1.9-3.2)). For older children (>12-18 years), there was a slightly higher increase in the incidence rate of 4.1 (95% CI: 3.4-4.8) per 100,000 person-years. Furthermore, the incidence rates in 2014 were the highest in the 0-≤1 yr, >1-4 yrs, and >4-8 yrs age cohorts compared to the other years.(Table 4-2)

Table 4-2 The incidence rates for the paediatric OHCA age group

	Population[a]	2014 [b]**(rate: 95%CI)**	2015 **(rate: 95%CI)**	2016 **(rate: 95%CI)**	2017 **(rate: 95%CI)**	2018 **(rate: 95%CI)**	2014-2018 **(rate: 95%CI)**
Total cases		N=689	N=586	N=520	N=514	N=553	N=2862
0-≤1 yr	664,183	37.9 (33.2-42.6)	27.4 (23.4-31.4)	27.8 (23.8-31.8)	26.3 (22.4-30.3)	28.5 (24.3-32.6)	29.9 (25.5-34.2)
>1-4 yrs	2,083,834	7.7 (6.5-8.9)	6.8 (5.6-7.9)	7.3 (6.1-8.5)	7.1 (5.9-8.3)	5.6 (4.6-6.6)	6.9 (5.7-8.1)
>4-8 yrs	2,694,325	2.7 (2.1-3.4)	2.4 (1.8-3.0)	2.4 (1.8-2.9)	2.6 (2.0-3.1)	2.6 (2.0-3.2)	2.6 (1.9-3.2)
>8-12 yrs	2,455,268	2.9 (2.2-3.6)	2.4 (1.7-3.0)	3 (2.4-3.7)	2.8 (2.2-3.4)	1.7 (1.2-2.2)	2.5 (1.9-3.2)
>12-18yrs	3,694,091	3.4 (2.8-4.0)	3.6 (3.0-4.2)	4.8 (4.1-5.6)	5.1 (4.3-5.8)	3.7 (3.0-4.3)	4.1 (3.4-4.8)
0-18 yrs	11,591,701	5.9 (5.5-6.3)	5.0 (4.6-5.4)	5.6 (5.2-6.0)	5.5 (5.1-5.9)	4.7 (4.2-5.0)	5.3 (4.9-5.7)

Age group and population data from Office of National Statistics (mid estimation 2014 data).

[b] Rates expressed as admissions per 100,000 population (95% confidence interval)

4.4.5 Patients’ characteristics and incidence rates across EMS regions

The number and proportion of OHCA cases varied across EMS regions throughout the study period: see Table 4-3. Data were available from 11 EMS regions; however, one EMS region submitted data in 2018 only and had very small numbers (n=3), so it was excluded from the analysis. Two EMS regions did not submit data in 2016 and 2017 (EMS 1 and EMS 10). EMS 3 contained the largest proportion of OHCA cases (20.6% (590/2862)), whereas EMS6 contained the smallest proportion of the OHCA cases (4.2% (121/2862)).Five EMS regions reported the highest OHCA cases in 2014 (EMS1,EMS3,EMS4,EMS8 and EMS10),one EMS region in 2015 (EMS6), two EMS regions in 2016 (EMS2,EMS9)and one EMS regions in 2017 (EMS5). Figure 4-3 shows the geographical location of the English EMS regions.

Table 4-3 OHCA across EMS regions by the year of the incident

	Year of Incident						
EMS	**2014 n(%)**	**2015 n(%)**	**2016 n(%)**	**2017 n(%)**	**2018 n(%)**	**2014-2018 n(%)**	**P value**
Overall	689	586	520	514	553	2862	<0.0001
EMS 1[a]	72 (10.4)	51 (8.7)	n/a	n/a	41 (7.4)	164 (5.7)	
EMS 2	54 (7.8)	47 (8.0)	55 (10.5)	51 (9.9)	37 (6.6)	244 (8.5)	
EMS 3	136 (19.7)	110 (18,7)	110 (21.1)	118 (22.9)	116 (20.9)	590 (20.6)	
EMS 4	64 (9.2)	29 (4.9)	34 (6.5)	40 (7.7)	32 (5.7)	199 (6.95)	
EMS 5	81 (11.7)	79 (13.4)	85 (16.3)	88 (17.1)	72 (13.0)	405 (14.1)	
EMS 6	21 (3.0)	32 (5.4)	24 (4.6)	20 (3.8)	24 (4.3)	121 (4.2)	
EMS 7	47 (6.8)	43 (7.3)	52 (10.0)	56 (10.8)	52 (9.4)	250 (8.7)	
EMS 8	64 (9.2)	52 (8.8)	57 (10.9)	63 (12.2)	60 (10.8)	296 (10.3)	
EMS 9	72 (10.4)	91 (15.5)	103 (19.8)	78 (15.1)	58 (10.4)	402 (14.0)	
EMS 10	78 (11.3)	52 (8.8)	n/a	n/a	61 (11.0)	191 (6.6)	

[a]Results expressed as numbers (percent).

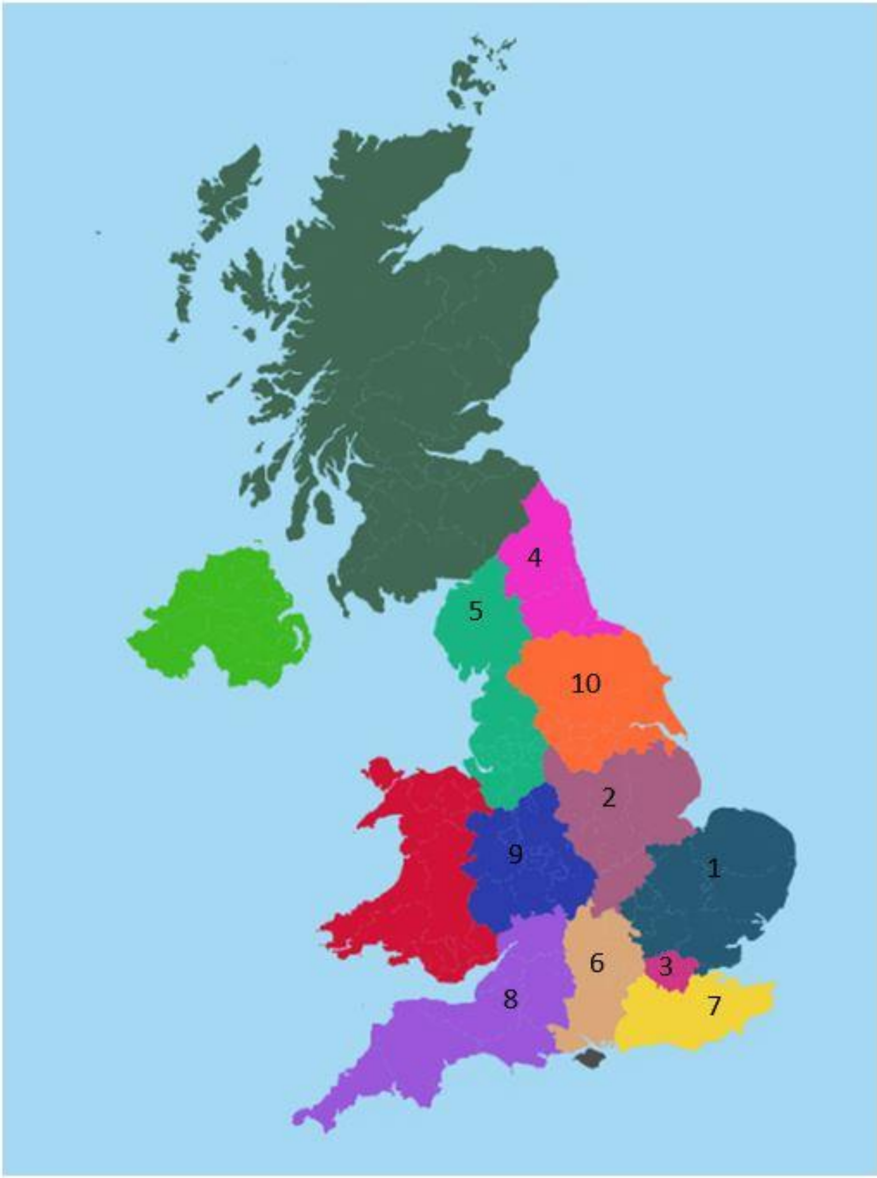

Figure 4-3 Location of EMS regions 1 to 10 across England.[140]

The overall incidence rate by EMS region ranged from 2.6 to 7.6 per 100,000 person-years. EMS 4 recorded the highest incidence rate in 2014 at 12.2; however, it had the smallest population (526,418). The incidence rate for EMS 6 remained low across the study period, ranging from 2.2 to 3.5 per 100,000 person-years. Five EMS regions recorded their highest incidence rate in 2014 (EMS1, EMS3, EMS4, EMS8 and EMS 10). See Table 4-4.

In all EMS regions, the total number of males was higher than females. Infants were the largest age group in six EMS regions (EMS1, EMS2, EMS3, EMS5, EMS6 and EMS10), children aged 1-4 years in two regions (EMS4 and EMS9), and adolescents aged 12-18 years in two regions (EMS7 and EMS8): see Table 4-5. Medical cause was the leading cause in all regions. Witnessed CA ranged from 30.0% (EMS2) to 45.0% (EMS8), although this difference was not statistically significant across EMS regions ($p=0.053$). The rate of BCPR did differ significantly across EMS regions and ranged from 52.2% (EMS9) to 81.7% (EMS7) ($p<0.0001$). The overall rate of OHCA with an initial shockable rhythm was low with a significant variation across EMS regions (EMS3=6.0% to EMS10=11.8%) ;($p<0.001$); however, there was a large amount of missing data from EMS 10 regarding initial rhythm(70%(59/191)).

Survival to hospital discharge was lowest in EMS 7 (6.5%) and highest in EMS 1 (21.7%) and is displayed graphically in Figure 4-4. ROSC at any time was lowest in EMS 6 (17.5%) and highest in EMS 4 (57.7%). ROSC at hospital handover was lowest in EMS 6 (6.4%) and highest in EMS 7 (27.1%). Although EMS 7 recorded the lowest survival to hospital discharge rate, the percentage of those achieving ROSC at any time and ROSC at hospital handover were high within this region (36.7% and 27.1%, respectively)

Table 4-4 The incidence rate of OHCA across EMS regions by year

	Population[a]	2014 [b](rate: 95%CI)	2015 (rate: 95%CI)	2016 (rate: 95%CI)	2017 (rate: 95%CI)	2018 (rate: 95%CI)	2014-2018 (rate: 95%CI)
EMS 1	1,312,316	5.6 (4.3-6.8)	3.9 (2.8-4.9)	n/a	n/a	3.1 (2.1-4.0)	4.2 (3.0-5.2)
EMS 2	980,599	5.6 (4.1-7.0)	4.8 (3.4-6.2)	5.6 (4.1-7.0)	5.2 (3.7-6.5)	3.7 (2.5-4.9)	5.0 (3.5-6.3)
EMS 3	1,975,373	7.1 (5.8-8.2)	5.6 (4.5-6.6)	5.6 (4.5-6.5)	5.9 (4.8-6.9)	5.7 (4.6-6.7)	6.0 (4.8-7.0)
EMS 4	526,418	12.2 (9.2-15.1)	5.5 (3.5-7.5)	6.5 (4.2-8.6)	7.6 (5.2-9.9)	6.0 (3.9-8.1)	7.6 (5.2-9.9)
EMS 5	1,533,263	5.3 (4.1-6.5)	5.2 (13.1-17.0)	5.5 (4.3-6.7)	5.7 (4.5-6.8)	4.6 (3.5-5.7)	5.3 (4.1-6.4)
EMS 6	922,030	2.3 (1.3-3.3)	3.5 (2.2-4.7)	2.6 (1.5-3.6)	2.2 (1.2-3.0)	2.6 (1.5-3.5)	2.6 (1.5-3.6)
EMS 7	984,473	4.8 (3.4-6.2)	4.4 (3.0-5.7)	5.3 (3.8-6.7)	5.7 (4.1-7.1)	5.2 (3.7-6.6)	5.1 (3.6-6.4)
EMS 8	1,089,651	5.9 (4.4-7.4)	4.8 (3.4-6.1)	5.2 (3.8-6.5)	5.7 (4.3-7.1)	5.4 (4.0-6.8)	5.4 (4.0-6.8)
EMS 9	1,273400	5.7 (4.4-7.0)	7.2 (5.7-8.6)	8.1 (6.5-9.6)	6.1 (4.7-7.4)	4.5 (3.3-5.6)	6.3 (4.9-7.6)
EMS 10	1,152,552	6.8 (5.3-8.3)	4.5 (3.3-5.7)	n/a	n/a	5.2 (3.9-6.5)	5.5 (4.1-6.8)

[a] Population data from the Office of National Statistics (mid 2014-2018 statistics).

[b] Rates expressed as admissions per 100,000 population (95% confidence interval)

Table 4-5 Characteristics of paediatric OHCA by EMS region

	Total n(%)	EMS 1	EMS 2	EMS 3	EMS 4	EMS 5	EMS 6	EMS 7	EMS 8	EMS 9	EMS 10	P value[b]
Overall[a]	2862 (100)	164	244	590	199	405	121	250	296	402	191	
Sex	2787 (97.3)	153 (93.2)	242 (99.1)	588 (99.6)	194 (97.4)	404 (99.7)	121 (100)	230 (92.0)	296 (100)	400 (99.5)	159 (83.2)	
Male	1646 (59.0)	87 (56.8)	153 (63.2)	359 (61.0)	122 (62.9)	218 (54.0)	82 (67.8)	136 (59.1)	154 (52.0)	238 (59.5)	97 (61.0)	0.02
Female	1141 (41.0)	66 (43.1)	89 (36.7)	229 (39.0)	72 (37.1)	186 (46.0)	39 (32.2)	94 (40.9)	142 (48.0)	162 (40.5)	62 (39.0)	
Age	2862 (100)	164 (100)	244 (100)	590 (100)	199 (100)	405 (100)	121 (100)	250 (100)	296 (100)	402 (100)	191 (100)	
≤1 yr	898 (31.3)	80 (48.7)	123 (50.4)	260 (44.0)	19 (9.5)	213 (52.5)	38 (31.4)	18 (7.2)	67 (22.6)	30 (7.4)	50 (26.1)	
>1 to 4 yrs	649 (22.6)	22 (13.4)	47 (19.2)	90 (15.2)	89 (44.7)	41 (10.1)	30 (24.7)	66 (26.4)	74 (25.0)	143 (35.5)	47 (24.6)	
>4 to 8 yrs	325 (11.3)	11 (6.7)	8 (3.2)	54 (9.1)	32 (16.0)	20 (4.9)	10 (8.2)	44 (17.6)	40 (13.5)	72 (17.9)	34 (17.8)	
>8 to 12 yrs	303 (10.5)	13 (7.9)	14 (5.7)	51 (8.6)	12 (6.0)	41 (10.1)	11 (9.0)	49 (19.6)	32 (10.8)	53 (13.1)	27 (14.1)	<0.0001
>12 to <18 yrs	687 (24.0)	38 (23.1)	52 (21.1)	135 (22.8)	47 (23.6)	90 (22.2)	32 (26.4)	73 (29.2)	83 (28.0)	104 (25.8)	33 (17.2)	
Aetiology	2679 (93.6)	160 (97.5)	204 (83.6)	579 (98.1)	198 (99.4)	404 (99.7)	17 (14)	229 (91.6)	296 (100)	401 (99.7)	191 (100)	
Medical	1901 (70.9)	124 (77.5)	204 (100)	381 (65.8)	160 (80.8)	264 (65.3)	12 (70.5)	208 (90.8)	205 (69.2)	231 (57.6)	112 (58.6)	
Trauma	182 (6.7)	13 (8.1)	0 (0.0)	64 (11.0)	9 (4.5)	21 (5.2)	2 (11.7)	7 (3.0)	30 (10.1)	32 (7.9)	4 (2.0)	
Drowning	42 (1.5)	3 (0.0)	0 (0.0)	9 (1.5)	3 (1.5)	5 (1.2)	2 (11.7)	2 (0.8)	6 (2.0)	11 (2.7)	1 (0.5)	
Drug overdose	33 (1.2)	0 (0.0)	0 (0.0)	3 (0.5)	2 (1.0)	9 (2.2)	0 (0.0)	1 (0.4)	12 (4.0)	4 (1.0)	2 (1.0)	<0.0001
Asphyxia	194 (7.2)	5 (3.1)	0 (0.0)	60 (10.3)	20 (10.1)	32 (7.9)	1 (5.8)	9 (3.9)	40 (13.5)	21 (5.2)	6 (3.1)	
Other	327 (12.2)	15 (9.3)	0 (0.0)	62 (10.7)	4 (2.0)	73 (18.0)	0 (0.0)	2 (0.8)	3 (1.0)	102 (25.4)	66 (34.5)	
Witness status	2606 (91.0)	162 (98.7)	226 (92.6)	579 (98.1)	109 (54.7)	399 (98.5)	93 (76.8)	203 (81.2)	289 (97.6)	400 (99.5)	146 (76.4)	
Yes	1060 (40.6)	67 (41.3)	68 (30.0)	253 (43.7)	47 (43.1)	162 (40.6)	34 (36.5)	86 (42.3)	130 (45.0)	157 (39.2)	56 (38.3)	0.053
No	1546 (59.3)	95 (58.6)	158 (69.9)	326 (56.3)	62 (56.8)	237 (59.4)	59 (63.4)	117 (57.6)	159 (55.0)	243 (60.7)	90 (61.6)	
Bystander CPR	2605 (91.0)	163 (99.3)	226 (92.6)	583 (98.8)	115 (57.7)	403 (99.5)	103 (85.1)	175 (70)	285 (96.2)	402 (100)	150 (78.5)	
Yes	1716 (65.8)	103 (63.1)	153 (67.7)	352 (60.3)	84 (73.0)	291 (72.2)	72 (69.9)	143 (81.7)	203 (71.2)	210 (52.2)	103 (68.60)	<0.0001
No	891 (34.2)	60 (36.8)	73 (32.3)	231 (39.6)	31 (26.9)	112 (27.7)	31 (30.1)	32 (18.2)	82 (28.7)	192 (47.7)	47 (31.3)	
Shockable	2425 (84.7)	143 (87.1)	222 (90.9)	549 (93.0)	110 (55.2)	387 (95.5)	107 (88.4)	217 (86.8)	269 (90.8)	362 (90.0)	59 (30.8)	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Table 4-5 (continued) Characteristics of paediatric OHCA by EMS region

	Total n(%)	EMS 1	EMS 2	EMS 3	EMS 4	EMS 5	EMS 6	EMS 7	EMS 8	EMS 9	EMS 10	P value
Yes	178 (7.3)	12 (8.3)	12 (8.3)	33 (6.0)	8 (7.2)	30 (7.7)	9 (8.4)	24 (11.0)	20 (7.4)	23 (6.3)	7 (11.8)	<0.001
No	2224 (91.7)	131 (91.6)	209 (94.1)	513 (93.4)	102 (92.7)	356 (91.9)	96 (89.7)	193 (88.9)	247 (91.8)	327 (90.3)	50 (84.7)	
Other	23 (0.9)	0 (0.0)	1 (0.4)	3 (0.5)	0 (0.0)	1 (0.2)	2 (1.8)	0 (0.0)	0 (0.7)	12 (3.3)	2 (3.3)	
Survival to discharge	2372 (82.8)	69 (42.7)	217 (88.9)	555 (94.0)	106 (53.2)	385 (95.0)	26 (21.4)	200 (80.0)	272 (91.9)	361 (89.8)	181 (94.7)	
Yes	260 (11.0)	15 (21.7)	20 (9.2)	55 (9.9)	16 (15.0)	38 (9.8)	5 (19.2)	13 (6.5)	25 (9.1)	51 (14.1)	22 (12.1)	<0.007
No	2112 (89.0)	54 (78.3)	197 (90.8)	500 (90.1)	90 (85.0)	347 (90.2)	21 (80.8)	187 (93.5)	247 (90.9)	310 (85.9)	159 (87.9)	
ROSC at anytime	2588 (90.4)	162 (98.7)	244 (100)	586 (99.3)	123 (61.8)	405 (100)	80 (66.1)	223 (89.2)	290 (97.9)	402 (100)	73 (38.2)	
Yes	647 (25.0)	42 (25.9)	49 (20.0)	133 (22.7)	71 (57.7)	76 (18.7)	14 (17.5)	82 (36.7)	67 (23.1)	90 (22.3)	23 (31.5)	<0.0001
No	1941 (85.0)	120 (74.1)	195 (80.0)	453 (77.3)	52 (42.3)	329 (81.3)	66 (82.5)	141 (63.3)	223 (76.9)	312 (77.7)	50 (68.5)	
Hospital ROSC	2578 (90.0)	157 (95.7)	244 (100)	586 (99.3)	123 (61.8)	405 (100)	78 (64.4)	206 (82.4)	288 (97.2)	401 (99.7)	90 (47.1)	
Yes	513 (20.0)	40 (25.4)	40 (16.3)	119 (20.3)	21 (17.0)	71 (17.5)	5 (6.4)	56 (27.1)	60 (20.8)	80 (19.9)	21 (23.3)	<0.005
No	2065 (80.0)	117 (74.6)	204 (83.7)	467 (79.7)	102 (83.0)	334 (82.5)	73 (93.6)	150 (72.9)	228 (79.2)	321 (80.1)	69 (76.7)	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

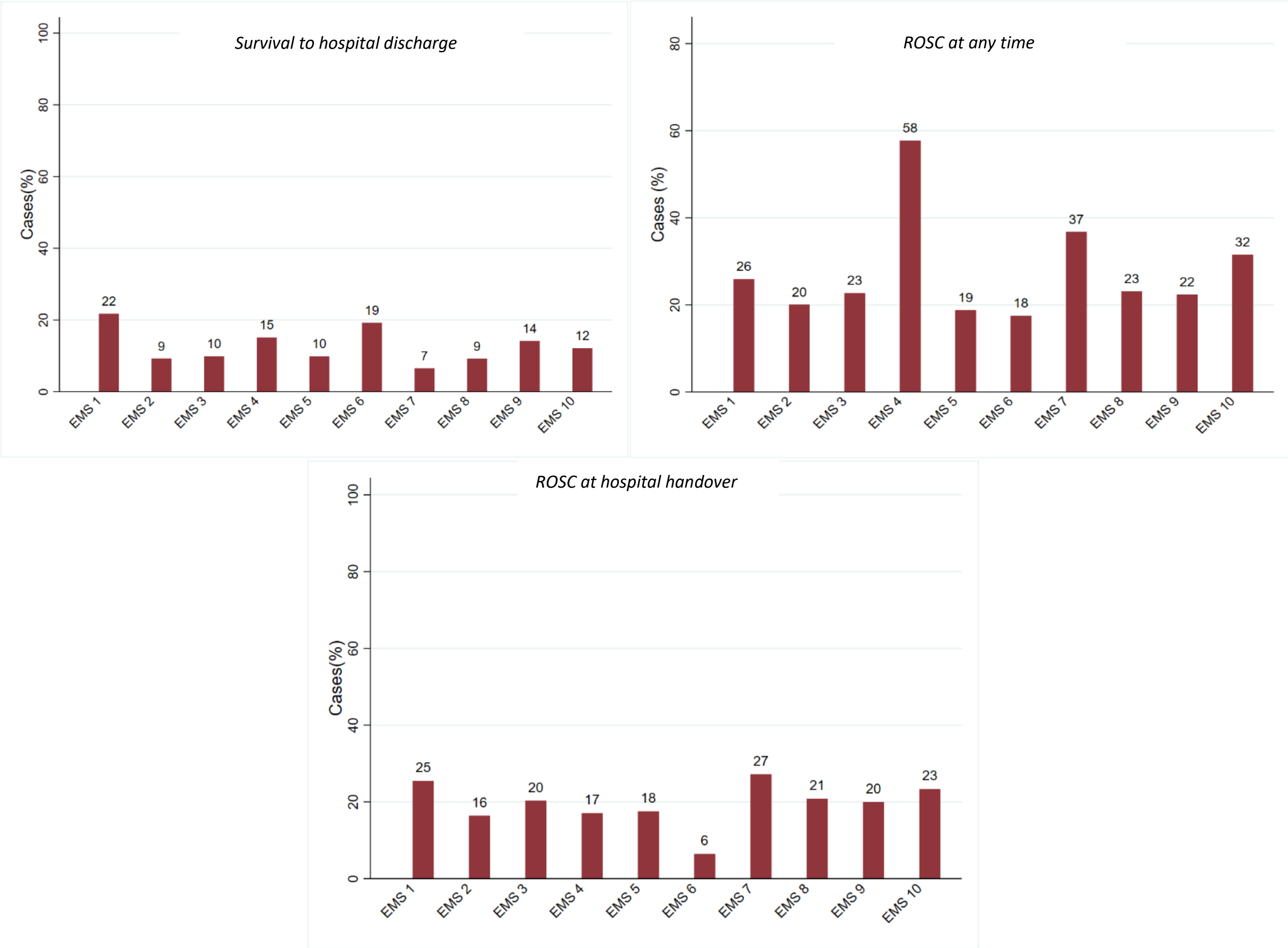

Figure 4-4 Survival to hospital discharge, ROSC at any time and ROSC at hospital handover across EMS regions. Information about missing data for the outcomes can be found in table 4-5

4.4.6 Sensitivity analysis of survival outcomes for the total group and EMS regions

There were 490 (17.1%) missing data in the survival to hospital discharge. The percent of missing data by EMS services ranged from 5.2% in EMS10 to 78.5% in EMS6 for survival to hospital discharge outcome. There was a wide range in the percentage of those who survived to hospital discharge between the two groups. EMS regions with large missing data (EMS1 9.1%-67.1%); EMS4 8.0%-54.8%); EMS6 4.1%-82.6) showed a wide range between the two groups. (Appendix 8-8, 224)

For ROSC, at any time, 9.5% were missing. Missing data by EMS regions ranged from 0% in two EMS three EMS regions (EMS2, EMS5, EMS9) to 61.7% in EMS10. Comparing group one (all missing data for ROSC at any time categorised as "achieved ROSC at any time") and group two (All missing data for ROSC at any time categorised as "did not achieve ROSC at any time"), the wide variation observed in the regions with large missing data (EMS4, EMS6, EMS10). (Appendix 8-9, p225) For hospital ROSC data were missing in 9.9%. The data were largely missing in EMS4,EMS6 and EMS10(38.3%,35.5%,52.8%) respectively.(Appendix 8-10, p226)

4.5 DISCUSSION

This is the first and largest study to describe the epidemiology of paediatric OHCA in England using the OHCA registry data. In infants and children aged less than 1 year to <18 years between January 2014 and November 2018, the overall incidence rate of paediatric OHCA per year across England was 5.3 per 100,000 person-years. The number of paediatric OHCA cases differed by EMS region, and the incidence rates varied from 2.6 to 7.6 per 100,000 person-years. Overall a quarter achieved ROSC at any time, one-fifth achieved ROSC at arrival to the hospital, and eventual survival to hospital discharge was 11%. Key differences in CA resuscitation factors and ROSC and survival outcome rates were identified across age groups and EMS regions.

4.5.1 Age

Our data identified that most OHCAs in England occurred in infants aged one year or less. This is similar to other paediatric studies. Nitta et al.[(141)], in a Japanese prospective study that included 875 children, reported that 39.6% (347/857) of paediatric OHCA cases were in those less than one year of age. Similarly, the proportion of infants in a US study that included non-traumatic OHCA by Fink et al.[(34)] was 43.9% (615/1429). However, this is not the case in all paediatric studies, as other published reports have found other age groups to have higher OHCA cases compared to infants. In a cross-sectional study that included 23,514 EMS responses to paediatric cases, the highest OHCA cases were found in children aged 13-17 years at 35.9% (8435/23514).[(142)] The latter study included traumatic and non-traumatic CA. However, cases with missing data on age were excluded, which could partially explain the findings.

Arrest due to medical cause was the most common aetiology among all age groups. This can be explained by the broad definition following the updated Utstein Style guidelines of medical causes, including presumed CA, unknown, and other medical causes.[69] This update has not been internationally adopted, and therefore most published paediatric studies do not use it. In fact, studies have followed different approaches when defining aetiology. For example, arrest cause can be categorised as cardiac vs non-cardiac or traumatic vs non-traumatic.[29, 84, 118] Another approach is more detailed in that it sub-categorises cardiac and traumatic causes.[42, 43, 71, 141] Furthermore, some studies exclude traumatic causes.[34, 43, 143] Given this disparity, making a comparison between our findings and other studies is challenging. Because infant were the largest age group in our study and since the medical cause was the most common cause of CA among this group, there is a high possibility that SIDS was the leading cause in the infant group. Unfortunately, the way aetiology was categorised in the OHCA registry does not allow for tracking SIDS as a cause specifically. Several reports have shown that SIDS is a leading cause in infant OHCA.[144, 145] Although there is no clear explanation in how SIDS occurs, there are risk factors. Genetic factors have been linked to a higher incidence rate of SIDS. In fact, a study showed that the rate of SIDS is three times higher in African Americans compared to the national average.[144] There are also risk factors related to the mother, including young age, no or less breastfeeding, smoking, poor education and occupation, that affect the occurrence of SIDS.[146, 147] Finally, sleeping in the stomach position and bed sharing were also associated with increasing presence of SIDS.[144] Understanding these factors would help identify and target parents who might be at higher risk and would eventually help decrease the incidence of paediatric OHCA in infants.

Traumatic CA was the second most common cause of OHCA in our study. Again, as mentioned, there are issues in defining traumatic OHCA aetiology. Some studies include hanging, drowning and asphyxiation as part of the traumatic cause, whereas others do not.[35, 36, 121] This might affect the sample size for a traumatic cause as well as the impact on the outcome rate; however, in our study, drowning and asphyxiation were not part of trauma, yet trauma was the second most common cause of CA. Similar to Nitta et al.[141], CA due to trauma was observed more in older children. This is perhaps due to the CA location, as CA in older children occurs more frequently outside the home. Older children are more likely to engage in adventurous activities and to be involved in road traffic collisions outside the home. Vassallo et al.[36], in a study focused on paediatric traumatic CA, found that over 55% of the traumatic cases were due to road traffic collisions. Unfortunately, we could not obtain data about the mechanism of injury in the traumatic cause. Asphyxia was responsible for 7.1% (194/2679) of all OHCA cases in our report. Similar to the cause of trauma, more than half of asphyxia arrests occurred in children aged 12-18 at 52.5% (102/194). This finding suggests that the potential cause of asphyxiation is more related to the nature of an injury than the pathophysiological cause. To explain, older children, especially adolescents, are similar to adults in the pathophysiology of the traumatic CA, which therefore limits the possibility of asphyxiation being related to a pathophysiological cause that is often seen in younger children's age groups. Hence, the possible explanation of our finding is that the high number of asphyxia cases in older children might be due to hanging or attempts of suicide, as these causes are more common in older children. Nehme et al.[37] also reported similar results, where CA due to asphyxiation in adolescents was 73.6% (42/57). To summarise, although the aetiology differed by the patient's age, there was an issue related to defining the cause of CA and how it was categorised. Therefore, comparison between paediatric OHCA studies is highly challenging.

Children aged 12-18 years had a higher rate of hospital survival than infants (11.0% vs 8.4%); however, this difference did not reach statistical significance in our study. We found that the rate of ROSC at any time and ROSC at the time of hospital admission were higher in older children. In a multicentre cohort, Tham et al.(28) reported a superior survival rate in children aged 13-17 (13.8% vs infant 6.1%). Fink et al.(34), reported better pre- and hospital ROSC for adolescents compared to infants (36.7% vs 7.6%; 31.5% vs 6.2%). This could be explained by OHCA factors related to older children in that they are more often have CA outside the home compared to younger age groups and therefore have a better chance to be witnessed, to receive BCPR and to have a shockable rhythm as the initial rhythm.(34, 141) This is consistent with our findings in this report as children aged 12-18 years were witnessed and had shockable rhythm more often than infants (48.6%vs 31.3%; 15.2 vs 3.6%).

4.5.2 EMS regions

Variations in the patients, events, characteristics and outcomes were identified across EMS regions. In particular, the infant age group was the highest population in some EMS regions, and older age groups were higher in others. Rates of survival to hospital discharge, ROSC at anytime and hospital ROSC also varied across England's EMS regions.

This finding is consistent with the existing literature. Several OHCA registries have identified a significant regional variation in demographics, prehospital factors and outcomes.(2, 34, 101, 148) The patients' ages were different across EMS regions. Although infants were the largest age group in our study, some EMS regions had higher OHCA cases in other adolescent age groups.

This is similar to Fink et al.'s study, where two regions reported higher CA events in adolescents.[34] There was not a clear explanation for this variation in Fink et al.'s study. Similarly, in our study, the causes for having higher OHCA cases among the adolescent age group in some regions are also not clear. Some studies suggest that SES factors and the quality of EMS and health care services could partially explain this variation.[148-150] Therefore, it is important to examine those factors and whether there is a variation in the quality of the EMS care, especially because OHCA is not common in paediatric patients compared to adults, which makes it challenging for EMS providers.

Although witnessed CA did not significantly differ by EMS region, a variation in the cases being witnessed was observed (30.0% to 45.0%). This could be related to the low population densities in areas with fewer witnessed CA and, therefore, a lower chance to be witnessed. Another feature is that regions with low witnessed CA have higher infant CA than regions with high witnessed arrests. It is known that OHCAs in infants are usually unwitnessed.[29, 34, 141] BCPR also varied across EMS regions (52.2% to 81.7%). It is not clear why we found a significant variation in BCPR. Some published studies have linked the disparity in the BCPR rate to the location of the CA (private vs public).[41, 151] Others have suggested that the BCPR variability rate is driven by SES factors, including racial and neighbourhood characteristics. Therefore, a further examination of the factors that might have an impact on the BCPR rate is needed for paediatric OHCA in England.[82, 101] Shockable rhythm was low across all EMS regions. It is worth noting that a large amount of data was missing for the initial rhythm across EMS regions. Indeed, 70% of data were missing from EMS 10. Suppose we exclude EMS 10 from the analysis. In that case, we can observe a relationship between shockable rhythm and regions with high BCPR rates, as EMS 7 had the highest rate of BCPR and shockable rhythm of 81.7% and 11.0%, respectively.

Survival to hospital discharge rate did vary by EMS region, with the highest rate in the region EMS 1 (21.5%). Further, a significant variation in the rate of ROSC at any time and hospital ROSC was also identified across EMS regions ($p<0.0001$). Okamoto et al.[148], in a large prospective paediatric OHCA study, divided Japan into seven regions and identified variations in the survival rate. In their study, a more than three-fold difference in neurologically favourable survival rates across regions was observed. However, they did not identify any differences in pre-hospital ROSC between regions. The variations found might be related to the rate of submission of the data for the outcome. To explain, the EMS regions were not consistent in providing data for outcomes, with some submitting only 43% of total cases. In fact, the issue of missing data for the outcomes seems to have a significant impact on the association of EMS regions and outcomes as we identified in the sensitivity analysis. For example, the percentage of survival to hospital discharge for EMS1,EMS4 and EMS6 was the highest compared to other EMS regions(22% ,15% and 19%).However, EMS1, EMS4 and EMS6 were found to have the largest missing data for survival to hospital discharge outcome which strongly suggest that the reported result may not reflect the actual percent of survival (58%,46% and 78%). The extreme survival rate variation, in the sensitivity analysis, highlights caution in over interpreting the results of the data that is not missing. This therefore reinforces the need for improvement in the data registry data collection process, or to proceed with a prospective observational study, to more accurately assess the survival rate in each individual EMS region.

Combining the overall survival and ROSC rates across England was appropriate. But this analysis reinforces the concern that the survival rate reported by certain EMS region (eg EMS 6) may be inaccurate. This also suggests that we should be cautious about including EMS region in future logistic regression model as it highlights the missing data is unlikely to be random, but associated with individual data collection practices in each EMS.

An additional area of exploration is the potential differences in the training of EMS across England is important and has the potential for disparity due to the infrequency of paediatric CA exposure. The reason could be that the population size of children is greater in some regions than in others and thus the paramedics would have more experience in dealing with OHCA in children. Training across NHS and standardised systems should lead to a similar quality of care; however, some EMS regions may provide further training on paediatric resuscitation and therefore present a superior survival rate compared to others.

4.5.3 Incidence rates and outcomes

The average yearly incidence of paediatric OHCA in England was 5.3 per 100,000 person-years. Similar incidence rates have been reported from Korea and Australia, with 4.2 and 4.9 per 100,000 person-years, respectively.(37, 143) It is worth noting that both studies excluded CA due to a trauma cause, and the upper age limit differed from our age limit (Korean study upper age limit:<1-19 years; Australian study: upper age limit ≤16 years). Other paediatric studies from the US and Japan reported a higher incidence rate of 8.3 and 8.0 per 100,000 person-years.(3, 34) lower incidence rates were found in a Danish study, which included patients aged 21 or under, at 3.3 per 100,000 person-years(29); however, the high incidence rate in infants was common among all the studies previously mentioned. Similarly, in our report, the incidence rates in infants were the highest at 29.9 per 100,000 person-years compared to other age groups (1-4 years: 6.9 per 100,000 person-years; 4-8 years: 2.6 per 100,000 person-years; 8-12 years: 2.5 per 100,000 person-years; and 12-18 years: 4.1 per 100,000 person-years).

Variations in incidence rates across EMS regions were also identified. The incidence rate ranged from 2.6 to 7.6 per 100,000 person-years. The difference in incidence rate between regions was also observed in other paediatric studies. For example, in a US study, the incidence rate of paediatric OHCA cases varied from 5.8 to 12.7 across 9 regions.[34] A possible explanation for this is that the difference in SES factors and the patients' characteristics, including the population age, in some regions might have a lower infant population compared to others. To summarise, although our study findings were similar to some paediatric studies, heterogeneity in inclusion criteria, study design, the quality of EMS care and the data registry are still major issues in paediatric research, something which might leave us with an imprecise conclusion.

In our report, the rate of achieving ROSC at any time and hospital ROSC were 25% and 20%, respectively. There was a challenge in comparing the ROSC at any time rates with other studies due to the variations in defining ROSC or when it is measured. The closest comparable study was a retrospective analysis from Australia.[37] In their study, for over 900 paediatric OHCA cases, which included any pre-hospital ROSC, the rate was 22.5%. The hospital ROSC in our study was higher than in reports from the US and Korea (13.8% and 5.5%, respectively). The better ROSC rate in our study might be attributed to the high BCPR rate. Indeed, multiple published studies have identified better achievements in ROSC with higher BCPR rates.[34, 71, 119] Another possible explanation is that data were missing in 10% of the total cases, which might have led to an overestimation of both ROSC outcome rates we reported. The duration of CPR that the patients received, response time of the EMS provider and transfer period have also been linked to a higher chance of achieving ROSC. Studies have shown worse outcomes with longer CPR durations(152, 153); however, the OHCAO dataset did not provide this information to allow for a comparison. The inclusion of the duration of CPR would therefore be helpful.

The overall rate of survival to hospital discharge for all EMS-treated paediatric OHCA cases was 11.0% in England. There was a clear step-wise trend in the chance of surviving at these time points (1:4 had ROSC at any time; 1:5 had ROSC at hospital; 1:10 survived to hospital discharge). There is, therefore, an opportunity to improve the survival rate or reduce neurological injury, which often leads to the reason for eventual death. Many cases had achieved ROSC but did not survive to hospital discharge, and the potential reasons for this are multi-factorial and occur at different time points, some of which are out of scope for this thesis. In the prehospital setting, the time of the transport and the quality of CPR might affect the survival outcome after achieving ROSC. This would also affect the time when the Post Cardiac arrest Care starts within hospital and intensive care. The phases and management of the Post Cardiac Arrest Syndrome and its variable impact on patients are important to understand in this step-wise reduction in survival rate and are a key area of research for paediatric resuscitation investigators.(154)

At this point, two key findings have been widely shared about the survival outcomes in paediatric OHCA. First, the survival rate remains poor among paediatric OHCA.(49, 72, 118) Second, there is a significant difference in survival rates across studies.(34, 47, 49, 72, 118, 119, 155) Given that, the reported survival rate in our study was higher than reports from Japan, Korea, and Denmark (9.9%; 4.3%; 8.1%, respectively).(29, 71, 143) In a study from the US, Naim et al.'s

[11] study which included over 2000 paediatric patients using registry data reported similar survival to hospital discharge rates at 11.5%. Furthermore, a better survival rate was found in a study from the Netherlands, at 24%.[155] However, the study sample size was small compared to our study as they included only 233 patients. Comparing the differences in health care, EMS and resuscitation practices between the Netherlands and England (higher survival) and then Japan, Korea and Denmark (lower survival) may lead to identifying successful treatment strategies for countries with lower survival outcomes.

4.5.4 Witnessed status, bystander CPR and initial rhythm

Approximately 40% of all paediatric OHCA were witnessed, although the rate of witnessed CA varied by age. Infants OHCA were found to be witnessed less often compared to other age groups. This could be attributed to the large proportion of infant OHCA being in a private location (e.g. the home). Studies have suggested that over 90% of infant cases occur in a private site, with only 16% being witnessed.[141, 143, 155] This raises another issue related to BCPR. Although BCPR was performed in over 65% of all cases, there is a possibility that a large proportion was unwitnessed. Furthermore, even if infant cases were witnessed, the quality of CPR would possibly be lacking. Studies have suggested that poor quality CPR is performed in infant cases, even by a resuscitation trainee instructor.[156] This is due to the emotional stress that occurs when dealing with infants. It is important to note that both having a witness to an OHCA and receiving BCPR are favourable to better outcomes. In children's study including non-traumatic OHCA, Naim et al. reported a significant association between witnessed CA and BCPR with survival to hospital discharge (witnessed 26.8% vs unwitnessed 5.2%; BCPR 14.2% vs no-BCPR 8.6%.[41] A similar relationship was found by Okamoto et al. with one-month survival.[148] In the latter study, the adjusted odds ratio of survival for witnessed and BCPR were 5.15 (95%CI (3.25-7.54) and 1.63 (95%CI (1.16-2.30)). Further, in a prospective study, Kitamura et al.'s study (8), which included over 5000 paediatric patients, found favourable neurological outcomes for one-month survival with witnessed CA and BCPR being performed. However, in the same study, the author continued to examine the impact of BCPR on outcomes by dividing the patients according to age and CA cause. This approach showed an inconsistent association between BCPR and outcomes as infant cardiac cause showed fewer benefits of BCPR than in older children and non-cardiac cause. Another study by Fink et al. (34) did not find a significant association between BCPR and survival to hospital discharge at: aOR 1.33 (95% CI (0.80-2.19)). This difference in reporting BCPR with the outcome is attributed to study design, the definition of CA, or population size. There remains significant uncertainty, and a further examination is needed to evaluate the impact of BCPR on survival outcomes. Also, further exploration is needed to examine and identify any relation between the status of witness, BCPR and the paediatric age groups.

In our study, shockable rhythm was recorded as the initial rhythm in 7.3% of all OHCA. The reported shockable rhythm in paediatric OHCA studies is very low, ranging from 4% to 12%.(3, 29, 48, 127, 141) Unlike in adults, where cardiac aetiology is more common, CA in children is often secondary to respiratory failure or shock and, therefore, fewer cases have an identified shockable rhythm.(157) It is well-established that asystole is the most common rhythm among the paediatric population. Donoghue et al.(72), in a systematic review that included 41 studies, found that 78% of all paediatric OHCA had asystole as their initial rhythm. This is similar to the findings in this study as asystole was the most recorded rhythm of the paediatric cases (78.2%: 1899/2428). The high frequency of asystole might be explained by the large proportion of CA occurring among infants, where SIDS is a common CA cause. Studies that excluded SIDS cases reported a higher frequency of shockable rhythm in paediatric OHCA (19% to 24%).[37, 42, 158, 159] Several other factors are also crucial in increasing the proportion of children with a shockable rhythm. In our study, older children had a higher rate of shockable rhythm than infants (15% vs 3%). Similarly, Fink et al.[34] reported a similar relationship (19.4% vs 1.3%). This might be attributed to the fact that a primary cardiac cause of an OHCA (e.g. primary arrhythmia, Hypertrophic cardiomyopathy, myocarditis) is more common in older children and adolescents.[160] The early recognition of OHCA in older children is another important factor. To explain, CA in older children commonly occurs in public locations, increasing the chance of being witnessed, receiving BCPR and of having AED applied. In the current study, witnessed CA was higher in older children; however, the BCPR was similar across the paediatric age groups. It should also be noted that due to insufficient data for AED use, we could not measure its impact. Although a shockable rhythm is uncommon in children, a better survival rate has been reported with shockable rhythm in paediatric studies.[3, 41, 127, 159] Older children seem to benefit from this association as shockable rhythm is more common in their age group. In the current study, survival was not statistically associated with age; however, a higher survival rate was identified in older children. It is worth noting that the initial rhythm data were missing in 15% of total cases, which might have led to an underestimation of the association of shockable rhythm and survival outcome.

4.6 STRENGTHS AND LIMITATIONS

The key strength of this study is the use of the OHCA registry, as it covers all the English regions, which makes the results more generalisable. The data provided by the registry, therefore, improved the understanding of the incidence and epidemiology of England's population. It also helped identify areas where more BCPR training may be needed and identify any geographical challenges for EMS care. This will eventually reflect on the survival outcomes and how the strategy should be designed to improve the quality of care across EMS regions.

Compared to most paediatric OHCA studies, the paediatric sample size is large in our study. However, this study has some inherent limitations. First, this study was an observational study using registry data which means there was less ability to control for confounders to potentially introduce information bias, and to experience a loss to follow up, which leads to an increase in the amount of missing data. Second, there was a common issue with data registries regarding missing data. There was a variation in data completeness across the EMS regions. As previously stated, over 55% of survival to hospital discharge outcome data were missing in some EMS regions. Although the survival to hospital discharge rate was similar to other paediatric reports, data were missing in 18% (490 cases) of total cases, which might have led to an over/underestimation of the rate. Furthermore, the initial rhythm was also missing in 15% (436) of total patients, with a significant variety of data submitted by the EMS regions.

4.7 FUTURE RESEARCH

This study described the incidence and factors associated rate of OHCA in paediatrics. Some key areas for further exploration have been identified. We found that the incidence rate varies across paediatric age groups and EMS regions. There was also a variation in patients' characteristics, and survival to hospital discharge varied across EMS regions. The rate of BCPR being performed was one of the factors that varied across EMS regions. This suggests that much work is needed to improve the BCPR rate in regions with a low BCPR. However, firstly it is important to understand the factors related to BCPR variation and how strongly BCPR is associated with survival outcomes. Do the other patients' characteristics affect the BCPR rate?

If yes, how strong is their effect? Does the association of BCPR and other patients' characteristics affect the survival outcome? What are the causes of the BCPR rate variations across EMS regions?

4.8 CONCLUSION

This is the first analysis of paediatric OHCA in children aged under 18 years using the OHCA data registry in England. In this study, infants aged one year or less were the largest age group, although it was not the largest in all EMS regions. The survival rate was comparable to other published studies that included a similar sample size; however, there were significant variations across regions. The rate of BCPR was high, yet variations across regions were observed. To better understand survival and BCPR variations across the regions, future studies should evaluate the pre-/in-hospital care management, racial differences and SES factors.

4.9 ACKNOWLEDGEMENT

The OHCAO registry is funded by the British Heart Foundation and the Resuscitation Council UK. The data were collected by 11 EMS and stored in the OHCAO registry at the University of Warwick. We thank all the EMS staff who gathered the data and the clinical trial team members at the University of Warwick for sharing the data with us. We thank Mr Adam de Paeztron (Clinical Trial Manager (OHCAO)) for the help in clarifying the OHCA file codes.

5 Bystander versus no Bystander Cardiopulmonary Resuscitation for Paediatric Out of Hospital Cardiac Arrest in England

Part of this chapter has been published

Albargi H, Mallett S, Booth S, Hawkes C, Perkins G, Scholefield B. Impact of bystander cardiopulmonary resuscitation for paediatric out-of-hospital cardiac arrest in England. Resuscitation. 2020 Oct 1;155:S17-8.(161) (Abstract presented at the ERC conference, Oct 2020)

Albargi H, Mallett S, Berhane S, Booth S, Hawkes C, Perkins GD, Norton M, Foster T, Scholefield B. Bystander cardiopulmonary resuscitation for paediatric out-of-hospital cardiac arrest in England: An observational registry cohort study. Resuscitation. 2022 Jan 1;170:17-25.(162) (Paper)

5.1 ABSTRACT

Introduction: Bystander cardiopulmonary resuscitation (BCPR) is strongly advocated by resuscitation councils in the chain of survival for paediatric out-of-hospital cardiac arrest (OHCA). However, there are limited reports on the rates of BCPR in England and its relationship with return of spontaneous circulation (ROSC) or survival outcomes. The OHCA outcomes registry prospectively collects data across 11 English Emergency Medical Service (EMS) NHS organisations.

Objective: We aim to describe the rate of BCPR and its association with any ROSC and survival to hospital discharge

Method: We conducted a retrospective analysis of prospectively collected paediatric (<18 years of age) OHCA cases in England; we included specialist registry patients treated by emergency medical services (EMS) with known BCPR status and outcome between January 2014 and November 2018. Data included patient demographics, aetiology, witness status, initial rhythm, EMS, season, time of day and bystander status. Associations between BCPR and any ROSC and survival to hospital discharge outcomes were explored using multivariable logistic regression.

Result: There were 2363 paediatric OHCAs treated across 11 EMS regions (OHCA per EMS (Median 116(IQR 120-313). Patients were 3.1 years (IQR 0.5-11.5), and 58.7% were male (1357/2310). BCPR was performed in 69.6% (1646/2363) of the cases overall (range 57.7% (206/367) to 83.7% (139/166) across EMS regions). Only 34.9% (550/1572) of BCPR cases were witnessed. The medical cause was the leading CA cause, 82.8% (1862/2247). A shockable rhythm was recorded as the initial rhythm in 6.8% (144/2095). Overall, any ROSC was

achieved in 22.8% (523/2289) and survival to hospital discharge in 10.8% (225/2066). Adjusted odds ratio (aOR) for any ROSC was significantly improved following BCPR compared to no-BCPR (aOR 1.37, 95% CI 1.03-1.81), but adjusted odds ratio for survival to hospital discharge were similar (aOR 1.01, 95% CI 0.66-1.55).

Conclusion: BCPR was associated with improved rates of any ROSC but not survival to hospital discharge. Variations in EMS BCPR rates may indicate opportunities for regional targeted increase in public BCPR education, which may impact survival rates.

5.2 INTRODUCTION

Four crucial actions were introduced as a "chain of survival" for successful resuscitation: immediate recognition and a call for help, early CPR, early defibrillation, and optimal post-resuscitation care.(128) Except for the fourth link, the remaining three actions can be performed by a bystander. The International Liaison Committee on Resuscitation recommended applying any form of CPR over no bystander CPR in a paediatric population.(8, 70) However, the BCPR rate varied widely across paediatric studies from 20% to 86%.(28, 33, 44, 47, 63, 72, 73, 75, 81, 84, 120, 121) A lack of EMS dispatcher systems, community education programs, fear of responsibility, infection and variation of study sample size are potential factors leading to variations in BCPR rates in paediatric studies. In England, the data about the BCPR rate in paediatric patients is limited. A recent report from the OHCA registry reported that the BCPR rate is 48.7% in the paediatric population.(163) However, the variation of BCPR rates across regions has not been described. Therefore, there is a need to describe the BCPR rate and explore factors that might cause variation across regions in England. This may help us identify and target population with low BCPR and eventually improve the survival outcomes.

The survival rate of OHCA in children is poor and varies widely in paediatric studies.(34, 49, 72, 155) In adults, data shows an improvement in survival rates in countries where the bystander CPR rate is high. In Norway, for example, the rate of bystander CPR is 73%, and the survival rate is 25%.(164) Similarly, in Seattle, BCPR is at 66%, and the rate of survival to discharge is 22%.(165) Current evidence of the impact of BCPR on survival to hospital discharge in paediatric patients is mixed. In a study by Naim et al. (2017), the survival to hospital discharge almost doubled when BCPR was performed compared to no-BCPR (14.2 vs 8.6%).(41) However, other studies have not found a significant association between BCPR and survival.(121, 122) Limited evidence describing the association of BCPR and survival outcomes has been described in the BCPR systematic review (chapter three). Seven observational studies suggested that BCPR increases the chance of survival to discharge.[41, 44, 73, 77, 81, 121, 122] Two of these studies have a small sample number[44, 81], and two studies showed the association between BCPR and survival was not statistically significant.[121, 122] The heterogeneity among studies was also observed. Interestingly, none of the studies in the BCPR systematic review (chapter three) included patients from England. This demonstrates that there is a lack of knowledge of the association between BCPR and survival outcomes in England.

Several confounding factors, including demographic, event characteristics and post-resuscitation care, might affect the association between BCPR and survival outcomes. For instance, some studies have shown that BCPR increases the chance of survival as age increases.[41, 127] However, increasing the survival rate might not be directly related to BCPR in older children. Compared to infants, shockable rhythm is observed more often in older children, which might explain the high survival rate.[29, 127] Furthermore, most infant OHCA is due to sudden infant death syndrome (SIDS) [37, 47], and the chances of these occurrences being witnessed are low compared to older children.[34, 141] Understanding the epidemiology of the paediatric population will help us to find the main factors associated with survival outcomes. In addition, adjusting for these factors would give us a clear idea of how BCPR is related to survival outcomes.

The aim of this study is to examine the role and effect of BCPR in paediatric OHCA survival outcomes in England using data from the Out of Hospital Cardiac Arrest Outcomes Registry. The registry was established in 2012 by the University of Warwick, collecting data from the national ambulance services. The analysis of paediatric OHCA data from the OHCAO registry will help to examine the variation of bystander CPR rates across regions in England and the association between bystander CPR, demographic and pre-hospital factors and survival outcomes.

5.3 METHODOLOGY

5.3.1 Settings and participants

This is a retrospective analysis of a prospective cohort within the OHCAO registry. This registry collects data from all 11 English ambulance service (Emergency Medical Services (EMS)) regions. We included paediatric OHCA patients identified from January 2014 to November 2018 who were under 18 years of age and had resuscitation attempted by EMS providers. We excluded EMS witnessed OHCA and patients whose bystander CPR status and outcome were missing.

5.3.2 Description of the EMS

The description of the EMS in England was described elsewhere.(Section 1.8) Dispatcher CPR was provided during the study period and although there is not publish evidence our prior believe that this is provided for adult and paediatric CA.

5.3.3 Data Collection

Participating EMS clinical audit teams identify cases and extract data from routinely collected data recorded on Patient Report Forms and survival outcomes from admitting hospitals or from SPINE (https://digital.nhs.uk/services/spine), a secure national health and social care record sharing platform. The EMS clinical audit teams clean and verify their data before uploading it to the OHCAO registry servers. At this point, due to different terms used by each EMS region and to ensure data is mapped to the variables used in the registry, the data is transformed using service-specific rules. The OHCAO team verify and clean the data before it is analysed

5.3.4 Variable definitions

The primary intervention was BCPR. We looked for the effect of bystander resuscitation on survival outcomes compared to no-BCPR. We also examined the association between demographic and pre-hospital factors with both BCPR and survival outcomes. Age was divided into five groups based on the Utstein style[4]: infants (≤1 year); pre-school children (1-4 years); school children (>4-8 years); older school children (>8-12); and adolescents (>12-<18 years). Resuscitation characteristics included whether the OHCA case was witnessed by a member of the public. The initial cardiac rhythm was defined as shockable (ventricular fibrillation and pulseless ventricular tachycardia) or non-shockable (asystole and pulseless electrical activity). Bystander interventions included CPR and the use of an automated external defibrillator. Aetiology was categorised as medical (which included cardiac causes and non-cardiac causes), trauma, drowning, drug overdose and asphyxia. Daytime was defined as the period from 9.00 am to 4.59 pm, and night-time was defined as the period from 5.00 pm to 8.59 am. The seasons (spring, summer, autumn and winter) were categorised based on the meteorological seasons.[166]

The primary outcome was survival to hospital discharge and the secondary outcome was ROSC. Different stages of ROSC were captured and defined as follows: (1) pre-hospital ROSC, including cases where patients had ROSC at the scene or before the EMS arrival; (2) hospital ROSC, including cases where patients arrived at the hospital with ROSC; any ROSC, including both pre-hospital and hospital ROSC.

5.3.5 Statistical Analysis

The primary exposure of interest was BCPR. We examined the association between demographic and pre-hospital factors with BCPR, ROSC (pre-hospital, hospital and at-any-time) and hospital survival outcomes. A statistical analysis plan was prepared prior to data analysis, including outcomes and adjusted variables chosen based on the recommendation from the ILCOR community about these variables being important in the analysis of reporting CA, [4, 109] reviewing other paediatric observational studies examining factors that affect the BCPR output,[3, 41] and with clinical expertise (EMS and paediatric resuscitation) discussion about potential causal pathways. Descriptive statistics included means and standard deviations for normally distributed data and medians with interquartile ranges (IQRs) for skewed data. Comparison of BCPR and no-BCPR and outcomes were conducted using Chi-square tests for categorical variables, and the Mann-Whitney test was used for continuous data. We used univariable logistic regression analysis to calculate unadjusted odds ratio (OR) with a 95% confidence interval (CI) to examine the association between BCPR, age, sex, initial cardiac rhythm, CA cause, status of the witness, the time of day and the season, EMS characteristics with ROSC and survival. A multivariable logistic regression analysis of complete case data was created using the same factors to identify the adjusted odds ratio (aOR); however, EMS region was not included in the model for ROSC and survival outcome as some of the EMS services did not collect data for some of prehospital factors or outcomes have a large missing data (as highlighted in Chapter 4). Finally, post hoc subgroup analysis was performed after identifying a link between BCPR, age, witness status and shockable rhythm. Statistical analyses were performed using Stata 16.0 (Stata Corp., College Station TX, USA).

5.3.5.1 *Choice of modelling technique*

Two potential options for estimating exposure effects on outcome using observational data were available: logistic regression and propensity score methods.[167] Logistic regression is a statistical model that can estimate the probability of an outcome based on input features.[168] It can also provide interpretable parameters that can explain the relationship between the outcome and each predictor or confounder variable. One of the advantages of using the logistic regression model is that it can allow adjusting for multiple variables simultaneously and can handle both linear and non-linear effects on the outcome.[168] Results obtained using this model can be easily interpreted since the model produces odds ratios. However, logistic regression is prone to overfitting especially if there are too many predictor variables relative to the number of observations in the model. It thus requires a larger sample size to produce more precise estimation.

Another method which is less commonly used in studies with a similar design is propensity score matching. While logistic regression directly adjusts for confounders, the propensity score method controls for imbalances by matching exposed and unexposed patients (for e.g. BCPR and non-BCPR) using a score generated that summarises all confounders into a single value.[169] To estimate the effect of the exposure on the outcome, a different logistic regression is fitted with the outcome as the dependent variable and the exposure and propensity score as independent variables. An advantage of the propensity score is it provides less biased estimates compared to logistic regression when the number of patients with the outcome are low relative to the number of covariates.[170]

However, a limitation of propensity score matching is that since the confounders are collapsed into a single value, the effect of the other variables on the outcome, other than the exposure, will not be shown. In this study, we wanted to examine the association of ROSC and survival outcomes with BCPR in addition to age, sex, initial cardiac rhythm, CA cause, status of the witness, the time of day and the season. Another limitation of propensity is that matching is performed based on measured confounders and any imbalance due to unmeasured confounders will remain leading to biased estimates.[171]

Due to the above limitations of the propensity score, the logistic regression model was chosen for the analysis of the data.

5.3.6 Ethics

The University of Warwick hosts the OHCAO project which has approval from the National Research Ethics Service (13/SC/0361). Details of the registry have been previously summarised.[15] This study was additionally approved by the University of Birmingham Internal Review Board (RG 17-246. 14.11.2018).

5.4 RESULT

A total of 3173 paediatric OHCA cases were identified from the OHCAO registry over a period of 4 years and 11 months. We excluded 308 (18 years or older), 258 (missing BCPR status), 215 (EMS witnessed) and 29 (missing both ROSC and survival outcome) cases. A total of 2363 cases were included the analysis. BCPR was performed in 1646 (69.6%), while 717(30.4%) did not receive BCPR. In the BCPR group, 157 cases (10.8%) survived hospital discharge and 393 (24.6%) achieved ROSC at any time. For those who did receive BCPR, 68 cases survived to hospital discharge (11.1%) and 130 (18.6%) achieved any ROSC. Figure 5-1

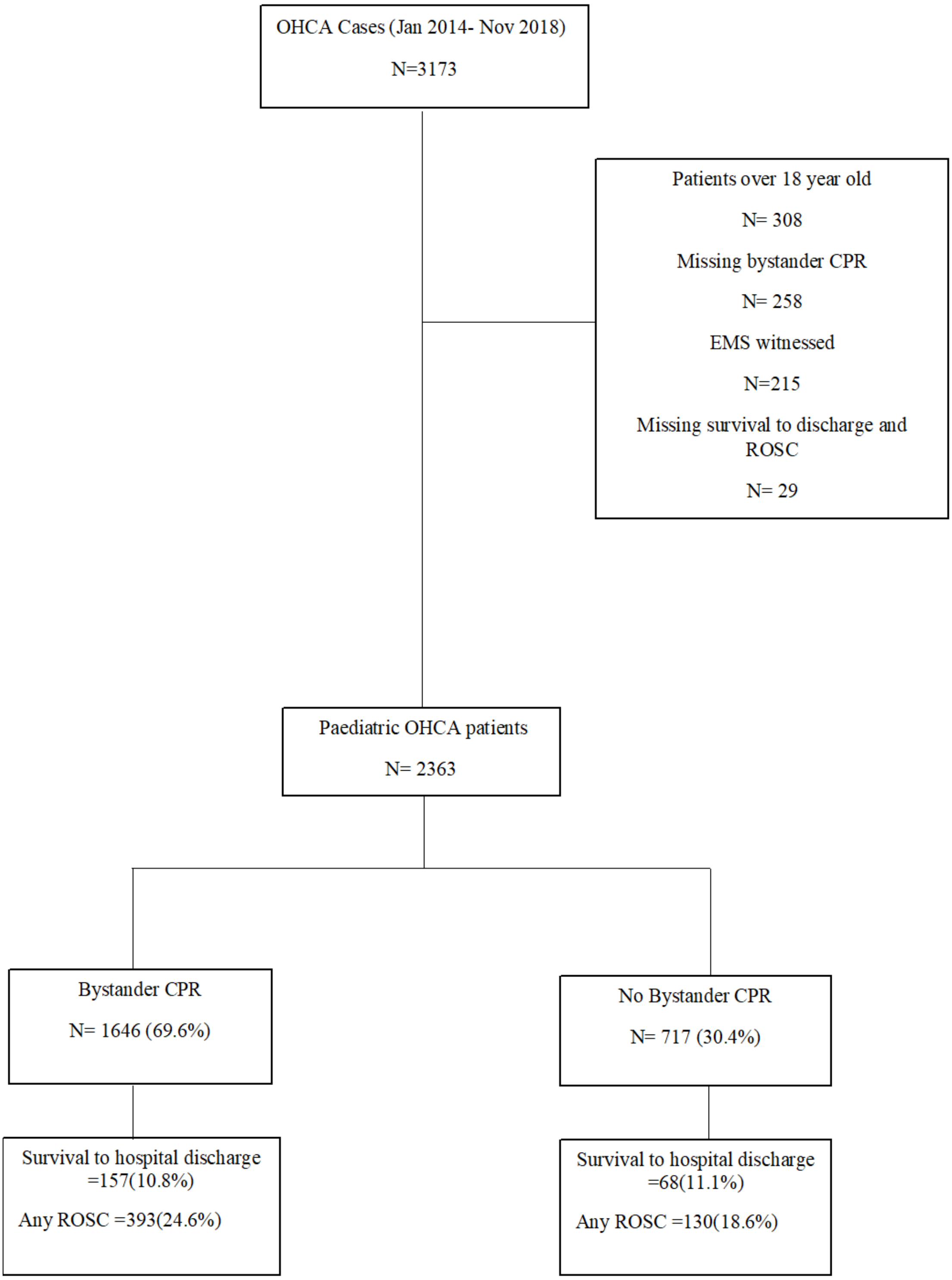

Figure 5-1 Patient flow chart. OHCA, out-of-hospital cardiac arrest; ROSC, return to spontaneous circulation

5.4.1 Demographics

The characteristics of included patients are detailed in Table 5-1. Median age of the cases was 3.1 years (IQR 0.5-11.5) and a third (33.4%) were less than 1 year of age. There were more males than females (58.7% vs. 41.3%). Medical causes accounted for 82.8% of all CA cases and 34.1% were witnessed. An initial shockable rhythm was recorded in 6.9% of cases and an automated external defibrillator was used in 2.4% of cases (Table 5-1). An OHCA occurred most frequently between 05:00 pm and 08:59 am, with the highest frequency reported between 07:00 am and 07:59 am (Figure 5-2). Overall, any ROSC was achieved in 22.8% of the cases, with 10.8% survival to hospital discharge.

BCPR was performed in 69.6% of all OHCA cases, of which 34.9% were witnessed. The number of cases per EMS region per year is outlined in Table 5-2. The rate of BCPR varied across EMS regions and ranged from 57.7 to 83.7%. The highest BCPR rate was recorded in 2018 at 74.3% (Figure 5-3). BCPR was less common for trauma-related OHCAs (62.5%). However, 79.1% of cases presenting with a shockable rhythm had undergone BCPR.

Table 5-1 Demographic of paediatric OHCA association with bystander CPR

	Total		BCPR		No-BCPR		p-value
	N	%	N	%	N	%	
Total	2363	100	1646	69.6	717	30.4	
Age[a]	2363						
(median, IQR)	3.4 (0.5-12)		3.4 (0.5-11.9)		3.1 (7.0-12.1)		
0-1 year	790	33.4	539	32.7	251	35.0	0.11
1-4 years	502	21.2	338	20.5	164	22.8	
4-8 years	276	11.6	195	11.8	81	11.3	
8-12 years	242	10.2	178	10.8	64	8.9	
12-18 years	533	23.4	396	24.0	157	21.9	
Sex[b]							
Male	1357	58.7	960/1610	59.6	397/700	56.7	0.19
Female	953	41.3	650/1610	40.4	303/700	43.3	
Aetiology[c]							
Medical	1862	82.8	1310/1577	83.0	552/670	82.3	0.23
Trauma	144	6.4	90/1577	5.7	54/670	8.0	
Drowning	40	1.7	29/1577	1.8	11/670	1.6	
Drug overdose	26	1.1	18/1577	1.1	8/670	1.1	
Asphyxia	175	7.7	130/1577	8.2	45/670	6.7	
Status of witness[d]							
Witnessed	776	34.1	550/1572	34.9	226/698	32.3	0.22
Initial rhythm[e]							
Shockable	144	6.8	114/1480	7.7	30/615	4.8	0.02
AED[f]							
AED use	35	2.4	35/943	3.7	0/472	0.0	<0.001
Time of day[g]							
Daytime	755	34.0	518/1541	34.0	237/679	34.9	0.55
Season							
Spring	640	27.0	443/1646	26.9	197/717	27.4	0.51
Summer	563	23.8	397/1646	24.1	166/717	23.1	
Autumn	600	25.3	428/1646	26.0	172/717	23.9	
Winter	560	23.7	378/1646	22.9	182/717	25.3	

Table 5-1 (continued) Demographic of paediatric OHCA association with bystander CPR

	Total		BCPR		No-BCPR		p-value
	N	**%**	**N**	**%**	**N**	**%**	
Year							
2014	485	20.5	348/1646	20.6	152/891	21.2	
2015	467	19.7	333/1646	18.6	166/717	23.1	
2016	441	18.6	301/1646	18.7	129/717	17.9	<0.01
2017	452	19.1	312/1646	18.8	137/717	19.1	
2018	518	21.9	385/1646	23.0	133/717	18.5	
Outcomes[h]							
Survival to hospital discharge	225	10.8	157/1454	10.8	68/612	11.1	0.83
Any ROSC	523	22.8	393/1592	24.6	130/697	18.6	0.002
Hospital ROSC	431	19.1	322/1566	20.5	109/688	15.8	0.009
Pre-hospital ROSC	412	21.8	310/1304	23.7	102/585	17.4	0.002

BCPR, bystander cardiopulmonary resuscitation; IRQ, Interquartile range; AED, automated external defibrillator. ROSC, return of spontaneous circulation;

a Age was treated as a continuous variable

Data were missing in

b Sex (n=53)

c Aetiology (n=116)

d Status of witness (n=93)

e Initial rhythm (n=268)

f AED (n=948)

g Time of the day (n=143)

h Survival to hospital discharge (n=297) and any ROSC (n=74)

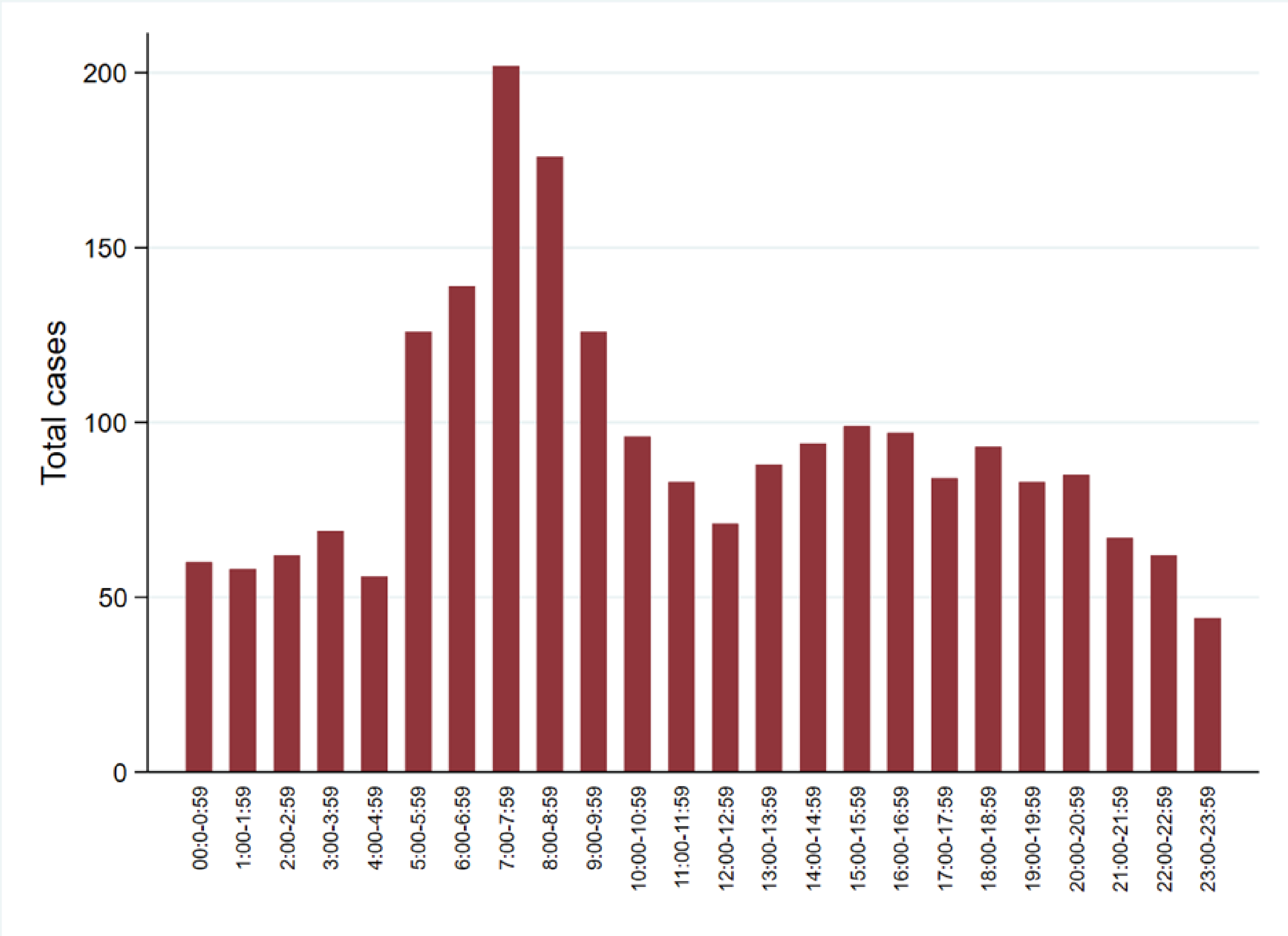

Figure 5-2 Paediatric OHCA by time of day

Table 5-2 The number of cases per EMS region per year

	Year				
EMS	2014	2015	2016	2017	2018
1	35	13	24	46	48
2 [a]	n/r	11	29	34	26
3	75	74	82	81	71
4	53	44	52	61	58
5[b]	40	49	n/r	n/r	50
6	27	34	55	51	37
7[c]	67	44	n/r	n/r	41
8[d]	n/r	n/r	n/r	n/r	3
9	110	99	102	108	108
10	13	19	5	3	24
11	65	80	92	68	52
Total	458	467	441	452	515

[a] No data available in 2014

[b] No data available in 2016 and 2017

[c] No data available in 2016 and 2017

[d] No data available in 2014,2015,2016, and 2017

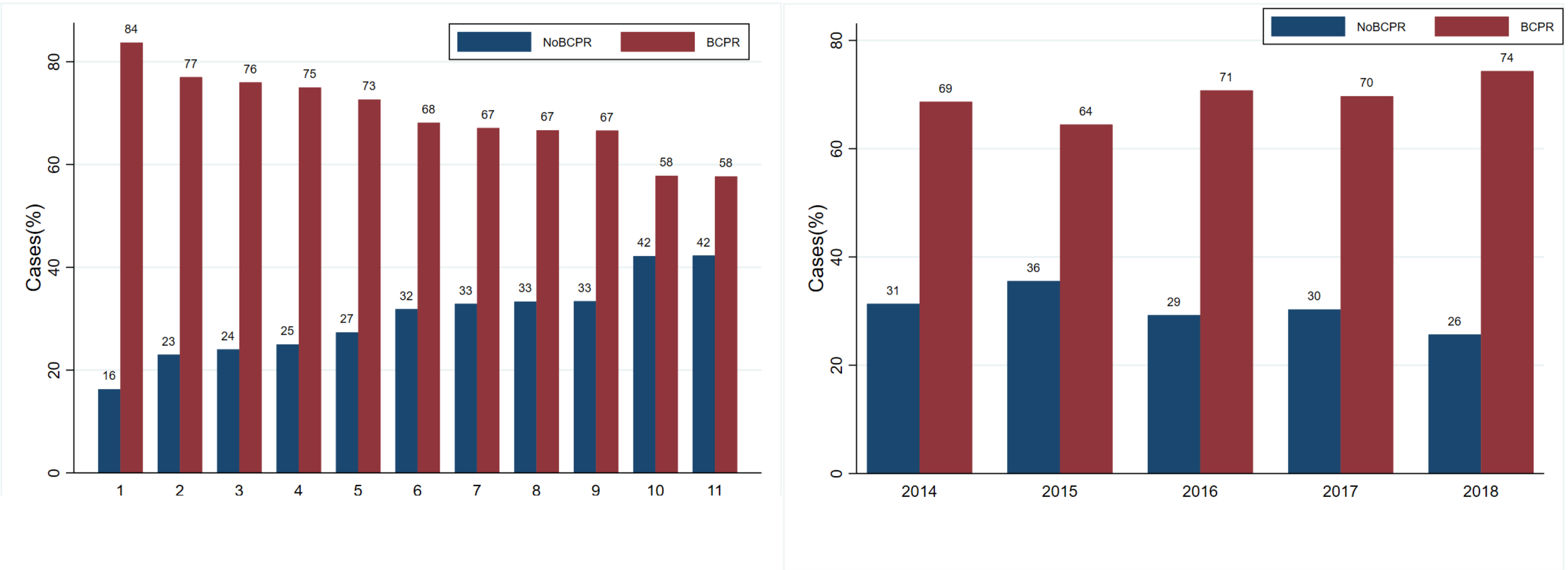

Figure 5-3 Bystander cardiopulmonary resuscitation (BCPR) rate: A) across EMS regions (ordered by decreasing BCPR rate), and B) by year

5.4.2 Association of Bystander CPR with other variables

In a multivariable logistic regression analysis, BCPR was less likely to be performed in trauma cause aOR (95% CI) 0.64(0.42-0.97) compared to medical cause (Table 5-3). The association between BCPR and ambulance services varied where four ambulance services were associated with more BCPR (EMS 1, 2, 3, and 4), one with less BCPR (EMS 11) and four showed no association with BCPR rate (EMS 5, 6, 7, and 10). The univariate analysis showed an association between shockable rhythm and BCPR OR (95% CI) 1.62 (1.07-2.46) but not after adjustment for the confounding factors aOR (95%) 1.40 (0.88-2.2). Figure 5-4 shows the adjusted OR with 95% CI for the association of BCPR and other factors.

Table 5-3 Odds ratios for BCPR for demographic characteristics of paediatric OHCA cases

	Unadjusted OR (95% CI)	**P value**	**Adjusted[a] OR (95% CI)**	**P-value**
Age[b]	1.01(0.99-1.02)	0.08	1.00 (0.98-1.02)	0.82
Female	0.88 (0.74-1.06)	0.19	0.95 (0.77-1.17)	0.66
Aetiology				
Medical		**Reference**		
Trauma	0.70 (0.49-0.99)	0.04	0.64 (0.42-0.97)	0.03
Drowning	1.11 (0.55-2.23)	0.76	1.00 (0.45-2.25)	0.98
Drug overdose	0.94 (0.40-2.19)	0.90	0.73 (0.28-1.86)	0.51
Asphyxia	1.21 (0.85-1.73)	0.27	1.13 (0.75-1.69)	0.54
EMS region[c]				
9		**Reference**		
1	2.58 (164-4.04)	<0.001	3.08 (1.72-5.51)	<0.001
2	1.67 (1.01-2.77)	0.04	1.91 (1.00-3.63)	0.04
3	1.58 (1.17-2.13)	0.002	1.51 (1.10-2.06)	0.009
4	1.50 (1.08-2.09)	0.01	1.64(1.09-2.46)	0.01
5	1.33 (0.88-2.01)	0.17	1.56 (0.75-3.27)	0.22
6	1.07(0.75-1.51)	0.69	0.97 (0.64-1.48)	0.91
7	1.02 (0.69-1.50)	0.90	0.98(0.60-1.60)	0.94
8[d]				
10	0.68 (0.40-1..16)	0.16	2.38 (0.51-11.1)	0.26
11	0.68 (0.51-0.90)	0.007	0.69 (0.51-0.94)	0.01
Witnessed	1.12 (0.92-1.35)	0.22	1.02 (0.81-1.29)	0.82
Shockable rhythm	1.62(1.07-2.46)	0.02	1.40 (0.88-2.2)	0.15
Time of day				
Daytime	0.94 (0.78-1.14)	0.55	0.86 (0.81-1.29)	0.18
Seasons				
Spring		**Reference**		
Summer	1.06 (0.83-1.36)	0.62	0.98 (0.66-1.19)	0.44
Autumn	1.10 (0.86-1.41)	0.41	0.99 (0.74-1.32)	0.95
Winter	0.92 (0.72-1.17)	0.52	0.83 (0.62-1.11)	0.22

BCPR, bystander cardiopulmonary resuscitation; OR, odds ratio.

[a] Odd ratios were calculated adjusting for age, sex, aetiology, ambulance services, status of the witness, initial cardiac rhythm, the time of day and the season

[b]Age was treated as a continuous variable.

[c] The number of cases by each EMS services : EMS 1=166, EMS 2=100,EMS 3= 383, EMS 4=268,EMS 5=139, EMS 6=204, EMS 7=152, EMS 8=3,EMS 9=527, EMS 10=64, EMS 11=357

[d] EMS region was excluded from the analysis due to the small sample size.

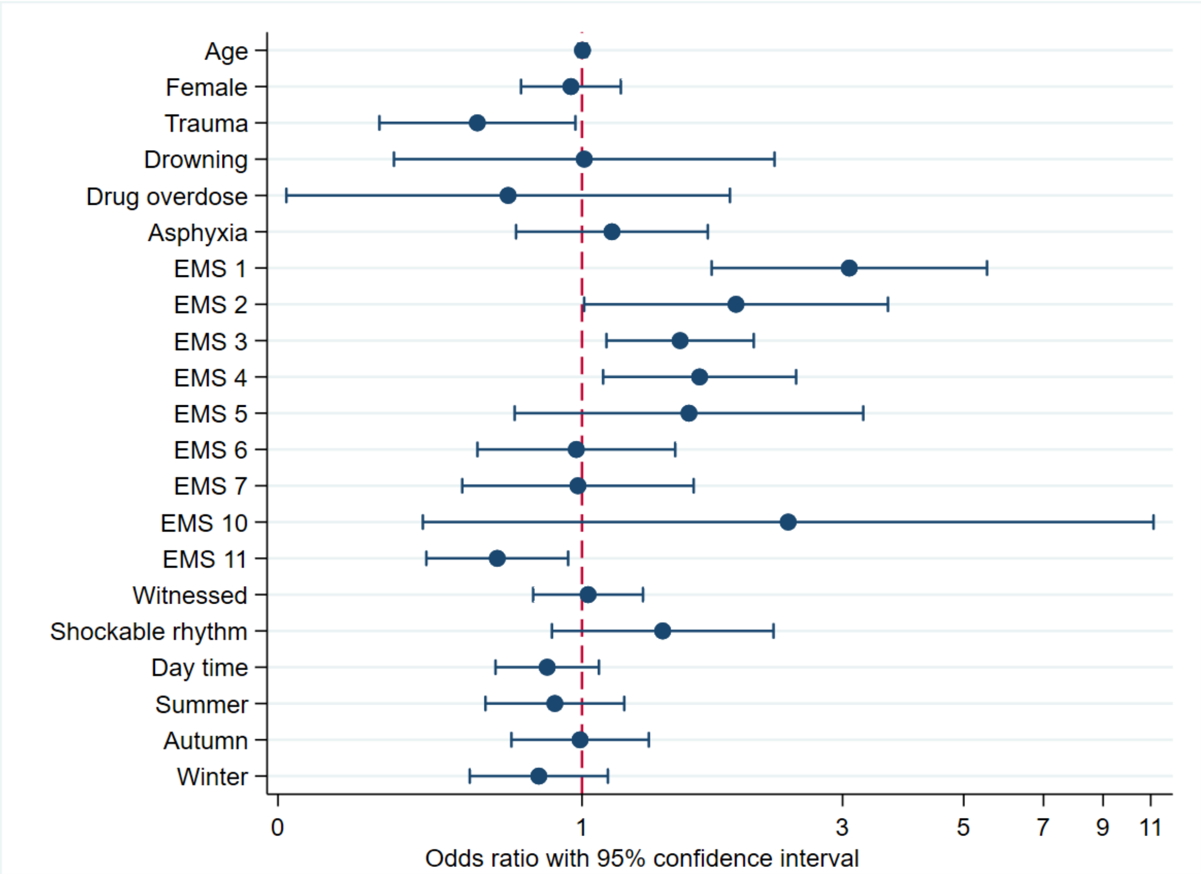

Figure 5-4 Adjusted OR with 95% confidence interval for BCPR association with other factors. EMS, emergency medical services,EMS 9 was excluded as it is the reference for EMS regions. EMS 8 was excluded due to the small sample size.

5.4.3 Association of Bystander CPR with survival outcomes

In our univariate analysis, BCPR was not associated with survival to hospital discharge (OR (95%CI) 0.96(0.71-1.30); p value =0.83). However, compared to no-BCPR, BCPR was associated with pre-hospital ROSC, hospital ROSC and ROSC at any time OR (95% CI) 1.47 (1.15-1.89); p value =0.002; 1.37(1.08-1.74); p value =0.009; 1.42(1.14-1.78) p value =0.002 respectively.

After adjustment, BCPR remained associated with pre-hospital ROSC (aOR 1.40 (95%CI 1.04-1.90) and ROSC at any time (aOR 1.37 (95%CI 1.03-1.81) but no association was found with survival to hospital discharge (aOR 1.01 (95% CI 0.66-1.55) and hospital ROSC (aOR 1.32(95% CI 0.98-1.78) (Figure 5-5)

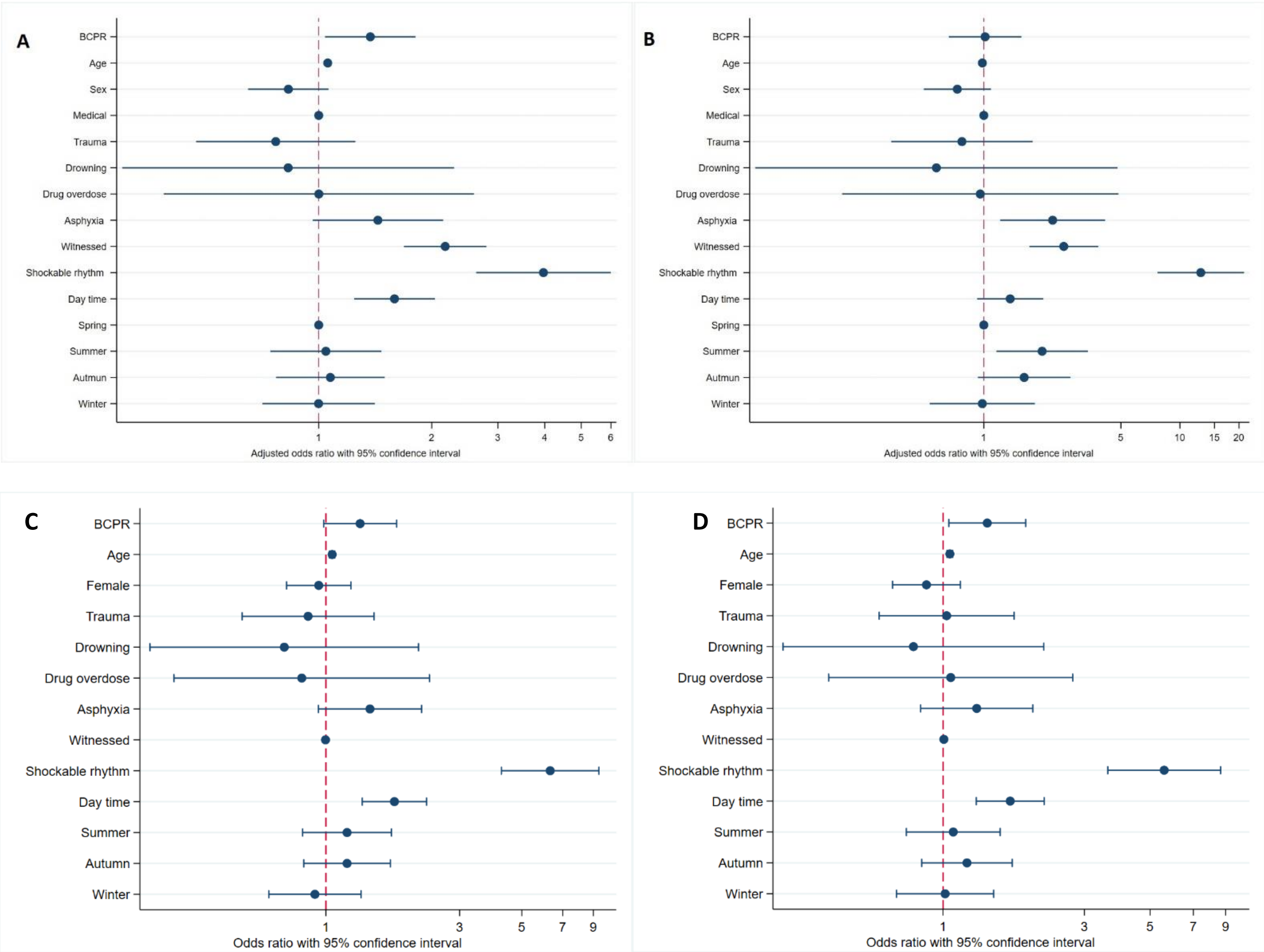

Figure 5-5 Adjusted odds ratio with 95% confidence interval for a) Any ROSC, b) Survival to hospital discharge , c)Hospital ROSC, d)Pre-hospital ROSC

5.4.4 The association of demographic and pre-hospital factors with survival outcomes

In the multivariable logistic regression analysis, survival to hospital discharge was associated with the presence of a witness (aOR 2.55, 95% CI 1.70-3.83), a shockable rhythm (aOR12.7, 95% CI 7.68-21.2), asphyxia (compared to medical 2.24, 95%CI 1.21-4.15) and summer (compared to spring, aOR 1.98,95% CI 1.15-3.39) but not BCPR (aOR 1.01, 95% CI 0.66-1.55). (Table 5-4)

Any ROSC was associated with BCPR (aOR 1.37, 95% CI 1.03-1.81), age (aOR 1.05, 95% CI 1.03-1.07), witnessed (aOR 2.17, 95% CI 1.68-2.79), shockable rhythm, (aOR 3.96, 95% CI 2.62-5.99), and daytime event (aOR 1.59, 95% CI 1.24-2.03) (Table 5-5)

The chance of hospital ROSC being achieved increased with increasing age (aOR 1.04(95% CI 1.02-1.07); asphyxia cause (compared to medical cause aOR, 1.58 95% CI 1.02-2.42), being witnessed (aOR 2.19 (95% CI 1.66-2.89); shockable rhythm (aOR 4.75 (95% CI 3.13-7.22); and CA at daytime (aOR. 1.62(95% CI 1.24-2.12) (Table 5-6)

Pre-hospital ROSC was associated with BCPR (aOR 1.38, 95% CI 1.01-1.87), age (aOR 1.05, 95% CI 1.02-1.07), witnessed (aOR 2.43, 95% CI 1.84-3.21), shockable rhythm, (aOR 3.95, 95% CI 2.50-6.23), and daytime event (aOR 1.53, 95% CI 1.17-2.01) (Table 5-7)

Table 5-4 Multivariable logistic regression for survival-to-hospital-discharge

	Total	Outcome		Unadjusted		Adjusted[a]	
	N=2066	N	%	OR (95% CI)	P-value	OR (95% CI)	P-value
Bystander	2066	225	100				
BCPR	1454	157/225	69.7	0.96 (0.71-1.30)	0.83	1.01 (0.66-1.55)	0.94
Age[b]	2066	225	100	1.01 (0.99-1.03)	0.14	0.98 (0.95-1.01)	0.32
Sex	2025	223	99.1				
Female	828	74/223	33.1	0.69 (0.51-0.92)	0.01	0.73 (0.49-1.08)	0.12
Aetiology[c]	1998	218	96.8				
Medical	1646	181/218	83.0	**Reference**			
Trauma	132	8/218	3.6	0.52 (0.25-1.08)	0.08	0.77 (0.33-1.77)	0.54
Drowning	36	4/218	1.8	1.01 (0.35-2.89)	0.98	0.57 (0.06-4.80)	0.60
Drug overdose	26	5/218	1.3	1.05 (0.31-3.55)	0.93	0.95 (0.18-4.85)	0.95
Asphyxia	158	27/218	10.0	1.30 (0.81-2.10)	0.26	2.24 (1.21-4.15)	0.01
Witness status	1989	215	95.5				
Witnessed	687	138/215	64.1	3.99 (2.97-5.37)	<0.001	2.55 (1.70-3.83)	<0.001
Initial rhythm	1832	161	71.5				
Shockable rhythm	120	56/161	34.7	13.3 (8.89-20.1)	<0.001	12.7 (7.68-21.2)	<0.001
Time of day	1933	208	92.4				
Daytime	667	95/208	45.6	1.69(1.26-2.26)	<0.001	1.36 (1.70-3.83)	0.11
Seasons[d]	2066	225	100				
Spring	562	49/225	21.7	**Reference**			
Summer	504	61/225	27.1	1.44 (0.96-2.14)	0.07	1.98 (1.15-3.39)	0.01
Autumn	531	67/225	29.7	1.51 (1.02-2.23)	0.03	1.60 (0.93-2.76)	0.08
Winter	469	44/225	21.3	1.19 (0.78-1.81)	0.40	0.98 (0.53-1.81)	0.95

OR, odds ratio; BCPR, bystander cardiopulmonary resuscitation.

[a] Odd ratios were calculated adjusting for age, sex, aetiology, status of the witness, initial cardiac rhythm, the time of day and the season

[b]Age in years was treated as a continuous variable

[c]Medical was used as the reference group for the aetiology ORs

[d] Spring was used as the reference group for the season OR

Table 5-5 Multivariable logistic regression for ROSC at any time

	Total	Outcome		Unadjusted		Adjusted[a]	
	N=2289	N	%	OR (95% CI)	P-value	OR (95% CI)	P-value
Bystander	2289	523	100				
BCPR	1592	393/523	75.1	1.42 (1.14-1.78)	0.002	1.37 (1.03-1.81)	0.02
Age[b]	2289	523	100	1.06 (1.04-1.08)	<0.001	1.05 (1.03-1.07)	<0.001
Sex	2261	519	99.2				
Female	933	189/519	36.4	0.76 (0.62-0.94)	0.01	0.83 (0.64-1.06)	0.14
Aetiology	2175	572	95.4				
Medical	1793	401/503	79.7	**Reference**			
Trauma	143	30/503	5.9	0.92 (0.60-1.39)	0.70	0.76 (0.47-1.25)	0.29
Drowning	40	10/503	1.9	1.15 (0.66-2.38)	0.69	0.82 (0.29-2.29)	0.71
Drug overdose	26	8/503	1.5	1.54 (0.66-3.57)	0.31	1.00 (0.38-2.59)	0.99
Asphyxia	173	54/503	10.7	1.57 (1.12-2.21)	0.009	1.43 (0.96-2.14)	0.07
Witness status	2219	510	97.8				
Witnessed	765	290/510	56.8	3.42 (2.79-4.20)	<0.001	2.17 (1.68-2.79)	<0.001
Initial rhythm	2083	431	81.1				
Shockable rhythm	143	85/431	19.7	6.75 (4.74-9.61)	<0.001	3.96 (2.62-5.99)	<0.001
Time of day	2148	489	93.6				
Daytime	724	216/489	44.1	1.79 (1.45-2.20)	<0.001	1.59 (1.24-2.03)	<0.001
Seasons	2289	523	100				
Spring	619	128/523	24.4	**Reference**			
Summer	548	122/523	23.3	1.09 (0.83-1.45)	0.51	1.04 (0.74-1.46)	0.80
Autumn	581	150/523	28.6	1.33 (1.02-1.74)	0.03	1.07 (0.76-1.49)	0.67
Winter	541	123/523	23.5	1.12 (0.85-1.49)	0.39	0.99 (0.70-1.40)	0.99

ROSC, return of spontaneous circulation; BCPR, bystander cardiopulmonary resuscitation; OR, odds ratio. [a] Odd ratios were calculated adjusting for the prespecified variables of age, sex, aetiology, status of the witness, initial cardiac rhythm, the time of day and the season [b]Age in years was treated as a continuous variable

Table 5-6 Multivariable logistic regression for hospital ROSC

	Total	Outcome		Unadjusted		Adjusted[a]	
	N=2254	**N**	**%**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Bystander	2254	431	100				
BCPR	1566	322/431	74.7	1.37(1.08-1.74)	0.009	1.32(0.97-1.78)	0.07
Age[b]	2254	431	100	1.05(1.04-1.07)	<0.0001	1.04(1.02-1.07)	<0.0001
Sex	2228	430	99.7				
Female	919	160/430	37.2	0.81(0.65-1.00)	0.05	0.93(0.71-1.22)	0.61
Aetiology	2149	414	95.4				
Medical	1773	332/414	80.1	**Reference**			
Trauma	140	22/414	5.3	0.80(0.50-1.29)	0.37	0.73(0.42-1.26)	0.26
Drowning	39	8/414	1.9	1.12(0.51-2.45)	0.77	0.87(0.28-2.67)	0.80
Drug overdose	26	6/414	1.4	1.30(0.51-3.26)	0.57	0.86(0.29-2.48)	0.78
Asphyxia	171	46/414	11.1	1.59(1.11-2.28)	0.01	1.58(1.02-2.42)	0.03
Witness status	2188	422	97.9				
Witnessed	755	250/422	59.2	3.62(2.91-4.52)	<0.0001	2.19(1.66-2.89)	<0.0001
Initial rhythm	2050	342	79.3				
Shockable rhythm	141	76/342	22.2	7.22(5.06-10.3)	<0.0001	4.75(3.13-7.22)	<0.0001
Time of day	2113	400	92.8				
Daytime	711	182/400	45.5	1.86(1.49-2.33)	<0.0001	1.62(1.24-2.12)	<0.0001
Seasons	2254	431	100				
Spring	611	103/431	23.9	**Reference**			
Summer	536	103/431	23.9	1.17(0.86-1.58)	0.29	1.14(0.78-1.65)	0.48
Autumn	578	128/431	29.7	1.40(1.05-1.87)	0.02	1.13(0.78-1.62)	0.50
Winter	529	97/431	22.5	1.10(0.81-1.50)	0.51	0.89(0.60-1.31)	0.57

ROSC, return of spontaneous circulation; BCPR, bystander cardiopulmonary resuscitation; OR, odds ratio. [a] Odd ratios were calculated adjusting for the prespecified variables of age, sex, aetiology, status of the witness, initial cardiac rhythm, the time of day and the season [b]Age in years was treated as a continuous variable

Table 5-7 Multivariable logistic regression for pre-hospital ROSC

	Total	Outcome		Unadjusted		Adjusted[a]	
	N=1899	**N**	**%**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Bystander	1899	412	100				
BCPR	1304	310/412	75.2	1.47(1.15-1.89)	0.002	1.38(1.01-1.87)	0.03
Age[b]	1899	412	100	1.05(1.04-1.07)	<0.0001	1.05(1.02-1.07)	<0.0001
Sex	1871	409	99.2				
Female	768	147/409	35.9	0.75(0.60-0.95)	0.01	0.85(0.65-1.12)	0.26
Aetiology	1798	400	97.0				
Medical	1481	314/400	78.5	**Reference**			
Trauma	110	25/400	6.2	1.09(0.68-1.73)	0.70	0.81(0.47-1.39)	0.45
Drowning	35	9/400	2.2	1.28(0.59-2.77)	0.52	1.07(0.38-3.04)	0.88
Drug overdose	26	8/400	2.0	1.65(0.71-3.83)	0.24	1.15(0.44-3.03)	0.76
Asphyxia	146	44/400	11.0	1.60(1.10-2.33)	0.01	1.55(0.99-2.42)	0.052
Witness status	1831	400	97.0				
Witnessed	638	230/400	57.5	3.39(2.69-4.26)	<0.0001	2.43(1.84-3.21)	<0.0001
Initial rhythm	1741	349	84.7				
Shockable rhythm	114	66/349	18.9	6.53(4.40-9.67)	<0.0001	3.95(2.50-6.23)	<0.0001
Time of day	1854	392	95.1				
Daytime	621	173/392	44.1	1.78(1.42-2.24)	<0.0001	1.53(1.17-2.01)	0.002
Seasons	1899	412	100				
Spring	509	101/412	24.5	**Reference**			
Summer	448	101/412	24.5	1.17(0.86-1.60)	0.30	1.03(0.71-1.50)	0.84
Autumn	506	122/412	29.6	1.28(0.95-1.72)	0.10	1.16(0.81-1.66)	0.41
Winter	426	88/412	21.3	1.05(0.76-1.44)	0.75	0.99(0.67-1.45)	0.96

ROSC, return of spontaneous circulation; BCPR, bystander cardiopulmonary resuscitation; OR, odds ratio. [a] Odd ratios were calculated adjusting for the prespecified variables of age, sex, aetiology, status of the witness, initial cardiac rhythm, the time of day and the season [b]Age in years was treated as a continuous variable

5.4.5 Analysis of witnessed status, shockable rhythm, and outcome subgroups.

Subgroup analysis of witness status showed a significant association with age (p<0.001). Infant CA were witnessed in 25.6% of all infant cases whereas older children aged 12-18 were witnessed in 40% of the cases. Traumatic witnessed cardiac arrest was more common than traumatic unwitnessed cardiac arrest (58.0% vs 42.0%). Out of 136 shockable cases, 103 (75.7%) were witnessed while only 33 (24.3%) cases had a shockable rhythm were unwitnessed (p<0.001). More than 40.0% of all witnessed cases occurred during day time. For survival outcomes, 20.1% of all witnessed cases survived to hospital discharge whereas only 5.9% of all unwitnessed cases survival to hospital discharge. ROSC at any time, hospital ROSC and prehospital ROSC were higher in witnessed group compared to unwitnessed. (respectively; 37.9%, 33.1%, 36.1% vs 15.1%, 12.0%, 14.2%). (Appendix 8-11, p227)

Of all cases where a shockable rhythm was recorded, children aged 12-18 years had the highest percentage compared to other age groups (55.6%). AED was used for 13.1% of all shockable cases compared to 1.7% of the non-shockable cases. For the survival outcomes, 46.7% of all shockable cases survived to hospital discharge compared to 6.1% of the non-shockable cases. Similarly, ROSC at any time, hospital ROSC and prehospital ROSC were higher in the shockable group compared to non-shockable (respectively; 59.4%, 53.9%, 57.9% vs 17.8%, 13.9, 17.3%). (Appendix 8-12, p227)

Although there were no statistically significant difference in survival to hospital discharge across the age groups (Chi squared for trend p=0.37, survival was slightly lower in infants compared to other older age groups (9% versus 11-12%). (Appendix 8-13, p231)

Subgroup analysis for the survival to hospital discharge and ROSC at any time were performed according to BCPR status with percentage witnessed and initial rhythm calculated within each group.

In patients who received BCPR and survived to hospital discharge, proportion of witnessed was higher than unwitnessed (20.7% vs 5.4%, p<0.001). Similarly, amongst those who received BCPR and achieved ROSC, proportion of witnessed cases was also higher than unwitnessed (40.3% vs 16.3%, p<0.001.

We identified a similar relationship in patients who did not receive BCPR and survived to hospital discharge, where the proportion of those witnessed was again higher than unwitnessed (18.5%% vs 7.2%, p<0.001). Similarly, amongst those who did not received BCPR and achieved ROSC, proportion of witnessed was over two times higher than the unwitnessed (32.1% vs 12.5%, p<0.001). (Appendix 8-14,8-15, p231,232)

In patients who received BCPR and survived to hospital discharge, the proportion of those who had shockable rhythm was higher than those who did not have shockable rhythm (46.2% vs 6.0%, p<0.001). Similarly, amongst those who received BCPR and achieved ROSC, proportion of cases with shockable rhythm was also higher in than the non-shockable (63.7% vs 19.1%, p<0.001). The relationship remained in patients who received no-BCPR with a shockable rhythm compared to no-BCPR with non-shockable group for both survival to hospital discharge and ROSC at any time outcomes (48.1% vs 6.4%, p<0.001);(43.3% vs 14.9%, p<0.001). (Appendix 8-15, p232)

5.5 DISCUSSION

We analysed more than 2300 paediatric OHCA cases, collected prospectively across 4 years from 11 EMS regions in England to describe the BCPR rate and its association with ROSC and hospital survival. Several key findings were identified. BCPR was performed in 69.6% of the paediatric OHCA cases; however, the rate of BCPR varied across regions in England. Although a shockable rhythm was seen more often in BCPR cases, two thirds of those receiving BCPR were initially unwitnessed. Further, BCPR was associated with any ROSC but was not associated with an improvement in the survival to hospital discharge rate.

In this study, BCPR was performed in two-thirds of paediatric OHCAs, a higher proportion than previous reports from the United States,(41) Korea(118) and Japan(77) (47%, 50%, 52%, respectively), but lower than a recent report from Sweden (75%).(120) Although previous studies have reported similar BCPR rates to ours, the study sample sizes were smaller compared to our cohort.(47, 122) The higher BCPR rate seen in our study may be due to national differences in the public's BCPR knowledge and education. In the UK, there has been a substantial investment in CPR training by the British Heart Foundation, Resuscitation Council and other organisations.(172) In a UK survey of the general public by Hawkes et al, 60% reported having been trained in CPR(173), and several programs targeting parents, schools and the workplace have been established to increase the proportion of people able to perform CPR.(171) Furthermore, the use of technology and the media to raise awareness of the importance of BCPR through the Lifesaver web application and the delivery of simple messages on how to act in OHCA situations may have also influenced the BCPR rate.(172)

The BCPR rate in paediatric OHCA did vary across EMS regions (ranging from 57.7% to 83.7%). This is consistent with previous published results combining a majority of adult cases with some paediatric cases from the OHCAO registry.[2] The authors of that study suggested that this was due to data quality, where some of the EMS sites had a considerable amount of missing data compared to others. In our study, not all EMS regions submitted data for each study year period which could partially explain the variation in the rates of BCPR. However, in England, there are differences in regional SES patterns, which could account for some of the variation as well. For example, some regions are more densely populated, some are more urban, while others are predominantly rural.[101] A recent adult study in England found that a low BCPR rate was associated with urban areas, a low education level and greater deprivation.[101] In that study, low BCPR rate in urban areas was due to greater level of deprivation compared to rural areas plus people may have believed EMS would rapidly arrive and therefore BCPR was not required. Another study included adult population showed that areas with low income and large elderly population were also linked to low BCPR rate.[174] The author suggested that elderly were not well-trained to perform BCPR compared to younger people. In paediatrics, a report from the United States also showed variation in BCPR between regions (26.2%-69.4%), but the reasons were unclear.[34] Other reports have linked the variation of BCPR rates to level of education [29] and have shown that these rates are lower in communities with a low education level (45%-54%). Further examination is needed to determine factors associated with regional variation in BCPR among children in England.

In this study the overall survival to hospital discharge rate was 10.8%, which is similar to previous findings from the USA [41] and by Donoghue et al in their systematic review [72], but higher than reports from Korea.[118, 119] However, unlike the USA and Korean reports, in our study BCPR was not associated with hospital survival improvement. A potential explanation was the low proportion of OHCA cases that were witnessed. Overall, only 34.1% of the cases were witnessed, and only 34.9% of the cases that received BCPR were witnessed. Although witnessed status was independently associated with ROSC and survival, the low proportion of witnessed patients that received BCPR may have affected any longer-term positive effect of BCPR due to delays in starting resuscitation efforts. Furthermore, the quality of the BCPR delivered was not assessed in our study has been demonstrated to be an important factor in in-hospital cardiac arrest setting.[175]

In this analysis, we have measured ROSC at different time points. Achieving ROSC before EMS arrival may suggest that good quality of BCPR was performed by the public members. It might also show the rapid response especially in witness cases. Where Hospital ROSC will be influenced by the quality of CPR performed by the public and the EMS team who will continue performing BCPR during the patient transfer to hospital. The overall any ROSC stage which include ROSC achieved before arriving to hospital and ROSC at hospital handover was 24.6%. BCPR was found to increase the chance of achieving ROSC at any time. However, it was difficult to compare the results with other paediatric studies, as they tend to not include pre-EMS arrival ROSC.[72] Pre-hospital ROSC rate was 21.8%% and have shown improvement when BCPR was performed (BCPR 23.7% vs no-BCPR 17.4%; P value=0.002). This confirms the findings in previous studies from Japan and Korea where the chance of achieving pre-hospital ROSC is higher when BCPR was performed.[3, 118] Hospital ROSC was achieved in 19.1% of the total cases. Similar to any ROSC and pre-hospital ROSC, cases where BCPR was performed had better chance to achieve hospital ROSC 74.7% (322/431). However, there was no association between hospital ROSC and BCPR in the adjusted analysis (aOR 1.32(95% CI 0.98-1.78), although the result was close to being statistically significant. Despite measuring different types of ROSC, the result clearly showed that performing BCPR is a key factor in achieving ROSC.

The rate of BCPR was similar across all age groups. However, infants comprised the largest proportion of OHCA cases (33.4%), a result similar to previous reports.[49] In our data, nearly two-thirds of infants received BCPR. However, infant OHCA cases, which include sudden infant death syndrome (SIDS), are often unwitnessed [29, 49], therefore have an unknown time prior to attendance to the infant and any attempted BCPR. This prolonged duration may increase the likelihood of a poor outcome although there will be a strong emotive drive for parents and carers to commence BCPR regardless of any time delay.

A shockable rhythm has been linked to better outcomes in children; however, it is less common in children compared to adults. In this study, while only a small proportion of cases had a shockable rhythm (6.9%), it was associated with a higher rate of BCPR. Previous reports on both adults and children have identified BCPR as being associated with higher rates of ventricular fibrillation/pulseless ventricular tachycardia.[3] In a Japanese study, 60% of cases where a shockable rhythm was identified had undergone BCPR.[3] Also in a study by Herlitz et al. [176], the occurrence of a shockable rhythm increased following BCPR in scenarios of both early and late EMS arrival times. Therefore, it is possible that BCPR may prolong the duration of a shockable rhythm and increase the likelihood of it being recorded as an initial rhythm by EMS teams. The physiological mechanism for this remains unclear, but is likely related to continued myocardial perfusion

There were four factors independently associated with improved outcomes, including the CA being witnessed, shockable rhythm, daytime, and asphyxia as a cause. Similar to previous reports, witnessed cases increase the chance of survival.[34, 37, 41] In the Donoghue et al. review [72], survival to discharge doubled in witnessed CA. In the review, 13% of those survive to hospital discharge were witnessed (62/475) where only 4.6% survive to hospital discharge in unwitnessed cases (44/956). Despite being less common in children, shockable rhythm was associated with a better outcome. Jayaram et al. [127] found that the rate of survival to hospital discharge increases five times in cases with shockable rhythm compare to non-shockable rhythm (adjusted RR 5.51;95% CI 3.86,7.87). Similarly, Nehme et al. [37], in a multivariable logistic regression analysis found that shockable rhythm is a crucial factor to improve survival to hospital discharge (Adjusted OR 9.55; 95% CI 4.31,21.14). In a Danish study, 40% (20/50) of those who had shockable rhythm survived to one month.[29]

Children who had OHCA during the daytime had a better chance of surviving. This result is consistent with previous study examining the association of survival and time of the day paediatric OHCA.[84] The study found that most of the cases occurred during night, which is similar to our findings (57%; 1870/3278). The survival to one month was lower during night compared to daytime (Adjusted OR 0.68; 95% CI 0.56,0.82) The author explained the result by the shortage of in-hospital staff during night compared to day time. The author also found that pre-hospital ROSC was not different depending on the time of day, which suggest that the shortage of in-hospital staff is the main reason for lower survival rate during night time. However, in our study, we found that during the daytime, the chance of pre-hospital ROSC increased compared to night time. This can be due to the higher chance of being witnessed during the daytime. Children might be at school in the daytime where witnessed BCPR or public access defibrillation (PAD) can be rapidly performed/applied.

Finally, our results showed improvement in outcomes when the CA was caused by asphyxia. This finding differs from pervious results reported in paediatric studies. For example, Nehme et al. [(37)] in a study included non-traumatic OHCA children aged 16 years or less, found that asphyxiation was not associated with survival to hospital discharge improvement. Young et al., in a study included children less than 12 years also found poor outcome when asphyxia is the arrest cause.[(43)] However, the inconsistency in defining CA cause makes it difficult to compare our results with this finding. In Nehme et al. study, respiratory causes and asphyxiation were categorised as different groups. Similarly, Young et al. categorise asphyxia as a subgroup branching from trauma cause. In our study, medical group is likely to include SIDS with a very high risk of mortality and therefore make the asphyxia group have a better survival rate compared to other causes. It is worth noting that in both Nehme et al. and Young et al. studies, SIDS was categorised as a separate CA cause.

5.6 STRENGTH AND LIMITATIONS

This is the first study using data from the OHCAO registry in England to examine the association between BCPR and survival outcomes focused on a paediatric population. The OHCAO registry minimises heterogeneity in case identification and variability in EMS reporting through the standardisation of OHCA data collection following the Utstein guidelines. Furthermore, our study sample was large, which increases the chance of accurate sampling from a population. In addition, the population variance is inversely related to sample size, therefore a larger sample will reduce population variance which is proportional to bias. Large sample sizes also increase chance of observing outliers but can inadvertently increase the chance of exaggerating a statistically significant difference which may not be clinically significant.[177]

However, there were several limitations. While the study covered all of the regions of England, the results may not be generalisable to other countries or healthcare settings. Also, inherent with observational study design, there may have been unmeasured confounding effects that could have influenced our results. Furthermore, there was a small proportion of cases excluded with missing BCPR (n=258; 10.9% of total) and survival outcome data (n=29; 1.2%). Most data were missing due to some centres not recording particular variables for separate, short time periods, so the analysis results are likely to remain robust with 90% BCPR cases included. The EMS characteristics were not included in the regression model for the ROSC and survival outcomes due to the large missing data in some EMS regions. Further, the type of chest compressions performed was unavailable for analysis. Data regarding the bystanders' level of CPR training or the use of dispatcher-assisted CPR (which is used by English EMS) were also unavailable, which could have affected the quality of the CPR given. Some studies have suggested that dispatcher-assisted BCPR has a better outcome than BCPR without EMS.[118]

5.7 FUTURE RESEARCH

In this study, we aimed to describe BCPR rate and its association with survival outcomes. We found that BCPR was performed in two third of paediatric OHCA; however, a large number of those who receive BCPR were unwitnessed. Therefore, it is important to examine the barriers that limit BCPR in witnessed cases. The rate of BCPR also varied across EMS regions. Understanding the SES factors in England regions is important to identify causes lead to BCPR rate variations. There is also need to describe the BCPR intervention performed by lay person only and examine whether the rate and outcome would differ compare to BCPR performed by both lay person and EMS. Describing the role of dispatcher assisted CPR and its impact of the proportion of people doing CPR and survival outcomes may also be a crucial step.

5.8 CONCLUSION

In a large national cohort of paediatric OHCA cases, two-thirds received BCPR, although the rate of BCPR varied across EMS regions. While BCPR increased the probability of achieving any ROSC, it did not improve the eventual survival to hospital discharge rate. A large proportion of cases that underwent BCPR did not have their OHCA witnessed. Further, there is a need to study the demographic and socio-economic factors that may underlie variation in the BCPR rate. More effort to increase education and training programs in the community might help in improving outcomes.

5.9 ACKNOWLEDGEMENT

The OHCAO registry is funded by the British Heart Foundation and the Resuscitation Council UK. The data was collected by 11 EMS and stored in the OHCAO registry at the University of Warwick. We thank all the EMS staff who gathered the data and members of the clinical trial team at the University of Warwick for sharing the data with us. We thank Mr Adam de Paeztron (Clinical Trial Manager (OHCAO)) for the help in clarifying the OHCA file codes. We also thank Prof. Gavin Perkins, Dr Claire Hawkes, Mr Scott Booth (Warwick clinical trial team), Prof. Michael Norton (North East ambulance service) and Ms Theresa Foster (Research manager at the east of England ambulance service) who were co-authors on the published paper, for their intellectual input and for revising the final version of the manuscript.

6 The Association between Socioeconomic Status and Bystander Cardiopulmonary Resuscitation Rate for Children following OHCA in England

6.1 ABSTRACT

Background: Our study in Chapter five showed a variation in bystander CPR (BCPR) rates across regions in England. Yet, the factors that lead to this variation are not clear. Socioeconomic status (SES) may be an important factor impacting the rate BCPR for children in England.

Aim: To describe the association between SES and BCPR in paediatric OHCA in England.

Method: A retrospective observational study in paediatric OHCA <18 years was conducted using the national OHCA data registry in England from January 2014 to November 2018. Data included demographics, aetiology, witnessed status, initial rhythm, EMS regions, BCPR intervention, season, and the year of the incident. After linking the postcode district to the BCPR status, we extracted the following SES factors: household deprivation, level of education, work level, and ethnicity for the geographical area of each case. Multivariable logistic regression modelling with backward selection was used to examine the relationship between SES factors and BCPR.

Result: Of 2865 patients, 2343 met the inclusion criteria. BCPR was performed in 65.6% of the cases (1539/2343). The median percentage of non-deprived households in the BCPR group was 39.8% (IQR 34.1 to 46.0) compared to 37.3% (IQR 31.8 to 44.2) in the no-BCPR group. There was a higher proportion of white ethnicity in the community where BCPR was performed (median percentage difference of 10.1%; p=0.0001) compared to areas with no-BCPR. There was no clear association between qualification levels within a community and the delivery of BCPR. In the unadjusted analysis, the odds of receiving BCPR increased in areas with more non-deprived households, high proportion of white ethnicity and high work levels.

However, after adjusting for clinical factors, only areas with high proportion of white ethnicity were associated with BCPR (OR (95% CI) 1.01 (1.01 1.02)).

Conclusion: Areas with higher deprivation, higher proportion of ethnic minorities and lower work level were less likely to perform BCPR. Although the BCPR association with most of the SES factors were no longer statistically significant after adjusting for clinical factors, BCPR remained associated with areas with large proportion of white ethnicity. Establishing a strategy to increase BCPR training in these areas higher deprivation is an important step that might improve the BCPR rate and survival outcomes.

6.2 INTRODUCTION

BCPR is a crucial factor in improving OHCA outcomes, as this thesis has demonstrated in chapter three, which identified the strong existing evidence for BCPR influencing ROSC, one-month survival and survival to hospital discharge. Although in chapter five, BCPR was not associated with survival to hospital discharge in paediatric OHCA in England, those who received BCPR were more likely to achieve any ROSC. In addition, we have explored the relationship between patient and resuscitation factors in chapter four; however, there was also a significant variation in the rate of BCPR rates in the English EMS ambulance service (chapter five). Several factors could contribute to this finding, including the quality of advice/instructions given to bystanders by EMS dispatcher, the CA circumstances, the resuscitation care, and SES.(101, 102, 141, 148) Compared to the other factors mentioned above, few studies have examined the impact of SES in BCPR on the paediatric population.(29, 119)

It is important to understand the characteristics of the community in which individual lives and works, as these may influence bystanders' willingness to perform CPR. Factors such as racial disparity, level of deprivation, education, and work have been shown to have an impact on the rate of BCPR.(149, 174) A study from the UK, including all ages, showed that a lower proportion of the population of ethnic minorities receives BCPR.(101) Similarly, a report from the United States found that adult patients in areas with a higher Hispanic community have less chance of receiving BCPR.(102) Those areas were also linked to other SES factors such as household deprivation, income, education, and work level. In the same UK study mentioned above, a low BCPR rate and a high incidence of OHCA were found in areas of high deprivation, low income, and low work levels. An Asian study, including adult patients, reported that BCPR was initiated more in higher SES areas (61% vs. 39%).[178] It is clear that SES factors influence the BCPR rate, yet the intersection between these factors makes it difficult to determine the most significant factor and those where social or education programmes may make an impact.

The current paediatric literature suggests that children living in low SES areas are prone to poverty, inadequate nutrition, limited access to health care facilities, and poor health outcomes.[98, 179, 180] However, data regarding the association between SES and the BCPR rate is limited. A Danish study examined whether education and income impact the BCPR rate.[29] The study found that parents of children who had OHCA with low income and education levels were less likely to perform BCPR (43% vs. 51%; 45% vs. 54%, respectively). Naim et al. reported low BCPR rates among people of non-white ethnicity, low education, low income, and high unemployment in a US neighbourhood.[82] A Korean study showed that BCPR was performed more in areas with high property value than in areas of the lower property value (18.5% vs. 12.5%).[119] These studies clearly show that SES could be having a significant impact into the delivery of BCPR in the paediatric setting. However, in the UK, no data have been published to describe the impact of SES in BCPR on paediatric OHCA. Thus, investment in this study area is needed to improve the knowledge about SES in paediatric OHCA.

Given the existing literature, it is hypothesised that SES of the community where an OHCA occurs is associated with the rate of BCPR. This chapter aims to examine whether SES has an effect on the rate of BCPR in paediatric OHCA in England.

6.3 METHODOLOGY

6.3.1 Design

Retrospective analysis of the OHCA registry data with post-code linked SES data from the Office for National Statistics (ONS).[181]

6.3.2 Study population

The study population comprised paediatric OHCA patients identified from January 2014 to November 2018 aged less than 18 years who were resuscitated by EMS providers. Patients with missing data for bystander intervention and/or postcode were excluded.

6.3.3 Data collection and variable definition

Full description of patient demographic and clinical characteristics data has previously been described in Chapter four. In brief, we included age, sex, witness status, aetiology of CA, initial cardiac rhythm, EMS service, time of day (day or night) and season.

6.3.4 Socioeconomic data

The OHCA registry did not record any personal characteristics, including the SES, of the bystander who performed CPR. Therefore, we chose to examine at a community level the SES of the community where each individual patient had a CA. Figure 6-1 describes the steps followed. First, we included OHCA cases with postcode districts available. For the cases with no postcode districts data, we checked for the availability of the street line address. If the street line address was found in the OHCA registry, a manual internet search was conducted to identify the postcode districts. The SES level was obtained using the following methods. The first 4 digits of the patient's postcode was linked to the postcode districts within a dataset downloaded from (www.nomisweb.co.uk). The Nomis web is a free accessible resource to access the ONS data. We selected postcode district and SES demographics including household by deprivation dimensions, ethnic group, highest of qualification, and SES classification. Figure 6-1 also shows the steps we followed in order to link the OHCA data with the SES data. The postcode district was selected as a proxy unit for the CA location to capture all cases analysed in this study. The ONS data reported the proportion of the population with each SES characteristic for each postcode district. For example, in postcode district AL1 (see Figure 6-1), total number of households were 14999, with 8567 (57.1%) households were not deprived in any dimension, 4138 (27.6%) deprived in one dimension, 1795 (12.0%) deprived in two dimensions, 451 (3%) deprived in three dimension and 48 (0.3%) deprived in all four dimensions.

The SES data was examined in two ways. First utilised the reported proportions as a continuous variable and therefore for each individual SES characteristics the median and IQR for the characteristic was compared for community areas where a patient received BCPR and in areas where patients received no-BCPR.

The second method allowed comparison across all postcode districts, the median proportion for each of the SES characteristics was calculated for all postcode districts included in the dataset and the resulting upper and lower 50th centile were dichotomised. This allowed comparison of community areas in the upper 50% centile for each SES characteristic compared to community areas in the lower 50% centile (e.g. less deprived community areas were defined as those in the upper 50% centile of 'households which were not deprived in any dimension' and compared with more deprived areas in the lower 50% centile). The ONS neighbourhood characteristics from the UK 2011 census are detailed in Table 6-1[181]

Table 6-1 Neighbourhood characteristics from the UK 2011 census

SES Domains	Categories
Household deprivation	zero, one, two, three, and four dimensions The four dimensions are employment, education, health and disability, and housing(182)
Ethnic group	White Asian Black Mixed ethnic Other ethnic
Nationality:	UK, EU Other.
Qualification:	Level 1, Level 2, Level 3, Level 4 apprenticeships or above, and other qualifications (183)
Work level:	1- Higher managerial, administrative and professional (e.g. scientists) 2-Lower managerial, administrative and professional (e.g. teachers) 3- Intermediate (e.g. office clerks) 4-Small employer and own account workers (e.g. self-employed and own account) 5-Lower supervisory and technical (e.g. telegraph and telephone line installers) 6- Semi routine (e.g. security guards) 7-Routine (e.g. cleaners) 8-Never worked, or long-term unemployed 9- not classified.

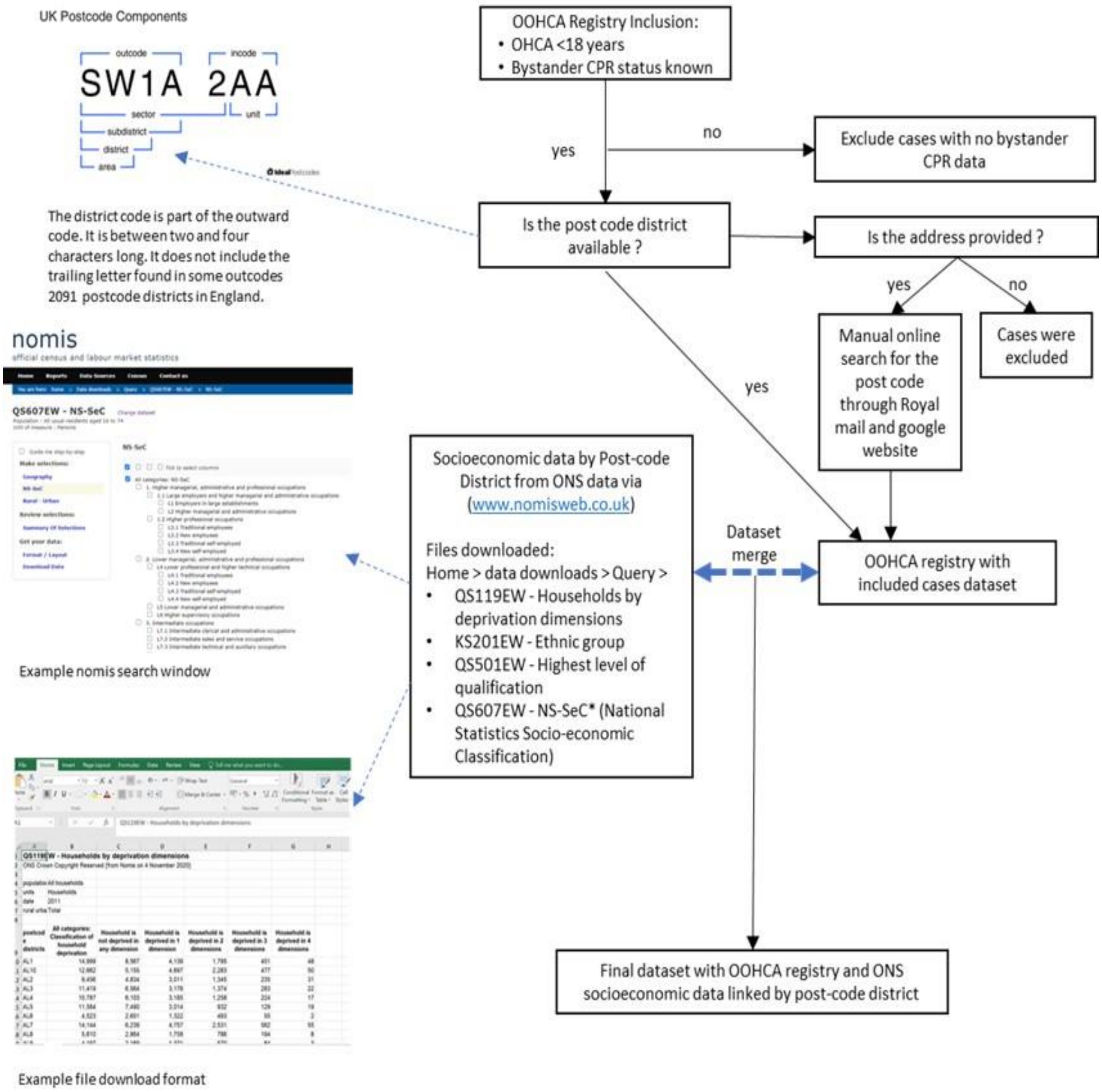

Figure 6-1 Step 1 database case selection and linking to socioeconomic data

Data for deprivation, qualification, work level and ethnicities were downloaded from www.nomisweb.co.uk

6.3.5 Statistical Analysis

Patient demographics, clinical and community SES factors were described according to bystander resuscitation status. Continuous variables were visually assessed by histogram and box plots. Data is presented either as mean with standard deviation or median with interquartile range. T-tests (parametric) and Wilcoxon rank-sum (non-parametric) tests were used to compare between normally distributed and skewed variables respectively. The chi-square test was used to compare between categorical variables. Continuous variables were presented as median with interquartile ranges, while categorical variables were presented as counts and percentages. A Pearson's correlation test accompanied by plots was applied to measure the strength of the linear association between continuous variables.

A geographical map was created using (https://maps.co/) to describe the distribution of the postcode districts where CA occurred and the relationship of BCPR and no-BCPR intervention across EMS regions.

To aid in the visualisation and interpretation of the theoretical relationship between SES factors at a community level, patient level resuscitation variables and BCPR as the outcome of interest, we created a Directed acyclic graph. This was to provide a simple and transparent diagram to identify our assumptions about causal relationship between variables using Daggity software (available at www.DAGitty.net). Directed acyclic graph is described by Tennant et al as the 'non-parametric diagrammatic representation of the assumed data-generating process for a set of variables in a specified context' (eg paediatric OHCA).[184] Variables are depicted as nodes connected by arrows (arcs) depicting the hypothesized relationship. A potential causal relationship is therefore depicted by two nodes connected by an arrow, although the diagram does not state the positive or negative relationship, magnitude or form of that the relationship.[185] Importantly, the advantages of Directed acyclic graph is that measured and un-measured confounders can be included and identified in a theoretical fashion and also where effects occur with and without mediators. The Directed acyclic graph was created with iterative development in consultation with experts in CA and epidemiology.

The association between each individual SES factors and the binary outcome BCPR or no-BCPR was examined using a univariable and multivariable logistic regression models. A P-value of <0.05 was considered statistically significant. Three multivariable logistic regression models were fitted to estimate the odds ratio (OR) for the association of BCPR with SES factors:

Model 1: SES factors only.

The correlation between all SES factors was assessed graphically and numerically. We excluded SES factors which were highly correlated. There was a theoretical risk that the qualification and work levels factors were part of the component for the four dimensions of deprivation. Therefore, we chose to not include this factor in the model. The model therefore included the following SES factors: non-deprived, and white ethnic. This model was developed to assess the association of SES factors, without including the patient level factors (e.g. age, sex, CA cause), and the binary outcome of receiving or not receiving BCPR.

Model 2: SES factors and patient level resuscitation factors.

Model 2 was based on the SES factors selected for model 1. In addition to SES factors (non-deprived, white ethnic), we also added the following pre-hospital factors: age, gender, status of witness, CA cause, initial rhythm, time of day, year of the incidence, season time and ambulance services.

Model 3: SES factors and patient level resuscitation factors using backward stepwise selection.

We used a similar selection criteria to model 2; however, utilised a backward stepwise selection method. Model 3 therefore included non-deprived and white ethnicity to represent the SES factors and, for the pre-hospital factors: age, gender, status of witness, CA cause, initial rhythm, time of day, year of the incidence, season time and ambulance services were included. In all three models, we used the continuous data for the SES factors. Data management and statistical analyses were conducted using Stata version 16.1 software.

6.3.6 Ethics statement.

The University of Warwick hosts the OHCAO project which has approval from the National Research Ethics Service (13/SC/0361). Details of the registry have been previously summarised.[15] This study was additionally approved by the University of Birmingham Internal Review Board (RG 17-246. 14.11.2018).

6.4 RESULT

6.4.1 Population demographics

2865 paediatric OHCA cases aged less than 18 year were identified from the OHCAO. We excluded 257 with missing BCPR data and 265 with missing address and postcode district. A total of 2343 patients were linked to the ONS data and included in the analysis; 1539 (65.6%) patients received BCPR and 804(34.4%) received no-BCPR. (Figure 6-2)

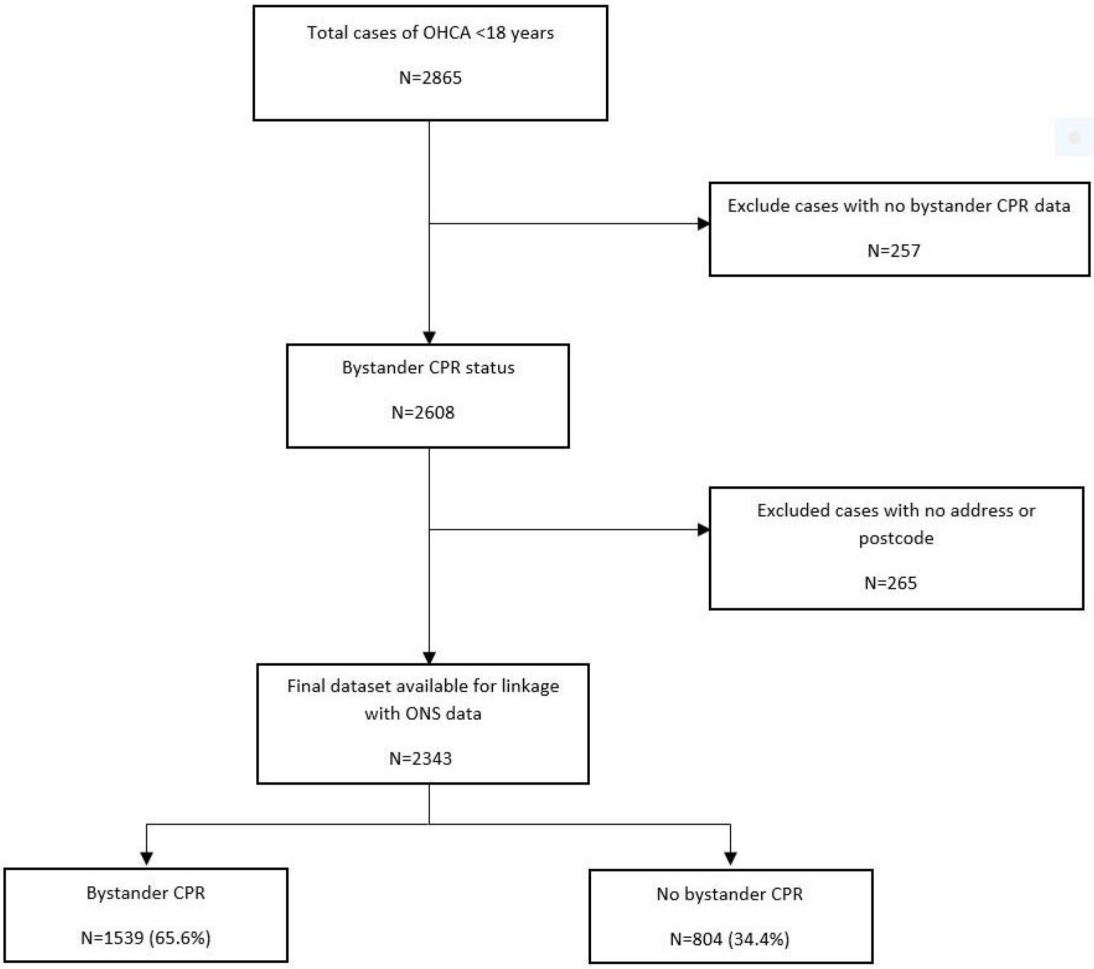

Figure 6-2 Flowchart for included cases

6.4.2 Demographics

The median (interquartile (IQR)) age was 3.2(IQR 0.6-11.7) months, with infants (<1 year) forming the largest group (32.6%) followed by children age 12-18 year (23.8%). Male cases were greater than female (58.7% vs 41.3%). Most common cause of CA was medical cause (81.6%) and 40% of the total cases were witnessed. A shockable rhythm was recorded as initial rhythm in 7.2% of the cases and an AED used in 2.4%. A third of OHCA cases occurred during daytime (34.4%). The proportion of CA cases varied across the 10 EMS regions (3.8% to 24.8%). The characteristics of included patients are detailed in Table 6-2.

BCPR was performed in 65.6% of the OHCA cases. Infants received the highest proportion of BCPR (32.7%) compared to other age groups. Witnessed CA cases were less likely to receive BCPR (36.6% versus 46%) Eight percent of BCPR had a shockable rhythm compared to 5.7% who received no-BCPR. The rate of BCPR varied across EMS regions ranging from 52.2% to 87.2%).

Table 6-2 Demographic of paediatric OHCA association with bystander CPR

	Total		BCPR		No-BCPR		p-value
	N	%	N	%	N	%	
Total	2343	100	1539	65.6	804	34.4	
Age	2343						
(median, IQR)	3.2 (0.6-11.7)		3.4 (0.5-11.6)		3.1 (0.7-11.8)		
0-1 year	764	32.6	503/1539	32.7	261/804	32.5	0.74
1-4 years	504	21.5	322/1539	20.9	182/804	22.6	
4-8 years	268	11.4	184/1539	12.0	84/804	10.4	
8-12 years	249	10.6	166/1539	10.8	83/804	10.3	
12-18 years	558	23.8	364/1539	23.7	194/804	24.1	
Sex[a]	2291						
Male	1344	58.7	891/1505	59.3	453/786	57.6	0.46
Female	949	41.3	614/1505	40.7	333/786	42.4	
Aetiology[b]	2207						
Medical	1802	81.6	1202/1452	82.8	600/755	79.5	0.006
Trauma	155	7.0	81/1452	5.5	74/755	9.8	
Drowning	37	1.7	25/1452	1.7	12/755	1.6	
Drug overdose	33	1.5	20/1452	1.4	13/755	1.7	
Asphyxia	180	8.2	124/1452	8.5	56/755	7.4	
Status of witness[c]	2246						
Witnessed	896	39.9	534/1459	36.6	362/787	46.0	0.0001
Initial rhythm[d]	2048						
Shockable	148	7.2	110/1378	8.0	38/670	5.7	0.058
AED[e]	1444						
AED use	35	2.4	35/890	4.0	0/554	0	<0.001
Time of day[f]	2310						
Daytime	795	34.4	513/1517	34.0	282/793	35.6	0.40
Season	2343						
Spring	617	26.3	409/1539	26.6	208/804	25.9	0.80
Summer	559	23.9	364/1539	23.6	195/804	24.3	
Autumn	618	26.4	413/1539	26.8	205/804	25.5	
Winter	549	23.4	353/1539	23.0	196/804	24.4	
Year	2343						
2014	463	19.8	296/1539	19.2	167/804	20.8	0.007
2015	498	21.3	302/1539	19.6	196/804	24.4	
2016	469	20.0	319/1539	20.7	150/804	18.7	
2017	433	18.5	280/1539	18.2	153/804	19.0	
2018	480	20.5	342/1539	22.2	138/804	17.2	
EMS region[g]	2342						
EMS 1	580	24.8	351/1538	22.8	229/804	28.5	0.0001
EMS 2	98	4.2	62/1538	4.0	36/804	4.5	
EMS 3	188	8.0	126/1538	8.2	62/804	7.7	
EMS 4	111	4.7	82/1538	5.3	29/804	3.6	
EMS 5	403	17.2	291/1538	19.0	112/804	13.9	
EMS 6	89	3.8	60/1538	4.0	29/804	3.6	
EMS 7	117	5.0	102/1538	6.6	15/804	1.9	
EMS 8	206	8.8	153/1538	9.9	53/804	6.6	
EMS 9	402	17.2	210/1538	13.7	192/804	23.9	
EMS 10	148	6.3	101/1538	6.6	47/804	5.8	

Legend for table 6-2:
BCPR, bystander cardiopulmonary resuscitation; IRQ, Interquartile range; AED, automated external defibrillator. ROSC, return of spontaneous circulation;
Data were missing in
[a] Sex (n=52)
[b] Aetiology (n=136)
[c] Status of witness (n=97)
[d] Initial rhythm (n=295)
[e] AED (n=899)
[f] Time of the day (n=33)
[g] EMS regions (n=1)

6.4.3 Geographical data

There were 2091 postcode districts in England. CA occurred in 52.7% (1104/2091) of post-code districts with a median of 2 (IQR 1 to 3) with a range of 1 to 21 cases per postcode district. CA cases were not evenly distributed across postcode districts. The map, shown in Figure 6-3, indicates clustering of cases in metropolitan (city) areas (e.g. London, Birmingham and Manchester) and the distribution of CA location by BCPR intervention.

6.4.4 Socioeconomic factors

In geographical postcode districts where CA cases were identified, the median percent of households which were non-deprived in any dimension of deprivation was 39.0% (IQR 33.0 to 45.6). Only 0.5% (IQR 0.3 to 0.9) were deprived in all four dimension of deprivation (Table 6-3). White ethnicity represented 87.6% of the population, 23.3% of the population had no education and 6.0% of population never worked.

6.4.5 Directed acyclic graph

Figure 6-4 shows the theoretical directed acyclic graph illustrating our assumptions of the potential causal pathways connecting individual patient level data, community SES data, bystander individual data with BCPR as the outcome of interest. We identified a number of important theoretical causal pathways connecting SES factors and BCPR. For example, ethnicity and race connect to the level of education which could lead on CPR training confidence and eventually impact the BCPR intervention. Importantly, it illustrates the unobserved variables related to the individual bystander who may have been present at the CA and whether they would perform or not perform BCPR (labelled 'bystander personal factors') (Figure 6-4).

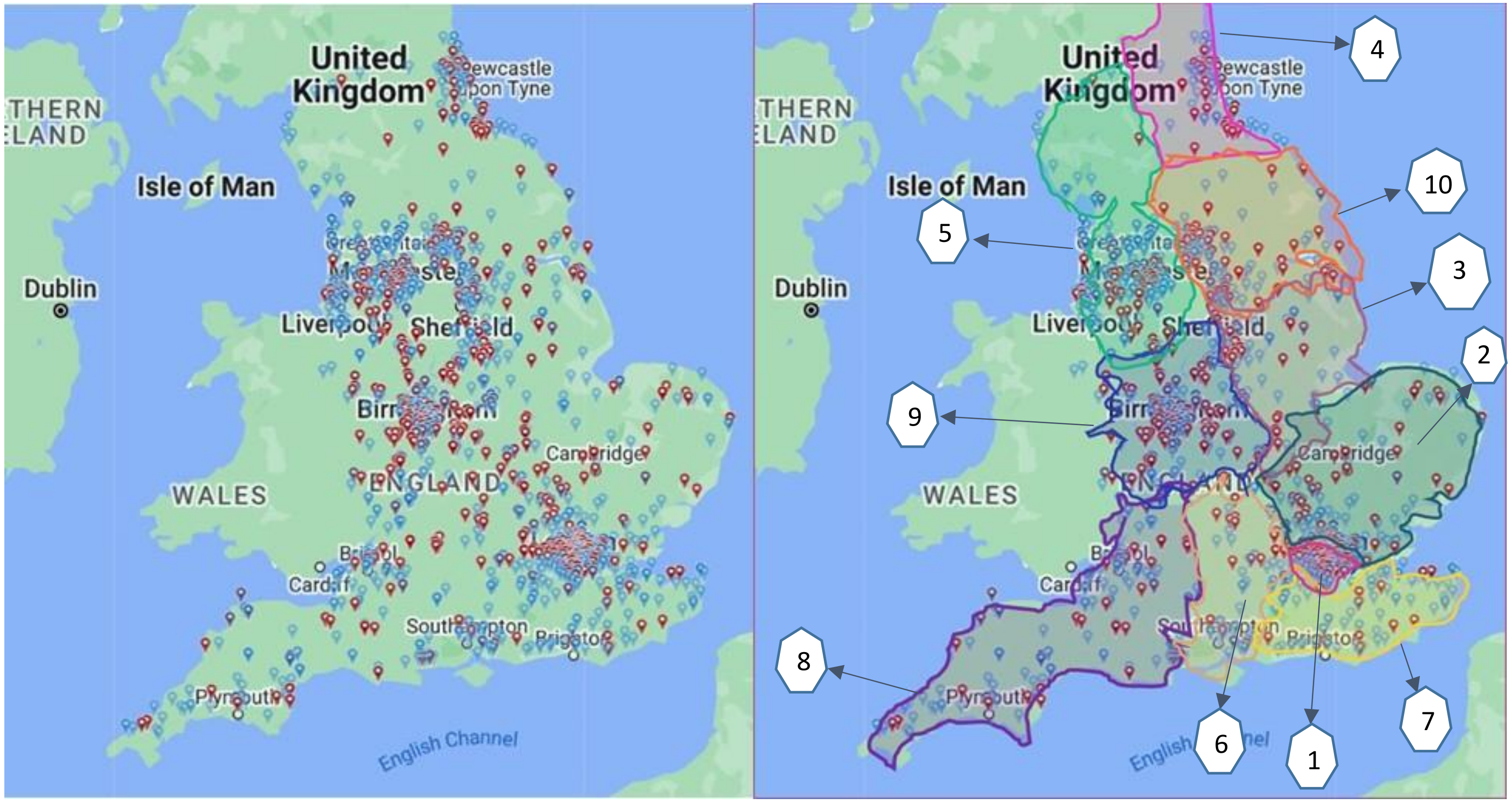

Figure 6-3 In the left figure: The distribution of BCPR (blue pins) and no-BCPR (red pins) cases. In the right figure: distribution of BCPR (blue pins) and no-BCPR (red pins) cases across EMS regions.

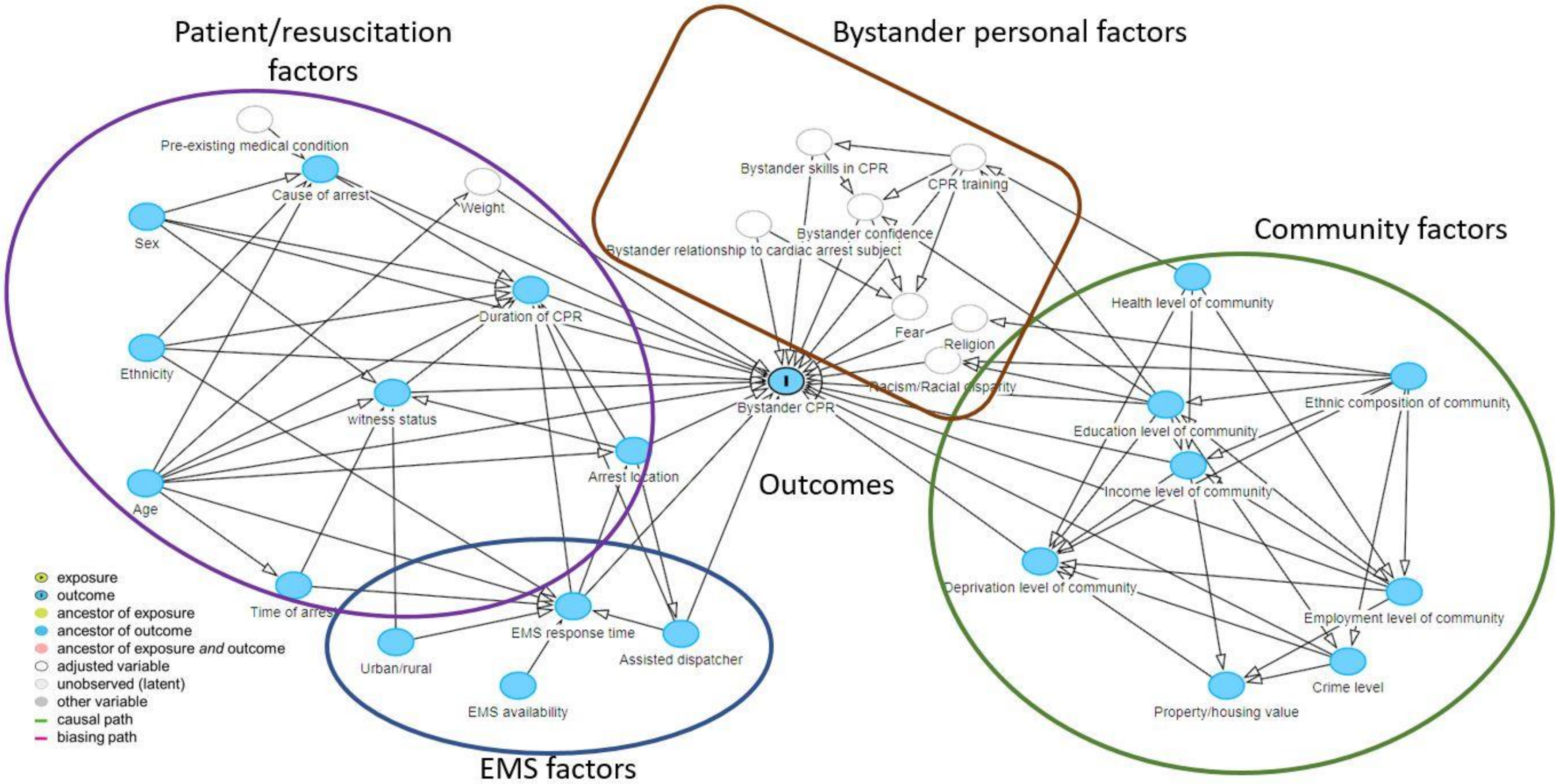

Figure 6-4 Directed Acyclic Graph of theoretical causal pathways connecting patient level, EMS, community and bystander factors with delivery of bystander CPR

6.4.6 Socioeconomic status and BCPR outcome

There was a statistically significant difference in the median percentage of non-deprived households in any deprivation dimension, with fewer non-deprived households in the no-BCPR group (39.8% versus 37.3%; percentage difference 2.4%; P value=0.0001). There was a statistically significant difference in the median percentage of patients of white ethnicity. There was a higher proportion (median percentage difference 10.1%; p=0.0001) among patients of white ethnicity in the BCPR group. Concerning nationality, patients receiving no-BCPR were in postcode districts with a higher proportion of non-UK citizens (P value=0.0001). Regarding education level, a significant difference in the median percentage between BCPR and no-BCPR was identified in qualification level 2, Apprenticeship, level 3 and other qualification. Most work levels showed a significant difference in the median percentage between BCPR and no-BCPR, as shown in Table 6-3.

In Table 6-4, the postcode districts were dichotomised into non-deprived vs. deprived; white ethnic vs. non-white ethnic; UK citizen vs. non-UK citizen; non-qualified vs. qualified, and never worked vs. worked and compared with BCPR status. The results were similar to the finding in Table 6-3, there was a higher proportion of BCPR in postcode districts in the non-deprived group, higher proportion of white ethnicity, higher UK nationality and work group.

Table 6-3 Patients' characteristics based on socioeconomic factors

Median (%) and IQR	Total= 2343	BCPR n=1539	No-BCPR n=804	P value
Deprivation levels				
Non-deprived	39.0 (33.0-45.6)	39.8(34.1-46.0)	37.3 (31.8-44.2)	0.0001
Deprived in one dimension	32.8(31.6-34.2)	32.7(31.5-34.0)	33.0(31.8-34.4)	0.0003
Deprived in two dimensions	20.6(17.4-24.0)	20.3(17.2-23.6)	21.3(18.1-25.2)	0.0001
Deprived in three dimensions	5.8 (3.9-7.9)	5.6(3.7-7.6)	6.4(4.4-8.4)	0.0001
Deprived in four dimensions	0.56 (0.32-0.91)	0.52 (0.31-0.84)	0.66(0.38-1.0)	0.0001
Ethnicity				
White	87.6 (66.2-96.8)	90.7 (71.7-97.2)	80.6(58.3-95.6)	0.0001
Mixed	2.0 (1.1-4.0)	1.8 (1.0-3.8)	2.8 (1.3-4.7)	0.0001
Asian-British	5.6 (1.4-13.8)	4.3(1.2-12.3)	8 (2.1-17.7)	0.0001
Black	1.5 (0.4-7.4)	1.2 (0.3-6.2)	3.2(0.6-10.8)	0.0001
Other	0.6 (0.2-1.9)	0.5(0.2-1.6)	0.9(0.2-2.5)	0.0001
Nationality				
UK	89.1 (72.0-94.7)	90.2(78.2-95.2)	86.2(65.5-93.6)	0.0001
EU	3.0 (1.6-5.7)	2.8(1.5-5.0)	3.3(1.8-6.5)	0.0001
Other	7.1 (2.7-20.1)	6.0(2.5-16.2)	9.2(3.4-24.8)	0.0001
Education				
No qualification	23.3 (18.7-28.3)	23.0(18.6-28.1)	23.8(18.9-29.0)	0.068
Level 1 qualification	13.8 (11.7-15.2)	13.8(11.9-15.2)	13.8(11.5-15.1)	0.095
Level 2 qualification	15.6 (13.5-16.6)	15.7(14.0-16.7)	15.1(12.5-16.4)	0.0001
Apprenticeship	3.4 (2.09-4.31)	3.5 (2.38-4.40)	3.1(1.60-4.04)	0.0001
Level 3 qualification	11.5 (10.4-12.5)	11.6(10.6-12.5)	11.2(10.1-12.3)	0.012
Level 4 or above qualification	24.1 (18.7-31.9)	24.5 (19.0-31.8)	24.0(18.4-31.9)	0.999
Other qualification	5.2 (4.1-8.1)	4.9(4.1-7.2)	5.8(4.3-9.1)	0.0001
Work level				
Higher managerial	8.2 (5.9-11.7)	8.3(6.2-11.9)	7.9(5.6-11.5)	0.045
Low managerial	19.3 (16.1-23.2)	19.8 (16.6-23.4)	18.6 (15.1-22.6)	0.0001
Intermediate	12.4 (10.8-14.0)	12.6(11.0-14.2)	12.1(10.4-13.5)	0.0001
Small employers	8.6 (7.2-10.1)	8.7 (7.3-10.4)	8.4 (7.0-9.7)	0.0001
Low supervisory and technic	7.0(5.7-8.1)	7.1 (5.7-8.2)	6.8 (5.5-7.9)	0.003
Semi routine	14.4 (11.9-17.0)	14.4 (12.0-17.0)	14.4 (11.7-17.0)	0.819
Routine	11.2 (8.5-14.6)	11.2(8.4-14.6)	11.5(8.6-14.6)	0.265
Never worked	6.0 (3.8-9.4)	5.6 (3.5-8.6)	7.1(4.2-10.4)	0.0001
Not classified	7.4 (6.1-11.2)	7.2(6.0-10.2)	8.2(6.3-12.1)	0.0002
	Median and interquartile range used to represent the data			

Table 6-4 Number (and proportion) of patients in the post-code districts within the dichotomised SES characteristics

	BCPR n=1540	No-BCPR n=806	P value
Deprivation levels			
Non-deprived	822(70.0%)	352(30.0%)	0.0001
Deprived	717(61.3%)	452(38.7%)	
Ethnicity			
White	844(72.2%)	325(27.8%)	0.0001
Non-white	695(59.2%)	479(40.8%)	
Nationality			
UK	802(71.4%)	321(28.6%)	0.0001
Other	737(60.4%)	483(39.6%)	
Education			
No qualification	761(64.4%)	420(35.6%)	0.200
Qualified	778(67.0%)	384(33.0%)	
Work level			
Never worked	710(59.9%)	476(40.1%)	0.0001
Worked	829(71.6%)	328(28.4%)	

6.4.7 Socioeconomic factors BCPR and outcome

In a univariate analysis (Table 6-5), the odds of receiving BCPR was 2% higher with every percentage increase in non-deprived households within the postcode district (1.02 (95% CI 1.01-1.03), p<0.0001). There was a trend of decreasing odds of receiving BCPR with each additional dimension of deprivation as shown in Figure 6-5. For example, there was a 43% reduction in the odds of receiving BCPR per percentage increase in households deprived in all four dimensions within the postcode district. Odds of BCPR was higher in post-code districts with an increasing proportion of white ethnicity (OR (95% CI) 1.01 (1.01-1.02), p<0.0001) but lower with mixed, Asian-British, black, and other ethnicities (Figure 6-6). Every percentage increase in people with UK nationality led to 1% higher odds of receiving BCPR (1.01 (95% CI 1.01-1.02, p=0.0001)), while decreasing odds were found among EU and other nationalities (OR (95% CI) 0.94(0.92-0.96), p=0.0001 and 0.97(0.96-0.98), p=0.0001, respectively) (Figure 6-7). Concerning education, the odds of receiving BCPR have risen by 9% and 4% with every percentage increase in Level 2 and 3 qualification in the postcode district (OR (95% CI) 1.09 (1.05-1.12), p=0.0001; 1.04 (1.00-1.07), p=0.016); however, there was no statistically significant association between BCPR and non-qualified, Level 1 qualification, and Level 4 qualification; OR (95% CI) 0.98 (0.97-1.00); 1.02 (0.99-1.06); 0.99 (0.99-1.00) (Figure 6-8). Concerning work levels, odds of BCPR was higher among those communities with high managerial (p=0.044) and intermediate (p=0.0001) occupations; however, the odds were lower in areas with a larger proportion who never worked (p=0.0001) and who were non-classified workers (p=0.0001), as shown in Figure 6-9.

Table 6-5 Unadjusted odds ratios for socioeconomic factors and BCPR

	Unadjusted OR (95% CI)	P value
Deprivation levels		
Non-deprived	1.02 (1.01-1.03)	<0.0001
Deprived in one dimension	0.93 (0.90-0.97)	0.001
Deprived in two dimensions	0.95 (0.94-0.97)	<0.0001
Deprived in three dimensions	0.91 (0.89-0.94)	<0.0001
Deprived in four dimensions	0.57 (0.47-0.69)	<0.0001
Ethnicity		
White	1.01 (1.01-1.02)	<0.0001
Mixed	0.87 (0.83-0.90)	<0.0001
Asian-British	0.98 (0.97-0.98)	<0.0001
Black	0.97 (0.96-0.98)	<0.0001
Other	0.87 (0.83-0.91)	0.0001
Nationality		
UK	1.01 (1.01-1.02)	0.0001
EU	0.94 (0.92-0.96)	0.0001
Other	0.97 (0.96-0.98)	0.0001
Education		
No qualification	0.98 (0.97-1.00)	0.065
Level 1 qualification	1.02 (0.99-1.06)	0.093
Level 2 qualification	1.09 (1.05-1.12)	0.0001
Apprenticeship	1.21 (1.14-1.29)	0.0001
Level 3 qualification	1.04 (1.00-1.07)	0.016
Level 4 qualification or above	0.99 (0.99-1.00)	1.000
Other qualification	0.91 (0.89-0.94)	0.0001
Work level		
Higher managerial	1.01 (1.00-1.03)	0.044
Low managerial	1.03 (1.01-1.05)	0.0001
Intermediate	1.10 (1.06-1.14)	0.0001
Small employers	1.08 (1.04-1.12)	0.0001
Lower supervisory/technic	1.07 (1.02-1.13)	0.004
Semi routine	1.00 (0.97-1.02)	0.819
Routine	0.98 (0.96-1.00)	0.265
Never worked	0.93 (0.91-0.95)	0.0001
Not classified	0.97 (0.96-0.98)	0.0001

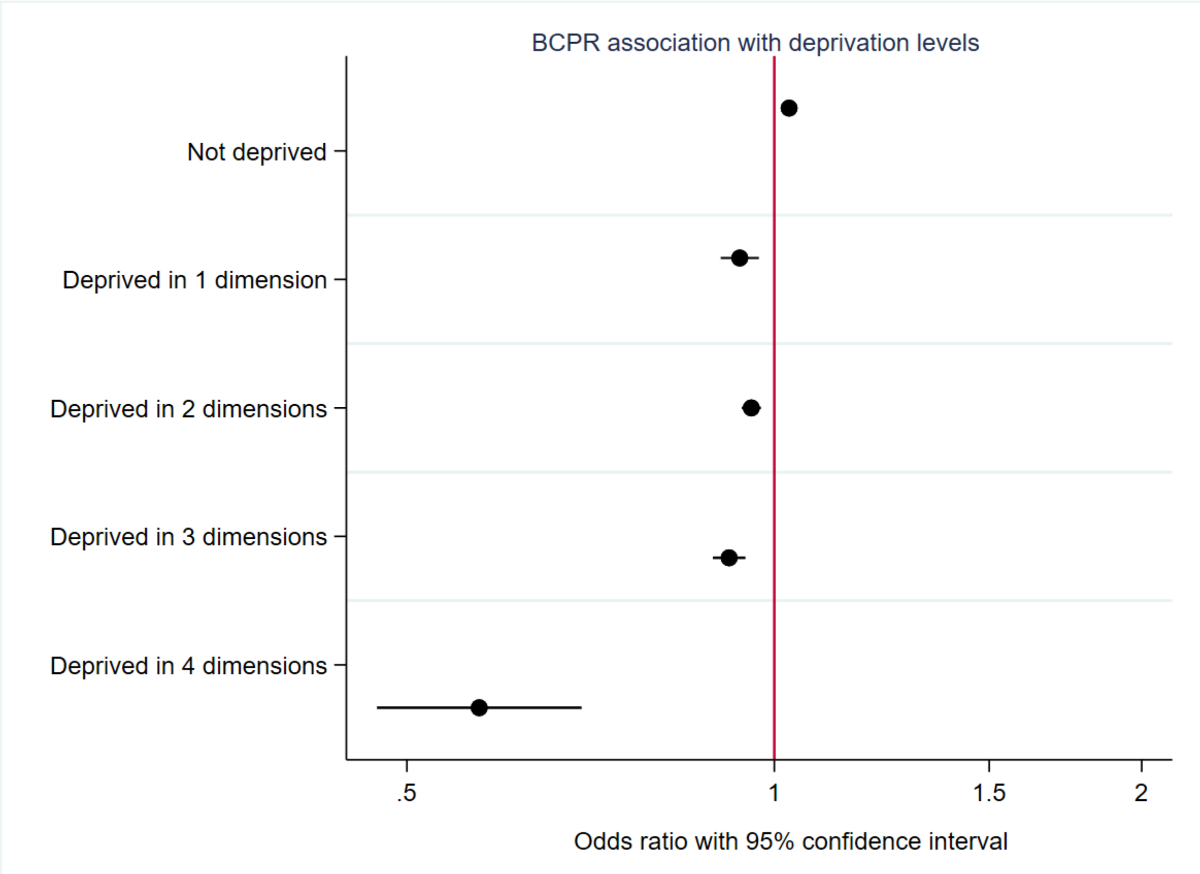

Figure 6-5: Unadjusted OR (with a 95% CI) for receiving BCPR for different deprivation levels

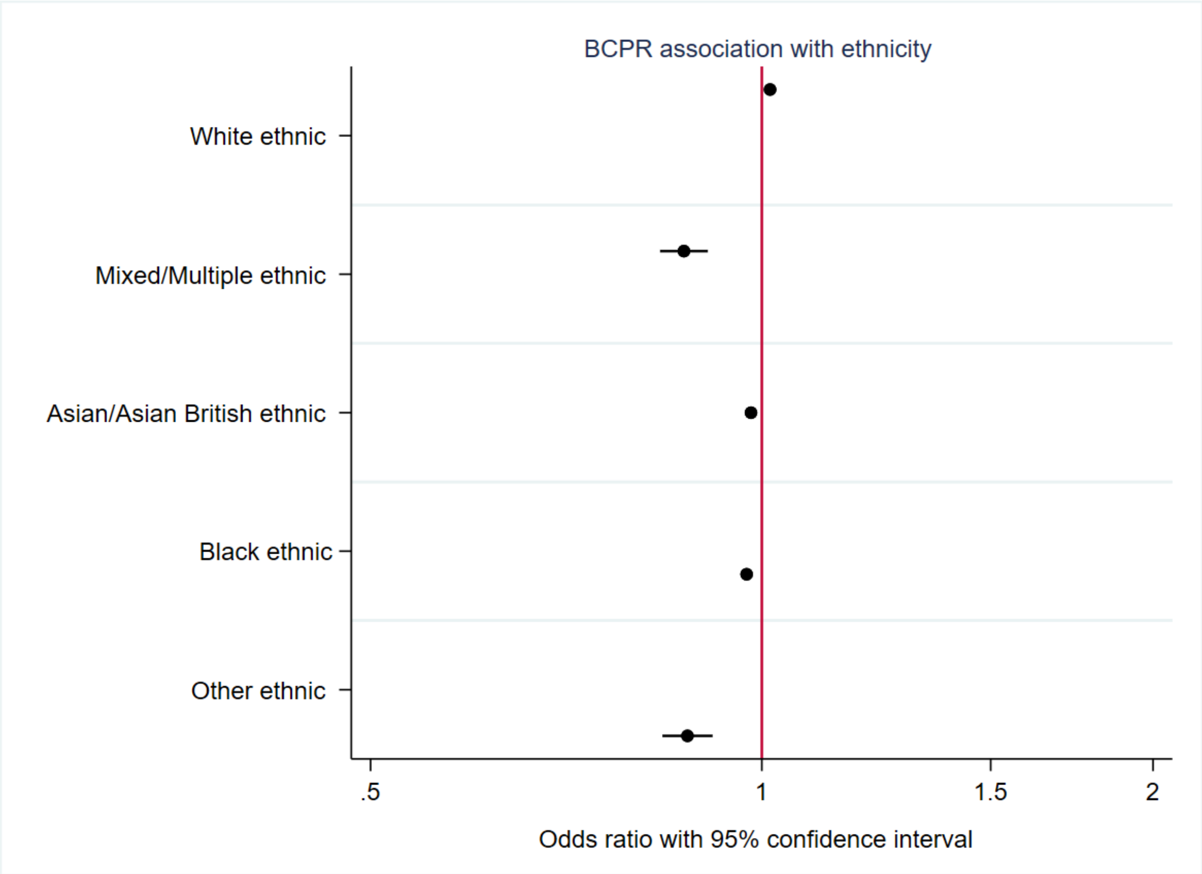

Figure 6-6: Unadjusted OR with a 95% CI for receiving BCPR association with ethnicity

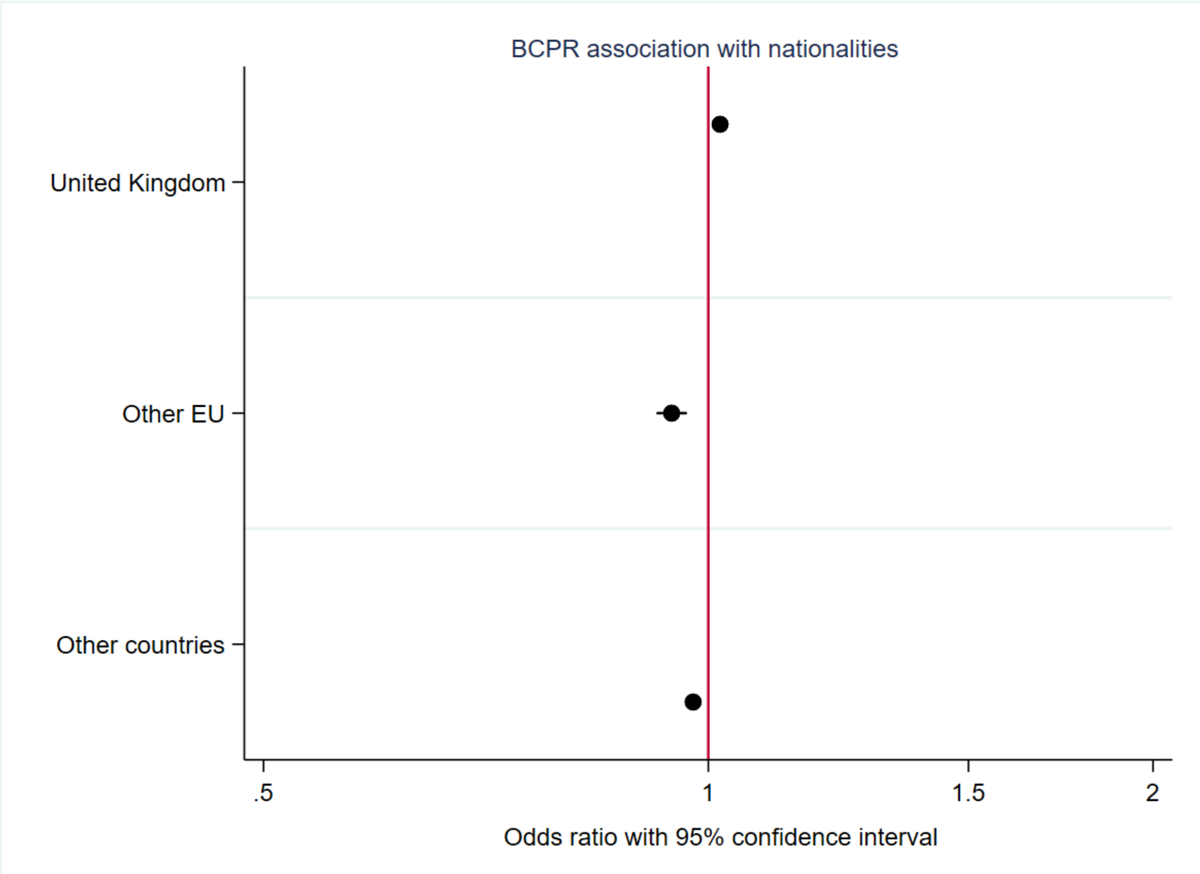

Figure 6-7: Unadjusted OR with a 95% CI for receiving BCPR association with nationality

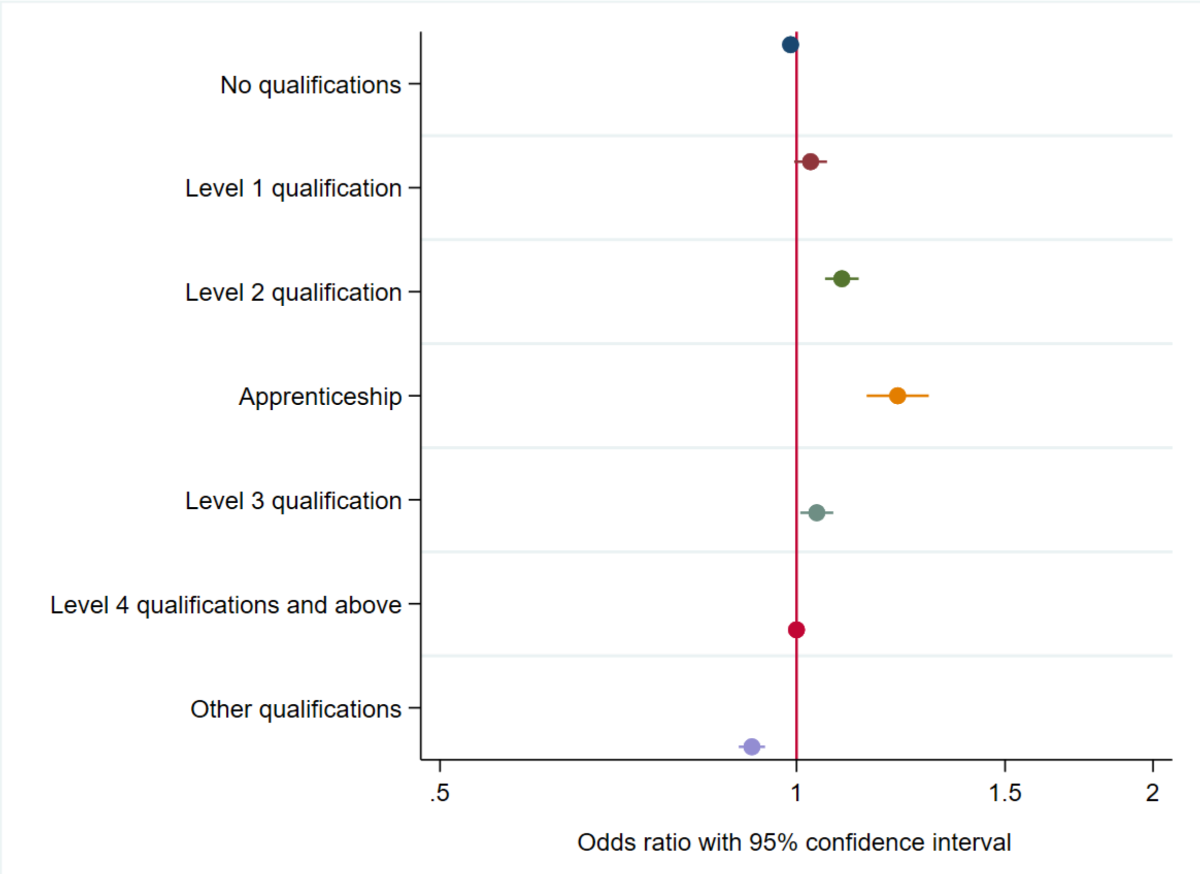

Figure 6-8: Unadjusted OR with a 95% CI for receiving BCPR association with level of education

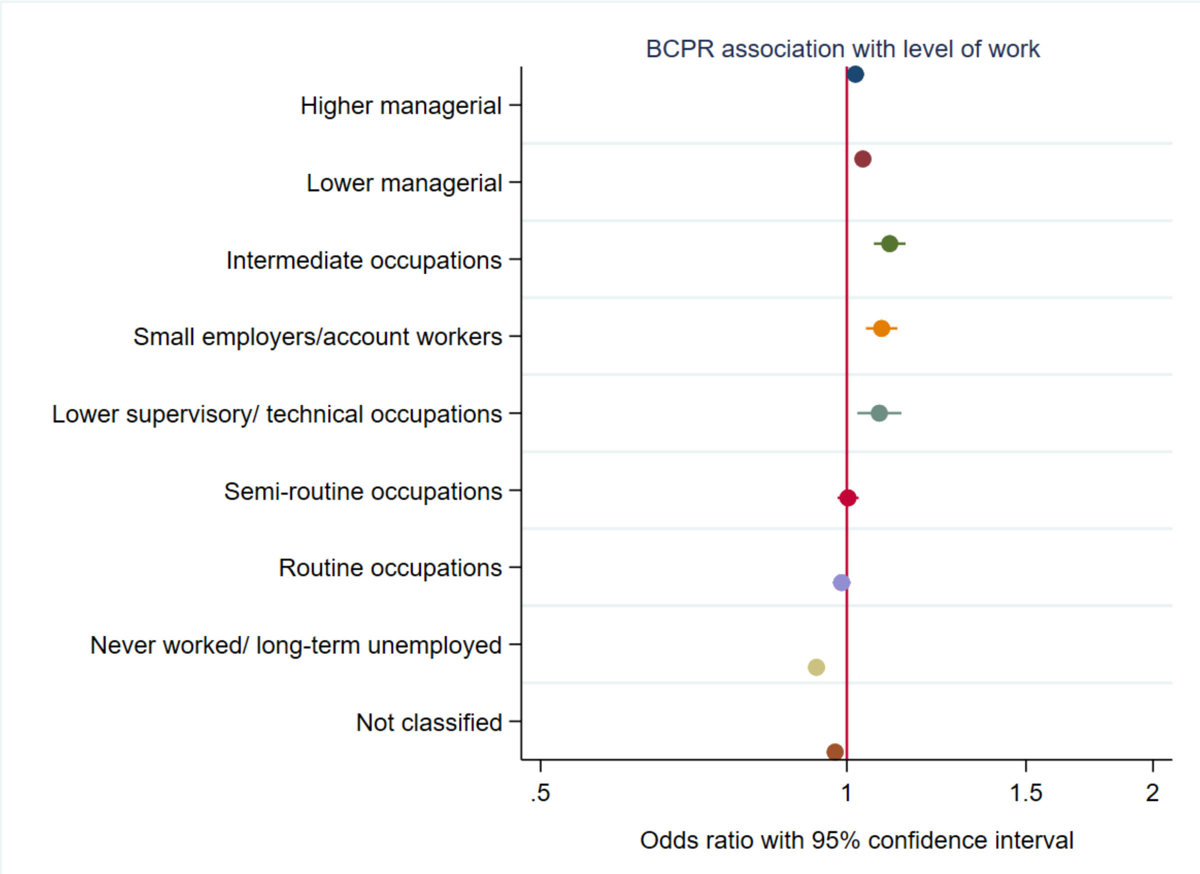

Figure 6-9: Unadjusted OR with a 95% CI for receiving BCPR association with work level

6.4.8 Multivariable regression model

Due to the correlation between the SES factors, we only included the non-deprived dimension and the white ethnicity group SES factors.(Appendix 8-16, p233)

In model one, we kept non-deprived and white ethnicity as SES factors to avoid data overlapping as work level is part of the deprivation dimensions, we found that the odds of receiving BCPR was 1% higher with every percentage increase in people with white ethnicity within the postcode district (OR (95% CI) 1.01 (1.01.1.02), p=0.0001); however, after adjustment, non-deprived dimension was not independently associated with receiving BCPR .(Apppendix 8-17, p238)

In the second model, we included non-deprived dimension and white ethnicity. We also included the pre-hospital factors in this model. We found similar association between SES and BCPR performance as BCPR was higher in post-code district areas with a higher proportion of households of white ethnicity (OR (95% CI) 1.01 (1.001.1.02), p=0.0001). The odds of receiving BCPR was 35% lower when the CA was witnessed (vs non-witnessed, p=0.0001). Compared to presumed medical aetiology of CA, the odds of receiving BCPR was 40% lower if the CA was secondary to trauma (p=0.009). There was also a 37% decrease in odds of BCPR in EMS 9 compared to EMS 1 (p=0.006). The odds of receiving BCPR was also over 5.6 times higher in EMS region 7 compared to region 1 (p=0.001). In cases with an initial shockable rhythm, compared to no shockable rhythm, there was a 58% increase in the odds of receiving BCPR. (Appendix 8-18, p238)

In the third model (Table 6-6), after backward selection, pre-hospital factors – the presence of witnesses and shockable rhythm – as well as trauma aetiology, EMS region and white ethnicity SES factor remained associated with the BCPR outcome. We found that postcode districts with increasing proportion of households of white ethnicity led to higher odds of receiving BCPR (OR (95% CI) 1.01 (1.01.1.02), p=0.0001). For pre-hospital factors, the presence of witnesses led to lower odds of BCPR being performed compared to no witnesses (OR (95% CI) 0.65 (0.52-0.80), p=0.0001). CA cases due to trauma also reduced odds of receiving BCPR compared to presumed medical aetiology of CA (OR (95% CI) 0.59 (0.40-0.85), p=0.005). One ambulance service region (EMS7) was associated with higher odds of receiving BCPR (OR (95% CI) 5.70 (1.99-16.28), p=0.001), while EMS9 was associated with lower odds of BCPR (OR (95% CI) 0.57 (0.42-0.78), p=0.0001) both compared to EMS1.(Figure 6-10)

Table 6-6 Odds ratio of BCPR in socioeconomic and pre-hospital factors (Model 3)

Total n=1856	**OR (95% CI)**	**P value**
Pre-hospital factors		
Witnessed	0.65 (0.52-0.80)	0.0001
Shockable rhythm	1.52 (0.99-2.33)	0.053
Aetiology		
Medical	**Reference**	
Trauma	0.59 (0.40-0.85)	0.005
Drowning	0.76 (0.35-1.64)	0.497
Drug overdose	0.62 (0.27-1.39)	0.250
Asphyxia	1.00 (0.69-1.45)	0.928
EMS region		
EMS 1	**Reference**	
EMS 2	0.70 (0.41-1.19)	0.195
EMS 3	0.71 (0.45-1.12)	0.149
EMS 4	1.14 (0.62-2.09)	0.654
EMS 5	1.08 (0.76-1.52)	0.646
EMS 6	2.26 (0.47-10.97)	0.307
EMS 7	5.70 (1.99-16.28)	0.001
EMS 8	1.19 (0.76-1.86)	0.439
EMS 9	0.57 (0.42-0.78)	0.0001
EMS 10	1.10 (0.57-2.12)	0.771
Socioeconomic factors		
White ethnicity	1.01 (1.01-1.02)	0.0001

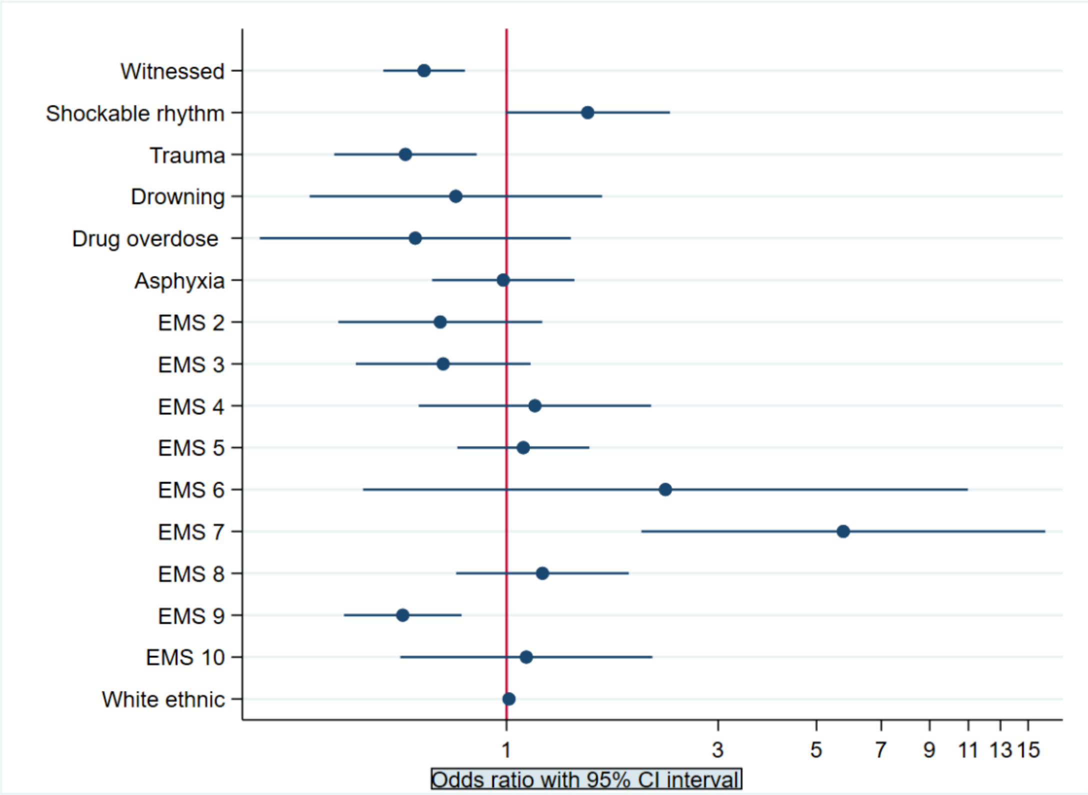

Figure 6-10: Adjusted OR with a 95% CI for BCPR association with pre-hospital and socioeconomic factors

6.5 DISCUSSION

In this study we assessed the association between SES factors and the delivery of BCPR to paediatric OHCA by combining the OHCAO registry postcode data with Office of National Statistics socioeconomic community level data. In the univariate analysis, we found that the rate of BCPR was significantly increased in communities with a higher proportion of households who were classified as non-deprived (with no dimension of deprivation)), white ethnicity, UK nationality, higher education, and higher work levels. However, when adjusting the community SES factors with known patient-level, pre-hospital factors in a multivariable logistic regression model, only higher proportion of households registered as white ethnicity remained associated with a higher BCPR rate. Similar to Chapter four, we also identified witness status of CA and traumatic cause of CA as important patient level factors associated with whether patients received BCPR.

6.5.1 Deprivation dimensions and BCPR

In our study, the deprivation measurements included employment, education, health and disability, and housing and we used the community level deprivation score where the CA was recorded by postcode district. This deprivation measurement was available as it links to the postcode district which is the first part of the full post code. However, by using the postcode district, only the characteristics of the overall population in a certain geographical area could be measured rather than the characteristics of the actual person at the scene of the CA. Given that, we found that the chance of receiving BCPR was higher in non-deprived areas compared to more deprived areas.

A number of other studies have assessed a similar question; however, used different deprivation scores and methods. Brown et al. [101] carried out a study among UK adults using the Index of Multiple Deprivation (IMD) score. IMD measures several domains: income and employment; education; skills and training; health and disability; crime; barriers to housing services, and living environment.[186] They found that a greater IMD deprivation score was associated with lower rates of BCPR (P value <0.05). Similar to the deprivation measurements we used, the IMD measures deprived area rather than individuals. Although the IMD includes more domains and over 30 indicators within these domains, data can only be link to the IMD using the full postcode which was not available in our study. In a South Korean study, using the Carstairs index as a deprivation measurement, they found that BCPR rate was almost double when CA occurred in less deprived areas compared to more deprived areas (25% vs 12.1%).[187] The Carstairs index includes: 1) male unemployment, 2) lack of car ownership, 3) overcrowded houses, and 4) low social class.[188] However, owning a car does not necessarily reflect the level of deprivation as for example people living in an area with good transportation services may not need to own a car. Further, people living in rural areas are more likely to own a car regardless of how poor they are. Finally, the linkage to the Carstairs index is limited to the availability of the postcode sector. In another South Korean paediatric study, the tax-assessed property value was used to define high and low-income areas and found that performing BCPR was lower in areas with low property value.[119] Finally, Naim et al. [82], in a US study, also found that BCPR was higher in high-income areas compared to low-income areas (52.2% vs. 42.8%). Given the disparity in the definitions of the level of deprivation, all definitions refer simply to “low income” areas, a phrase used heavily in studies describing the association between SES and OHCA.[174, 189] Despite the different definitions, our study agrees with the main body of literature associating higher level of deprivation with lower rates of BCPR.

Plausible explanations and causal pathways for the observed connection between deprivation level and BCPR have been theoretically mapped in the Directed acyclic graph (see Figure 6-4). One potential explanation could be that people living in high-deprivation areas usually have a lower chance of receiving or accessing CPR training due to the cost of the training. Indeed, other barriers were found in high-deprivation areas, such as the inability to recognise OHCA and the difficulty of communicating with EMS in OHCA events. A survey conducted by Dobbie et al. (190) found that people living in areas of a low social grade were less confident about performing BCPR if talked through the process by a call handler than those living in areas of a high social grade (78% vs. 86%). These findings clearly show the need to focus on increasing BCPR training and examine other challenges faced in high-deprivation communities.

6.5.2 Education level and BCPR

We did not find a clear association between BCPR and education level in our study. In the unadjusted analysis, the rate of performing BCPR was found to be higher among people with Level 2 and 3 qualifications compared to no-BCPR. However, among those communities with the higher proportion of Level 4 qualification, no statistical differences were found between rates of BCPR compared with the communities with less Level 4 qualification households. Using data on the individual who performed BCPR, rather than the community, an adult study from Australia identified a decrease in the odds of receiving BCPR with a higher education level qualification with either a high school completion (OR 0.87 (95% CI 0.81-0.94)) or a bachelor's degree (OR 0.79 (95% CI 0.69-0.91)).(150) The author also commented that another report from the same region showed that higher education levels were associated with a longer time before seeking medical help.(191) However, this contrasts with other studies that identify an association between BCPR and education level. In a paediatric study, Rajan et al.

[29] found that parents with a high educational level are more likely to perform BCPR than parents with a low educational level (54% vs. 45%). Naim et al. [82] also identified a higher BCPR rate among participants with a high education level compared to a low education level (50.7 % vs 40.2%). A potential mechanism for this connection was described by Blewer et al.[100] In their survey including over 9000 adult members of the public , they found that participants with graduate school education or higher, were more likely to be trained in performing CPR compared to those with a high school education or lower (OR 3.36 (95% CI 1.60-7.09)). Therefore, targeting low-education areas by increasing CPR and AED training may be crucial to improving rates of BCPR and subsequent OHCA outcomes.

6.5.3 Work levels and BCPR

The BCPR rate increased in the communities with a higher proportion of people with high and intermediate occupations while it significantly decreased in people who never worked. As illustrate in the Directed acyclic graph there is a theoretical connection between education, employment and deprivation levels. This is consistent with a UK adult study, which found a higher BCPR rate in communities with more high level occupation (mean percentage (standard deviation) 31.6% (12.6%) vs. 30.5 % (12.6%); p value<0.01) and intermediate level occupations (22.5% (5.2%) vs. 21.8% (4.9%), p value<0.01.[101] Another study from the US in paediatric OHCA found that patients in low-unemployment neighbourhoods are more likely to receive BCPR than those in high-unemployment neighbourhoods (52.1% vs. 40.3%).[82] These findings may be attributed to the fact that working people have a better chance of being trained in CPR. A UK survey study of 2084 respondents showed that full or part-time work significantly increased the odds of CPR training (OR 1.57 (95% CI 1.29-1.91)). Further, in the latter study, the training location in over 50% of those who received CPR training was at work. Similarly, a

Norwegian survey study of 1000 participants found that first aid training was mostly conducted in the workplace (52%).[192] Thus, alternative strategies to teach CPR are needed to reach those living in high-unemployment areas and those who do not work.

In summary, SES factors, including deprivation, education, and work level have been associated with BCPR. Although the association with education level and BCPR was inconsistent, two education levels were associated with increasing the odds of receiving BCPR (Levels 2 and 3). With this in mind, it is worth noting that the deprivation level included education and work level as two dimensions. Therefore, it could be argued that work level carried more weight in this study's deprivation result than education level. Nonetheless, the three factors are directly related to each other. These relationships are attributed to the fact that people with no or low education levels are less likely to have a job, leading them to live in highly deprived areas. Much work is needed to identify this area and explore the challenges that affect increasing the rate of BCPR.

6.5.4 Ethnicity and BCPR

Most previous reports examining the association between BCPR and ethnicity were from the US.[82, 99, 100, 174, 189] There were a few reports from other countries, such as the UK and Singapore, but none of them focused on paediatric OHCA.[101, 193, 194] In the US studies, ethnic groups usually include white and black, with some adding Hispanic and other ethnic groups. Many of these studies found that compared to patients of white ethnicity, patients of other ethnicities are less likely to receive BCPR. For example, a study by Sasson et al.[99] found that patients of black and Hispanic ethnicities were 30% less likely to receive BCPR compared to white ethnic groups. Naim et al. [82], in a paediatric OHCA study, also found that more BCPR was initiated for patients of white ethnicity compared to black, Hispanic, and other ethnicities

(59.9% vs. 39.3%, 46.6%, and 40.9%). Blewer et al.[100] identified similar findings, where 40.7% (3152/7729) of white patients received BCPR, while the percentage of black and Hispanic patients who received BCPR was 21.4% (741/3448) and 28.9% (248/856). Interestingly, other racial-ethnic findings were reported in the latter study but with a significantly low number of cases showing a similar percentage of receiving BCPR to the white ethnic group, such as those of Asian ethnicity (243/521; 46.6%). In view of this, in our study, ethnic groups were categorised as white, mixed, Asian-British, black, and other. This shows that there are differences in categorising ethnic groups, which should be considered when comparing results. BCPR was more likely to be performed in areas where larger proportion of white ethnicity live (OR 1.01 (95% CI 1.01-1.02)), while areas with larger proportion of ethnic minorities (mixed, Asian-British, black, and other) were associated with decreased odds in receiving BCPR. This is similar to the findings from the US studies mentioned above, although the ethnic groups are slightly different. In an adult study from the UK, the author identified that mixed and non-white ethnic groups live in high-risk areas.[101] The author defined high-risk areas as areas with a high incidence of OHCA and low BCPR. However, another UK report that compared the white ethnic population to the South Asian population reported a higher BCPR percentage performed in white (34.4% vs 29.7%); however, there was no statistical difference between the two groups (OR 1.2(95% CI 0.9-1.7)).[194] It is worth noting that the latter study was based on the London region, and the ethnicity code was only available for 24% of all OHCA cases.

The interaction of race and health is a complex and controversial topic. In our Directed acyclic graph (Figure 6-4) we categorised a number of potential causal pathways linking race/ethnicity and deprivation domains leading to BCPR delivery. To further understand the issue of the racial disparities found in our study, it may be helpful to look at the relationship between ethnicity/race and health care in general. Several reports have examined different aspects of health care in adults and children and have shown the differences in health care quality and delivery secondary to race.[98, 195-198] The way in which some health care systems operate, which leads to a lack of access to health care and treatment, has also been linked to racial disparities.[195, 199, 200] A report from the US found that racial minorities were less likely to have health insurance compared to patients of white ethnicity.[198] Another issue related to the healthcare system is the behaviour of some healthcare providers. The Institute of Medicine (IOM) suggested that racial disparities might be explained by unconscious bias among health care providers.[201] Indeed, unconscious bias in the attitude of clinicians has been linked to black ethnicity.[199] Some reports have suggested that SES factors are also responsible for the racial disparities.[197, 202] The US Census Bureau in 2008 showed a higher percentage of poverty among black and Hispanic populations compared to the white population (24% vs. 20.6% vs. 10.3%).[203] Although the last report found that the gap in education level narrowed between white and black populations, educational level of the Hispanic population remained low compared to those groups.

In the UK, health care access is free at the point of service for emergency care (e.g. OHCA and EMS); therefore, the UK does not see so overtly the impact of lack of insurance on health care access. However, despite this, we did identify an ethnicity difference in our study. Given the variety of explanations for the racial disparities, studies examining the association between BCPR and ethnicity/race usually raise the possibility of the impact of SES being responsible. Sasson et al.[99] found that the probability of receiving BCPR was approximately 50% lower in low-income black neighbourhoods compared to high-income non-black neighbourhoods. The variation in the BCPR rate among ethnic groups could also be attributed to language barriers. The time needed to explain how to recognise CA might be longer due to difficulties in communication with emergency dispatch. Further, instructions given to the bystander to perform CPR might also be affected by communication challenges.

To summarise, the impact of race on BCPR initiation might have several causal pathways, yet few studies have investigated this. It might also be helpful to look at other aspects besides the SES factors, such as factors linked with different health outcomes (e.g. unconscious bias in health care providers). For those ethnic populations with low BCPR initiation, improved communication with emergency dispatch is needed and campaigns should be run to improve their recognition of CA. Establishing CPR training that targets those high risk communities may also increase the BCPR rate and improve OHCA outcomes.

6.5.5 Socioeconomic and pre-hospital factors

In our study, before adjusting for confounders, deprivation, qualification level, work level, and ethnicity were associated with performing BCPR. Yet, after applying backwards stepwise regression, BCPR remains significantly associated with white ethnicity only. Uber et al.[(204)], in a US adult study, found that after adjustment for confounders, SES factors were not independently associated with BCPR (median household income aOR 1.00 (95% CI 0.99-1.00), proportion unemployed aOR 0.07 (95% CI 0.01-1.38)). Interestingly, there was no association between BCPR and ethnicity in the latter study (proportion Caucasian aOR 1.35(95% CI 0.60-3.05)). The author suggested that these findings are attributed to the homogenous population, with 80% being Caucasian. In an Australian study, Straney et al. [(150)] identified in Local Government Areas of Victoria, Australia that after adjusting for confounders, there was no statistical difference in the odds of receiving BCPR and education level. However, the latter included only witnessed OHCA. In contrast, in a US study, Sasson et al. showed that despite adjusting for pre-hospital factors, the median household income and racial composition are significantly associated with BCPR initiation.[99] Similarly, Moon et al.[205] found that CA that occur in higher poverty rate areas were less likely to receive BCPR compared to low poverty rate areas (aOR 0.74 (95% CI 0.65-0.85)) in multivariable logistic regression. Also reported in the latter study, Hispanics were less likely to receive BCPR compared to non-Hispanics (aOR 0.62 (95% CI 0.44-0.89)).

The inconstancy between studies describing the relationship between SES factors and BCPR initiation after adjustment for confounders is attributed to several causes. First, the population base that has been studied differs from one study to another. For example, studies covering most of the US population tend to find a strong association between SES factors and BCPR.[82, 99] However, in the US, there are regions in which a specific ethnic minority population is high compared to other regions. Studies in those areas showed different findings than regions with a larger white population. For example, a survey from Arizona in the US, where the Hispanic population is considered to be high, found that BCPR is performed less in high-poverty areas.[205] In contrast, a study from Kent County, also in the US, where most of the population is Caucasian, found no association between race and SES factors and the rate of BCPR.[204] This is important because it shows how cultural background and the size of a specific ethnic group could affect the impact of SES factors. The population characteristics of the UK are not the same as the US. In the UK, the percentage of ethnic minorities is 14%, and the Asian ethnic group is the second largest group after white ethnicity (7.5% and 86% respectively).[206] However, in the US, ethnic minorities form 42.2% of the total population, with Hispanic or Latino as the second largest ethnic group, with a percentage of 18.7%, after the white ethnic group (57.8%).[207] Therefore, ethnic diversity in the UK is far less than in the US, which might explain in our findings why the impact of SES factors was not found after adjusting for clinical factors. Another explanation could be the distribution of clinical factors across SES factors. A UK study showed that Asians are more likely to be witnessed if they have a CA compared to patients of white ethnicity.[194] Further, other clinical factors such as response time, initial rhythm, and BCPR were comparable between the white and Asian groups. In contrast, several studies showed that Hispanic and black ethnic groups were more likely to have a non-shockable rhythm as an initial rhythm and receive BCPR.[208-210] This can be attributed to other factors such as EMS response time, CPR training, or language barriers as well as underlying health conditions which are more prevalent in ethnic groups (e.g. type 2 diabetes). Second, adjustment for confounders differs between studies. This is due to the data availability, the purpose of the study, and the author's decision on which factors should be considered as a confounder. We identified in our Directed acyclic graph a number of potential unmeasured confounders in both the patient level and community level data which could be considered essential in future epidemiological studies. Finally, the way SES factors are categorised and measured could also explain our findings as different measurement tools were used across studies.

In summary, the impact of socioeconomic factors is driven by clinical factors, which might explain why being witnessed was strongly associated with BCPR in the full-adjusted model. Other factors that could not be measured, such as the location of CA (private/public), response time, and patient weight, affected our findings.

6.6 STRENGTHS AND LIMITATIONS

This is the first paediatric OHCA study to examine the association of BCPR and SES factors in the UK using data from the OHCA registry. The strength of OHCA registry data has been described elsewhere (chapter four). Although the sample size of this study was large, there are some limitations in this study. The address code was unavailable for 10% of the BCPR data (262/2608=10%) and due to other missing data case wise selection, our multivariable logistic regression model was calculated using only 79% (1856/2343) of the original dataset.

Further, we could not examine the association between BCPR and SES factors at the individual level, which could affect our conclusion. We used a community-level assessment to measure the characteristics of bystanders. In an ideal world, we would know who the bystander or the witness was, what their SES was; and use this information to measure the influence of SES in bystander intervention on the individual. As I have shown in the Directed acyclic graph, the unmeasured variables related to the individual include the actual training they have received, what is their actual SES, what are their concerns, fears and expectations of performing BCPR. Unfortunately, getting this type of data was not possible; therefore, we chose to use surrogates by looking at the community-level SES characteristics. Thus, there is potential that using data at the individual level may show different results.

We used the postcode district to capture a larger data sample. Since this is a retrospective analysis, we could not adjust for all confounders. However, we used Directed acyclic graph to help theoretically model and visualise the relationship of factors and explore the causal pathways for SES and BCPR rates. We did not have the data for the location of the CA (private/public). Further, data regarding BCPR training and the use of assisted dispatchers were unavailable, which could affect the recognition of CA and bystanders' willingness to perform BCPR.

A potential limitation of our approach to use backward stepwise models was the inability to control the relationship between variables included in the model. Due to its automated nature, applying different adjustments within the model is not possible. In our model, we included the EMS regions as a variable that has an association with patients factors as shown in the Directed acyclic graph. However, the EMS regions could be considered as a geographical factor and therefore may be correlated with the SES factors included in the model. It is therefore possible that including EMS regions in the backward selection model has affected the association strength of the SES factors and BCPR. A future approach to overcome this issue may be using two multivariable logistic regression models, the first one include patient's factors and EMS regions and the second one include patients factors and SES factors. This could prevent examining the geographic effect twice (EMS regions and SES factors correlation) and allow examining their effect on BCPR and patients factors separately.

6.7 FUTURE STUDY

In this study, we aimed to describe the association of SES factors on the rate of BCPR. We found that BCPR was low in areas with higher deprivation level, higher proportion of ethnic minorities and low work level. Therefore, further studies to identify the barriers and challenges in these areas is essential, e.g. how well the communities where BCPR found to be low are trained and the attitude of the people living in high-deprived area and ethnic minorities toward CPR training? Since we did not measure the association of BCPR and SES factors at the individual level, it might be interesting to examine the association at the individual level. Clinical factors such as witness CA and trauma shows a stronger association with BCPR than SES factors; except white ethnic. This poses questions about the relation between clinical factors and SES factors. For example, are CA which occur in high deprived area, witnessed less? Does the cause of CA differ in ethnic minorities? Finally, since we found an association between SES factors and BCPR, we should continue to pathway and examine the future impact of SES factors and patient level survival and neurodevelopmental outcomes.

6.8 CONCLUSION

This is the first and largest paediatric OHCA study to examine the association of SES factors and BCPR in the U.K. In areas with higher number of households with high deprivation level, higher proportion of ethnic minorities and low work level, children who have an OHCA were less likely to receive BCPR. Although the BCPR association with most of the SES factors were no longer statistically significant after adjusting for clinical factors, BCPR remained associated with areas with a large proportion of white ethnicity. Witnessed CA, trauma cause and some EMS regions were also associated with BCPR.

Further research is needed to identify barriers to performing BCPR in high deprived areas and areas with high ethnic minority populations. This should help establish strategies to improve the rate of performing BCPR in high deprived areas, as well as survival outcomes.

6.9 ACKNOWLEDGEMENT

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7 Summary and Conclusion

7.1 OVERVIEW

OHCA in children is a challenging event for the child's family, the public community, EMS providers and the hospital team. The outcome of such cases is mostly devastating due to several factors, including the patient demographic, the CA characteristics and the quality of the health care system, including prehospital care. In this thesis, we focused on a critical factor that can significantly impact survival outcomes after paediatric OHCA, which is the BCPR intervention. The journey we started in this thesis first compared BCPR versus no-BCPR for paediatric OHCA, conducted in a systematic review (chapter three). In this systematic review, we found that multiple outcomes improved when BCPR was performed compared to no-BCPR. However, we also identified a considerable variation of BCPR rate across paediatric OHCA studies. Therefore, before examining the BCPR rate and its impact on paediatric OHCA, it was essential to understand the population characteristics and the differences within this population. We, therefore, used the UK OHCA registry and linked it to ONS data to describe the incidence rate and the epidemiology of paediatric OHCA across EMS regions in England and explored variation in patient and EMS factors associated with ROSC and survival (chapter four). After setting the scene and understanding the patient demographics and the regional variation across EMS regions, we used the OHCA data registry to describe the BCPR rate and its effect on survival outcomes after paediatric OHCA in England (chapter five). Finally, to assess whether SES factors affect the BCPR rate, we used the OHCA data registry and linked it with Nomis to describe the association between SES factors and the BCPR rate in England (chapter six).

We set out to answer seven important research questions (chapter two) exploring the epidemiology of paediatric OHCA and the role of BCPR. The following section provides a summary our findings and identifies the original contribution this thesis provides to the existing literature for each question.

KEY FINDINGS

Question 1- Does bystander CPR during paediatric OHCA improve the rate of return to spontaneous circulation (ROSC), survival, or survival with a favourable neurological outcome?

To answer this question, a systematic review comparing BCPR versus no-BCPR after paediatric OHCA was conducted (chapter three). We identified that BCPR was significantly associated with increasing the chance of achieving ROSC and improving the survival to hospital discharge and survival at one month compared to no-BCPR. However, in the review, we also identified wide variations in the BCPR rate across paediatric studies, potentially affecting the relationship between BCPR and survival outcomes. We also found that heterogeneity was a significant issue in paediatric studies. The study sample size, the upper age limit, categorising the cause of the CA and the quality of the EMS system comprise a group of issues observed among paediatric OHCA. This systematic review contributes new knowledge on the impact of BCPR in different survival outcomes in paediatric OHCA studies. This builds significantly on the last systematic review, published over 18 years ago (2005), which explored the association of BCPR with survival, we have updated the methodological approach, included new literature and importantly expanded the reported outcomes.(72)

One key area for discussion was the primary clinical outcome available in the literature. Our primary outcome in this systematic review was the one-month favourable neurological outcome CPC1 or 2. We found a one-month favourable neurological improvement when BCPR was performed compared to no-BCPR; however, the reports were limited to one cohort of patients (Japan). Examining the association of BCPR and the neurological outcome was limited to studies from Japan and Korea. Most studies included in this review were based on a data registry, which might explain the issue of having limited reports for neurological outcomes. One of the main challenges for the OHCA registries is the high cost of collecting such data. This issue can be resolved by encouraging research funders to support this type of research as it will help in understanding factors affecting neurological outcomes in children and eventually help in identifying areas that can be improved to positively impact the neurological outcomes. The neurological outcome measurement used in the studies we identified was the Cerebral Performance Category scale (CPC).(211) Although it can be used in the paediatric population, the categorisation of the CPC slightly differs from the Paediatric Cerebral Performance Category, a scale designed for the paediatric population.(212) For example, Cerebral Performance Category 2 is a moderate cerebral disability, whereas Paediatric Cerebral Performance Category 2 is a mild cerebral disability.

Further, the Cerebral Performance Category consists of five categories, while the Paediatric Cerebral Performance Category consists of six. This might confuse the reader and affect the comparability between paediatric studies when some use Cerebral Performance Category and others use Paediatric Cerebral Performance Category. To improve consistency in reporting outcomes in paediatric studies, a recent report, the Pediatric Core Outcome Set for Cardiac Arrest, suggested a list of measurements that can be used to assess the life impact or the neurological outcome in paediatric CA. The list includes Paediatric Cerebral Performance Category for brain function, Paediatric Quality of Life Infant Scales for cognitive and physical function and Paediatric Cerebral Palsy module for daily life.(123) These scales could massively improve reporting the neurological outcomes and could provide longer outcome endpoints as these scales can assess the outcomes from hospital discharge to 12 months. Nevertheless, the data collection issue continues as the data require family contributions that may not be guaranteed in all cases, particularly when the study is based on registries. Moreover, this is considered a critical time for families and requires a trained person to communicate and choose the appropriate time to obtain the information needed. Given that, it would be beneficial to unify the evaluation scale for assessing neurological outcomes in paediatric CA studies to help determine which factors are associated with short-term and long-term outcomes.

Two new studies were published after completing this systematic review which could have potentially been included. The first study was an Australian study published in 2022 that included paediatric aged >4 days to 18 years.(213) The study examined the association of BCPR and ROSC on hospital arrival. There was no statistical difference in achieving ROSC when BCPR was performed compared to no-BCPR (P value=0.933). The second study is a Japanese study published in 2019 that included children aged 6 (elementary school) to ≥15 years (high school and technical college).(214) The study focused on CA cases that occurred during or after sports exercise. The study showed that BCPR was associated with one-month survival with Cerebral Performance Category 1 or 2 in a crude analysis OR 3.93 (95%CI 1.48-10.41), P value= 0.006. However, this study included OHCA cases between 2008-2015, which might overlap with the Japanese study we included in our systematic review. Furthermore, the sample size was small, and only a subset compared to the Japanese study was included in this review (188 vs 5170). Further, the upper age limit was not clear as ≥15 years might suggest that there were children over 18 years included in the study. However, knowledge of this new literature would not change our conclusions in chapter three.

Using the existing literature, BCPR improves the chance of ROSC and survival in paediatric OHCA; however, no data were available from the UK or the English population, and therefore further research to examine paediatric OHCA in the UK/English setting is justified.

Question 2- What is the current knowledge of the incidence rate, epidemiology and survival outcomes of paediatric OHCA in England?

To answer question 2, we linked data from ONS to the OHCA data registry in chapter four. The ONS database provided data about the population, including the distribution of the population by age, in each region of England. This enabled us to calculate the incidence rate for the paediatric population by age and by EMS region. The OHCA registry identified a median of 550 paediatric OHCA per year in England. The incidence rate for paediatric OHCA aged less than 18 years was 5.3 per 100,000 of the English population. Infants ≤1 year were found to have the highest incidence rate among the paediatric age groups (27.3 per 100,000 person-years). This is important and novel information for understanding the paediatric OHCA population in England, providing a benchmark for incidence and outcome rates across a whole national health care network. Although our reported incidence rates were confirmed to be similar to other countries, this is the first reported confirmation of this information.[29, 34] A variation in the incidence rate was found across EMS regions, ranging from 2.6 to 7.6 per 100,000. Following the high incidence rate in infants ≤1 year, infants were the largest age group in six EMS regions, where children aged >1-4 years in two regions and adolescents aged >12-18 years in two regions. We also identified that arrests occurred more often in males than females (59.0% vs 41%), the most common cause of OHCA was presumed cardiac origin

(Medical) (70.9%) and OHCA cases were witnessed in 40.6% of the cases. The cardiac initial rhythm was 'shockable' in 7.3% of OHCA cases. Older children aged >12 years were more likely to present with shockable rhythm than children aged <12. The rate of patients presenting with shockable rhythm was also found to vary across EMS regions.

The overall survival to hospital discharge was 11.0%. Although there was no statistical difference across age groups, infants ≤1 year had the lowest survival rate (8.4%). This might be related to important factors, including OHCA cause and witness status. To explain, CA due to a medical cause was the most common in all age groups but with a higher percentage in the infant group (85.8%). This could suggest that OHCA occurred as part of SIDS, which is known to have a very poor survival outcome. Moreover, infants comprised the age group least likely to have a witnessed OHCA (31.3%), which might also explain the low survival rate in the infant age group compared to other age groups. Finally, ROSC at any time and ROSC at hospital showed improvement as age increased.

Our examination of the OHCA registry has identified key epidemiological knowledge concerning paediatric OHCA in England. This novel information will be important to health-policy makers in considering the burden of paediatric CA and the allocation of resources to reduce the rate of CA. UK infant mortality rates are one of the highest in Europe, and CA is an important condition impacting these rates.[215] Targeting interventions to reduce the rate of CA and improving the outcomes following CA are therefore essential. In addition, a better understanding of the variation in the rates of CA across England EMS and the impact on clinically important patient outcomes may allow for lessons to be shared across the nation and EMS.

Question 3- Is there a regional variation in patient and EMS factors associated with ROSC and survival in England?

In chapter four, we identified a significant variation in survival rate across EMS regions (range: 6.5% to 21.7%). Similar patterns were also found in the rate of i) ROSC at any time (range: 17.5% to 57.7%) and ii) ROSC at hospital arrival (range: 6.4% to 27.1%). Although patient factors varied across EMS regions, their variation did not explain the variation in the survival outcomes in this study. Missing data may have been an important factor in our difficulty in exploring the variation. The amount of missing data in the OHCA registry by EMS ranged from 0.5% to 45.3% for witnessed status and 0.5% to 43.3% for BCPR. This illustrate one of the challenges when using a data registry. A similar issue was found in different OHCA registries. As we stated in chapter one, the way data were collected within a registry plays a major role in the quality of data. To explain, OHCA data can be collected by the EMS, the dispatcher and the hospital. Limiting the manner of collecting data to EMS responders might affect the quality of data. OHCA is a stressful situation, and EMS responders might not be able to recall all the information needed, which is true for bystanders as well. Therefore, one step that can mitigate the issue of missing data is using different scores of data collection. In the US, the Cardiac Arrest Registry to Enhance Survival combines data from 911 dispatch, EMS and hospital records.[216] This helps in comparing data between different resources and identifying any missing data between the sources. Another way to minimise the effect of missing data is by including a large sample size, which is similar to what had been done in our study. Furthermore, the statistical technique of Multiple Imputation has also been recommended as an approach to handling missing data. However, the use of Multiple Imputation in binary data is challenging and may not provide an accurate prediction.[217] Another possible explanation for the variation in ROSC and survival rates across EMS regions is the effect of SES factors. Unfortunately, the UK OHCA registry does not provide such data for individuals, which could have helped in understanding the factors associated with ROSC and survival variation across EMS regions. Factors such as BCPR may be related to the variation found in survival outcomes across EMS regions, and therefore a further examination was needed to describe the association of BCPR with ROSC and survival outcomes across EMS regions in England.

Question 4- Are demographics and prehospital factors associated with bystander CPR in paediatric OHCA in England?

To explore the answer to this question, we must first briefly highlight the importance of the of the BCPR rate identified within this thesis. Within the systematic review, we identified that BCPR was associated with multiple survival outcomes, and after describing the epidemiology of paediatric OHCA in England in chapter four, we described the BCPR rate and its impact on ROSC and survival hospital discharge using the UK OHCA registry. This is the first study to examine the association of BCPR with clinical factors and survival outcomes in England for infants and children. Although we limited the inclusion of OHCA cases to only those with no missing BCPR and survival outcomes, the rate of BCPR remained similar to those we reported in chapter four (69.6%). We identified an improvement in the BCPR rate between 2014 and 2018 (69% vs 74%). During this period, it is possible that initiatives to increase BCPR training (e.g. programs delivered by the British Heart Foundation) may have increased the BCPR rate in England. Linking the geographical data within the OHCA registry and training schedules in CPR would allow for research into this hypothesis.

One important finding was that many of those who received BCPR were unwitnessed. In this study, infants formed the largest age group, which is less witnessed than other age groups. Further, two third of the infant group received BCPR. Hence, there is a high possibility that BCPR was performed in many unwitnessed infant cases, which is eventually reflected in the association between BCPR and survival outcome.

Univariate and multivariable logistic regression models were applied to examine the association of BCPR with other prehospital factors. We found that BCPR was less likely in cases of CA secondary to trauma. CA in children is a stressful situation itself, and it has become more challenging when the CA is due to trauma. To explain, performing BCPR is more difficult in the traumatic events due to the mechanism of injury in some cases, when no one is around when event occurs, and in cases where more than one victims is involved in the traumatic event (e.g. motor vehicle collision). The low BCPR rate in traumatic CA was also found in other studies.(35, 218) Unlike CA due to presumed cardiac origin, traumatic OHCA usually occurs in public, so the bystander will probably be a non-family member. Therefore, the bystander may hesitate to perform BCPR, especially in traumatic cases, where bloodborne disease might be a concern. One possible suggestion to overcome this problem is using the EMS dispatcher, which might help bystanders approach such cases.

Understanding factors associated with the rates of BCPR are important; however, exploring the impact of BCPR on clinical important outcomes may provide further justification of the role of BCPR in the chain of survival.

Question 5- Does bystander CPR improve ROSC and survival to hospital discharge outcomes?

In chapter five, multivariable logistic regression model was used to examine the association between BCPR, other important clinical and pre-hospital factors and survival outcomes. We found that BCPR was associated with ROSC at any time but interestingly, not with survival to hospital discharge. This is important and novel information about the impact of BCPR on survival outcomes which suggest that other clinical factors are affecting the association between BCPR and survival. This finding is different from the findings in the systematic review in chapter three, where BCPR was associated with increased odds of both ROSC and survival to hospital discharge (pOR 2.30(95% CI 1.17-4.52)) and (pOR 2.30(95% CI 1.41-3.75). This finding could be explained by the fact that only 34.9% of the cases that received BCPR were witnessed. Another possible explanation could be that two thirds of the CA cases were infants aged one year or less, and this age group was linked to being less witnessed in chapter four, and the CA cause is possibly due to SIDS, which is known for its poor survival outcome. Factors related to the quality of CPR and the EMS response time, time to arrive at the hospital and the post-cardiac arrest care in the hospital might also explain why BCPR was associated with ROSC at any time but not with survival to hospital discharge.

Question 6- Is there a regional variation in bystander CPR rate in paediatric OHCA in England?

In chapter four, the overall BCPR rate was 65.8%; however, the BCPR rate varied across EMS regions (range: 52.2% to 81.7%). The CA was witnessed in 40.6% of cases, varying across age groups (31.3% to 52.5%) and EMS regions (30.0% to 45.0%). In chapter five, to allow for the analysis of the relationship between BCPR and survival, the dataset was limited to include only cases with BCPR and survival outcomes; therefore, the total cases included were slightly lower (n=2363) compared to chapter four (n=2862). Despite the smaller sample, the BCPR rate variation remained across EMS regions (57.7% to 83.7%). The data completeness issue, which was also found in chapter four, might be responsible for this association as some of the EMS regions did not submit their data for the whole study period (2014-2018). Also, the percentage of the BCPR data submitted to the registry also varied across EMS regions. Another possible explanation is that EMS regions with large infant age groups usually have fewer witness cases (chapter four). Further, a regional SES difference within each EMS region could also partly explain this finding. Several reports have linked SES factors, including the level of deprivation and education, with the variation in the BCPR rate. Therefore, examining the association of SES factors with the BCPR rate across EMS regions was a pivotal step in further exploring the variation in the BCPR rate. Nevertheless, the overall BCPR was considerably high compared to most other paediatric studies included in the systematic review (chapter three). This suggests that efforts to improve the public awareness about the importance of the BCPR had positively impacted the BCPR rate. However, there is always room for improvement, which includes examining the factors causing the variation of BCPR across the EMS regions and the relationship between performing BCPR and other clinical factors. Improving data collection for such factors through the OHCA registry could help to better estimate the BCPR rate. Understanding the association of BCPR and clinical factors might also help in identifying the causes of the BCPR variation across EMS regions.

Question 7-What is the impact of socioeconomic factors on the bystander CPR rate?

In chapter six, to assess the impact of SES factors on BCPR, we linked the OHCA registry data with available geographic postcodes to the SES data from the Office for National Statistics (ONS) through the Nomis website. This important area of research into socio-economic factors and its relationship with resuscitation factors has not been explored previously in the paediatric cardiac arrest population in England. This chapter provides unique data on the current relationship between population deprivation scores, SES and performance of BCPR for paediatric OHCA. While previous pediatric studies have reported on the association between BCPR and SES[82], none have examined this association in depth. Additionally, in this chapter, we have combined both SES and clinical factors into one model to comprehensively examine their effects on BCPR. The BCPR rate was similar to rates reported in chapters four and five, although we were required to select only cases with the postcode district. One of the challenges in linking the OHCA registry data with the ONS data was the format of the address or postcode. In several cases, the OHCA data offer an address line that requires a manual search through an online website to obtain the postcode district. Although we were careful not to convert the address line to an incorrect postcode district, there is still a possibility of data inputting error. More cases had enough data with a postcode district. However to calculate the Lower Layer Super Output Area (LSOA) and link more detailed SES data (e.g. Index of Multiple Deprivation score) would have required a more complete postcode, which would have limited the case selection and the sample size further. The SES data we were able to obtain from the ONS provide data included the level of deprivation, which consists of four elements: employment status, education, health and disability and house accommodation. Unfortunately, we could not measure the effect of each element of the deprivation levels separately. Therefore, we extracted separate variables from the ONS website to measure the impact of work level and education. This helped us to understand the extent of the element's impact within the deprivation measurement. As mentioned, using the postcode district limits the options of the deprivation measurement we can use. If the OHCA data registry provides the complete postcode for most cases, the choice of the deprivation measurement might be changed to, for example, the Index of Multiple Deprivations (IMD) as it includes more domains, and each domain can be separately measured using a ranking quintile scale from 1 to 10. However, for both deprivation measurements, rather than measuring the characteristics of the person at the scene of the CA, only the characteristics of the overall population could be measured, suggesting that there is no significant difference between the two measurements.

In this study, we found that some SES factors affect the rate of the BCPR in paediatric OHCA in England. Based on the univariate analysis, there were decreasing odds of receiving BCPR with each additional dimension of deprivation. We also found that a higher proportion of white ethnicity in the postcode district was associated with receiving BCPR. The relationship between the BCPR rate and education was inconsistent as only some education levels were associated with increasing the odds of receiving BCPR. BCPR was also higher in areas with higher work levels, whereas a low rate of BCPR was observed in those who never worked.

In the multivariable logistic regression model, that included both SES factors and prehospital factors, the likelihood of receiving BCPR was still associated with postcode districts with a higher proportion of the household of white ethnicity. The cases that were witnessed were less likely to receive BCPR. Similar to the findings in chapter four, there was a decrease in the odds of receiving BCPR in the CA cases due to trauma. One important finding related to the geographical variation is that the BCPR and EMS regions varied. Compared to the EMS region with the largest sample, some EMS regions showed a higher odds of receiving BCPR, some showed no statistical association, and some had lower odds of BCPR being performed. This confirmed what we found in chapters four and five, where the BCPR varied across EMS regions; however, this study suggests that the effect of the SES factors can explain the EMS regions' variations in the BCPR rate.

7.2 FUTURE RESEARCH

This thesis has demonstrated that there are vital areas of research that can be improved in future studies. One of these areas is the lack of longer term survival outcomes after paediatric OHCA. This was observed in our systematic review, where only one study published in 1995 reported a one-year survival outcome.[(44)] This suggests that future research should focus on describing the long term survival outcome rate after OHCA and factors that might influence its rate. Further, for both short and long term survival outcomes, the neurological outcomes should also be examined, especially because children who survive frequently suffer neurological injury. Perhaps the suggested measurements for the neurological outcome, published by Pediatric Core Outcome Set for Cardiac Arrest [(123)], should help unify the neurological measurement and increase the rate of publishing longer survival outcomes with neurological outcomes in paediatric OHCA studies.

In this thesis, we have also identified that survival to hospital discharge was comparable to other paediatric studies that included a similar sample size. However, chapters four and five found a variation in the clinical factors (e.g. status of witness, BCPR, shockable rhythm), ROSC and survival to hospital discharge. We were able to examine the association of the BCPR with

SES in this thesis; however, the impact of SES factors on survival outcomes was not examined. As mentioned in the discussion section, this was due to the limited data available for the patients' postcode addresses to link the SES factors with survival outcome data. Future work should consider examining the association between SES and survival outcomes, especially considering the association of SES factors and the BCPR rate identified in this thesis.

One of our key findings was that only one-third of OHCA that were witnessed received BCPR (chapter five). Although BCPR training has increased in recent years in the UK and technology instruction has become more available to the public, there seem to be other factors influencing the willingness to perform BCPR in children. In 2019, Hawkes and colleagues published a UK survey examining the bystander witness' willingness to perform CPR in OHCA cases.(173) They found that 59% were trained in CPR, which was crucial in increasing the willingness to perform BCPR. However, in this survey, over 90% of the participants were more likely to call EMS if they witnessed OHCA, and less than 60% would perform any form of CPR. This study did not specify the age of the CA victim, which suggests that a survey examining the witnessed bystander's willingness to perform CPR in paediatric OHCA might help identify barriers to not performing CPR in such cases. Interviewing those who witnessed paediatric OHCA might also help in better understanding the witness' characteristics and the influence of CPR training on the decision. The EMS dispatcher system plays a significant role in OHCA cases and the witness' willingness to perform CPR. Thus, it might be helpful to examine the effect of the EMS dispatcher on the BCPR rate among the paediatric OHCA population.

Chapter six identified an association between the BCPR rate and the SES factors. High deprived areas, areas with higher proportion of ethnic minorities and low work levels were less likely to receive BCPR. Targeting these areas might help improve the BCPR rate and the survival outcome. Designing a study to measure the barriers and challenges for areas associated with low BCPR rates might help in developing a strategy to improve the BCPR rate. Furthermore, exploring other factors related to SES, such as the differences in living in urban/rural areas and the population density and its association with the BCPR rate, will improve the understanding of the factors influencing the BCPR rate in the UK population.

7.2.1.1 **THE EMOTIONAL IMPACT OF PERFORMING CPR BY A BYSTANDER**

Throughout this thesis, I have discussed the importance of bystander CPR and its effects on the survival outcome. Several approaches were discussed to encourage the bystander to act during OHCA, including raising awareness levels within the community and introducing courses to train the public to recognise OHCA and perform CPR as soon as possible. Studies showed that people who received CPR training were more willing and confident to perform CPR than those who were not trained.[173, 190] However, acquiring skills to perform CPR is only one aspect that CPR training courses focus on. One of the main aspects that have received less attention is to what extent OHCA and the role of performing CPR influences the emotional and psychological states of bystanders.

A systematic review of predominantly adult studies exploring emotional aspect of initiating BCPR has summarized the key areas associated with initiation of CPR; these included: “the overwhelming emotion of the situation, perceptions of capability, uncertainty about when CPR is appropriate feeling unprepared and fear of doing harm”.[219] Most studies that investigated the willingness of the public to perform CPR in OHCA cases used questionnaire-based surveys of randomly selected member of the public. Although CPR training courses can help in improving the public's knowledge, skills, and confidence, the bystander's attitude might be completely different during the real event. Reports showed that in some OHCA cases, bystanders were unable to call for help due to the high stress they experienced.[220, 221] This stress is likely to continue to be a challenge for performing CPR in OHCA cases. Although, in a professional group, stress has also been reported among the EMS team members responding to OHCA cases.[222, 223] However, because of limited research in this field, it remains unclear if the emotional impact of the OHCA affects the quality of CPR performed by EMS members.

As stated above, being a bystander involved in OHCA events is very stressful at the time. The emotions and stress experienced by the bystander might also continue for weeks or even longer. Mathiesen et al. [224] interviewed 20 bystanders who provided BCPR in OHCA cases and found that these bystanders struggled emotionally. Some of these bystanders experienced sleeplessness and weight loss. Furthermore, the feeling of guilt and uncertainty about whether they caused injury to the OHCA victim were common among them. Anxiety about the outcome of the OHCA victim was prevalent among all bystanders who participated in this study. Also, getting information about the patient’s condition was a struggle and some of these bystanders waited for years to have this information. Axelsson et al.[225] reported that having information on the outcome of the OHCA victim was associated with the bystander reaction. The authors also showed that debriefing was associated with the bystander’s feeling toward participation in the OHCA event since those who did not talk about the event had a negative feeling towards the whole experience. Therefore, it may be important to encourage the EMS teams or receiving hospitals to offer emotional support to bystanders and encourage them to talk about the experience as this might help them to cope with emotional stress. These interventions will all require further research and exploration.

There is limited data about the impact on bystanders who participated in paediatric OHCA. OHCA in children is a very stressful experience for the EMS team and family members, who are usually bystanders. Although few studies showed that people are more willing to perform CPR on relatives than on strangers[226], other studies reported that they would be more comfortable doing CPR on an adult than on a child.[227] Based on a survey of 1000 participants who attended a BLS course, Savastano et al. found that the number of participants willing to perform CPR on an adult was more than those willing to perform CPR on a child (86.6% vs. 74.3%).[227] Fear of causing harm to the child was the main concern for those who were not willing or less comfortable doing CPR.

To summarise, involvement in OHCA can be traumatic and could negatively impact the bystander's life. EMS can play a significant role by comforting bystanders and helping them cope with emotional stress. Sharing the outcome of the OHCA victim with the bystander can mitigate the anxiety the bystander experience. There is limited data regarding the emotional impact on the bystander who performs CPR on their child; therefore, further investigation is needed to address this issue and to better understand and identify solutions for such cases.

7.3 CONCLUSION

The importance of performing BCPR has been shown to be paramount throughout the chapters of this thesis. First, the systematic review showed that performing BCPR improved the chance of achieving ROSC, survival to hospital discharge and survival to one month compared to no-BCPR. It also identified a better neurological outcome when BCPR was performed, although the data were limited, which prevented us from developing a strong conclusion regarding the association of BCPR and neurological outcomes.

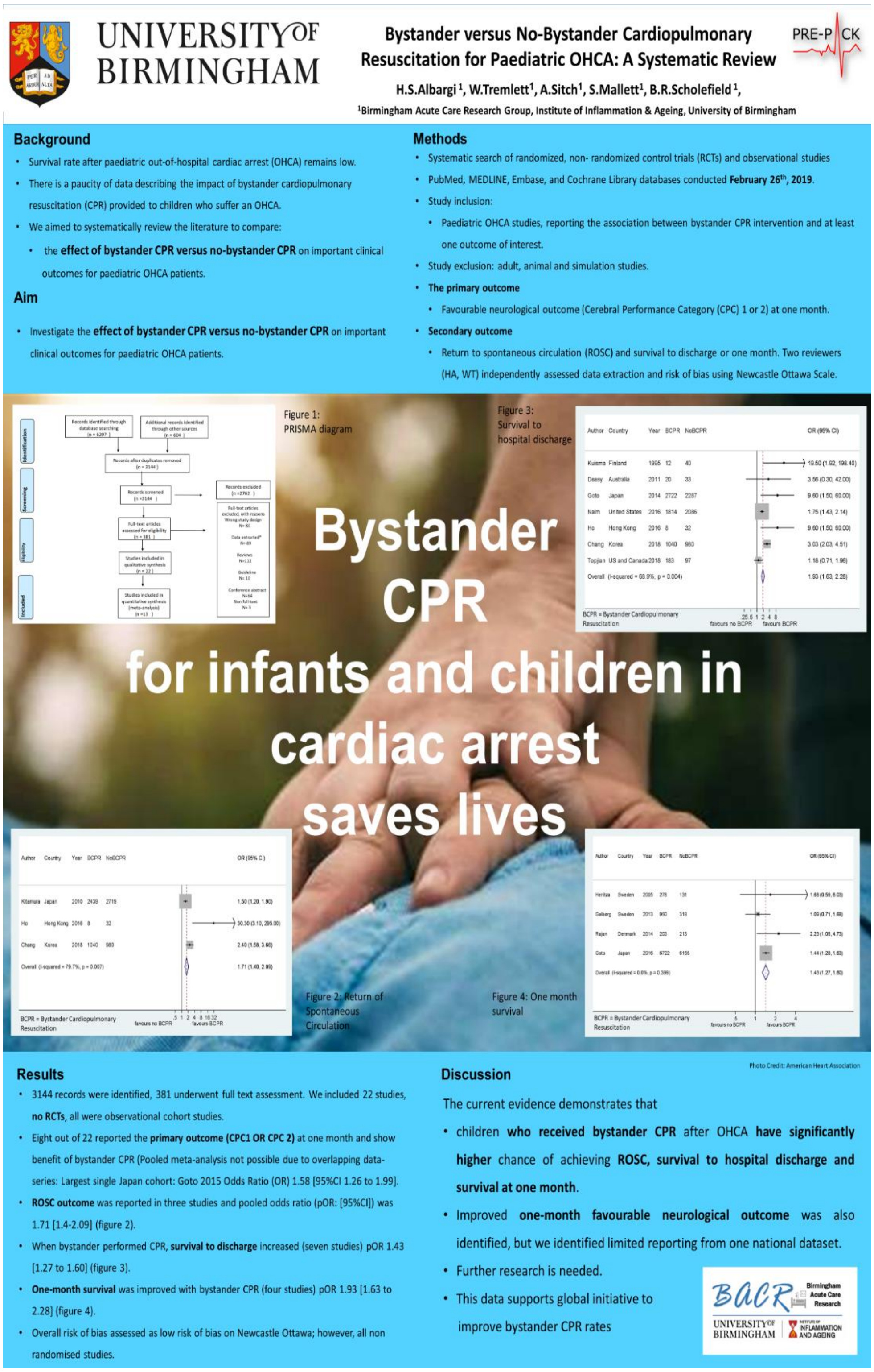
Second, in the UK, the paediatric OHCA survival outcomes were similar to studies with a similar design and sample size. Similar to the findings of the systematic review, a better odds of achieving ROSC existed when BCPR was performed; however, survival to hospital discharge did not show improvement when BCPR was performed compared to no BCPR. These findings were explainable by the large sample of the unwitnessed cases who received BCPR, which suggested that BCPR was not performed immediately after the OHCA event and therefore limited the impact of the BCPR on survival to hospital discharge.

Third, the rate of BCPR was higher in our study than in most paediatric OHCA studies included in the systematic review, and the BCPR rate increased from 69% in 2014 to 74% in 2018. This suggests an improvement in public awareness and BCPR training in England. However, the downside was that only one third of the OHCA cases who received BCPR were witnessed. This therefore suggests that further research is needed to identify the barriers that prevent witness bystanders from performing BCPR.

Finally, we identified a variation in the BCPR rate across EMS regions. Some EMS regions did not submit their data yearly, and the effect of SES factors on EMS regions, such as the level of deprivation and ethnicity, could partially explain this finding. Examining the geographical impact on the variation of BCPR across EMS regions and the performance of the EMS dispatch and responders might introduce other causes responsible for the BCPR variation.

8 Appendix

Appendix 8-1



Appendix 8-2

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 31
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 32-33
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 34
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 34
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 35
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 35
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 35
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 37-39
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 39

Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 37-38
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 39
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 40
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 40-41
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 40
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 40
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 40
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 40
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 40-41
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 40
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 40

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 41-42
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 43
Study characteristics	17	Cite each included study and present its characteristics.	Page 43-44
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 55
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 46-53
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 54-55
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 50-53
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 55
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 48-50
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 57-60
	23b	Discuss any limitations of the evidence included in the review.	Page 61
	23c	Discuss any limitations of the review processes used.	Page 61

	23d	Discuss implications of the results for practice, policy, and future research.	Page 61-62
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 35
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 35
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

Appendix 8-3

PubMed search strategy:	Cardiac arrest OR heart arrest OR heart collapse OR Cardiorespiratory arrest OR Cardiopulmonary arrest	Infan* or baby or baby* or babies or toddler* or kid or kids or child or child* or children* or schoolchild* or schoolchild or school child or school child* or adolescen* or youth* or teen* or pediatric* or paediatric* or peadiatric	Out- of hospital OR pre-hospital OR OHCA OR out of hospital OR out hospital	Resuscitation OR Cardiopulmonary resuscitation OR Heart message		TOTAL
1	98119	4223591	258621	118038		4698369
2	X	X				16326
3	X		X			8761
4	X			X		23935
5		X	X			74329
6		X		X		32076
7			X	X		8508
8	X	X	X			1431
9	X		X	X		5764
10		X	X	X		1858
11	X	X	X	X		855

Pubmed	Cardiac arrest OR heart arrest OR heart collapse OR Cardiorespiratory arrest OR Cardiopulmonary arrest.ti,ab.	Resuscitation OR Cardiopulmonary resuscitation OR Heart massage.ti,ab.	bystander* OR lay-person OR lay person OR witness OR rescue breath*.ti,ab.	bystander* OR lay-person OR lay person OR witness OR rescue breath*	Total
	99510	770917	25826	25927	
Final search					1728

Medline	Cardiac arrest OR heart arrest OR heart collapse OR Cardiorespiratory arrest OR Cardiopulmonary arrest.ti,ab.	Resuscitation OR Cardiopulmonary resuscitation OR Heart massage.ti,ab.	bystander* OR lay-person OR lay person OR witness OR rescue breath*	Total
	48371	63350	13696	
Final search				1357

Embase Database	exp heart arrest/ or exp heart failure/ or exp cardiopulmonary arrest/ or exp experimental heart arrest/ or exp "out of hospital cardiac arrest"/ or exp sudden cardiac death/	exp resuscitation/	exp pediatrics/	child/	infant/	adolescent/	Total
1	445230	101658	97271	1547781	545669	1404893	4142502
2	X	X					34886
3	X		X				1244
4	X			X			16718
5	X				X		8446
6	X					X	11678
7	X	X	X				280
8	X	X	X	X			137
9	X	X	X	X	X		50
10	X	X	X	X	X	X	19
11		X	X				1450
12		X		X			6264
13		X			X		3993
14		X				X	3397
15		X	X	X			514
16		X	X	X	X		153
17		X	X	X	X	X	51
18			X	X			44290
19			X		X		10800
20			X			X	18966
21			X	X	X		7017
22			X	X	X	X	3251
23				X	X		266016
24				X		X	619751
25				X	X	X	144316
26					X	X	154867

EMBASE	Cardiac arrest OR heart arrest OR heart collapse OR Cardiorespiratory arrest OR Cardiopulmonary arrest.ti,ab.	Resuscitation OR Cardiopulmonary resuscitation OR Heart massage.ti,ab.	bystander* OR lay-person OR lay person OR witness OR rescue breath*	Total
	78685	127803	31881	
Final search	[redacted]			2996

Cochrane Library	MeSH descriptor: [Heart Arrest] explode all trees	MeSH descriptor: [Pediatrics] explode all trees	MeSH descriptor: [Cardiopulmonary Resuscitation] explode all trees	child	infant	adolescent	out of hospital	Heart arrest	Cardiac arrest OR heart arrest OR heart collapse OR Cardiorespiratory arrest OR Cardiopulmonary arrest	Infan* or baby or baby* or babies or toddler* or kid or kids or child or child* or children* or schoolchild* or or schoolchild or school child or school child* or adolescen* or youth* or teen* or pediatric* or paediatric* or peadiatric	
1-	1657	611	943	129627	42453	118948	23836	3445	4592	239915	
2-	X	X									9
3-	X		X								517
4-	X			X							95
5-	X				X						56
6-	X					X					127
7-	X						X				484
8-	X									X	218
9-	X	X	X								7
10-	X	X	X				X				0
11-	X		X							X	105
12-			X				X				285

Cochrane	Cardiac arrest OR heart arrest OR heart collapse OR Cardiorespiratory arrest OR Cardiopulmonary arrest.ti,ab.	Resuscitation OR Cardiopulmonary resuscitation OR Heart massage.ti,ab.	bystander* OR lay-person OR lay person OR witness OR rescue breath*	Total
	4502	6668	1475	
Final search				215

Appendix 8-4

Group: Paper:

Assessment of quality of a cohort study – Newcastle Ottawa Scale	
Selection (tick one box in each section)	
1. Representativeness of the intervention cohort a) truly representative of the average, elderly, community-dwelling resident ★ b) somewhat representative of the average, elderly, community-dwelling resident ★ c) selected group of patients, e.g. only certain socio-economic groups/areas d) no description of the derivation of the cohort	☐ ☐ ☐ ☐
2. Selection of the non intervention cohort a) drawn from the same community as the intervention cohort ★ b) drawn from a different source c) no description of the derivation of the non intervention cohort	☐ ☐ ☐
3. Ascertainment of intervention a) secure record (eg health care record) ★ b) structured interview ★ c) written self report d) other / no description	☐ ☐ ☐ ☐
4. Demonstration that outcome of interest was not present at start of study a) yes ★ b) no	☐ ☐
Comparability (tick one or both boxes, as appropriate)	
1. Comparability of cohorts on the basis of the design or analysis a) study controls for age, sex, marital status ★ b) study controls for any additional factors (e.g. socio-economic status, education) ★	☐ ☐
Outcome (tick one box in each section)	
1. Assessment of outcome a) independent blind assessment ★ b) record linkage ★ c) self report d) other / no description	☐ ☐ ☐ ☐
2. Was follow up long enough for outcomes to occur a) yes, if median duration of follow-up >= 6 month ★ b) no, if median duration of follow-up < 6 months	☐ ☐
3. Adequacy of follow up of cohorts a) complete follow up: all subjects accounted for ★ b) subjects lost to follow up unlikely to introduce bias: number lost <= 20%, ★ or description of those lost suggesting no different from those followed c) follow up rate < 80% (select an adequate %) and no description of those lost d) no statement	☐ ☐ ☐ ☐

NB Underlined text 'customised' for the intervention being reviewed

NOS – CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort (NB exposure = intervention)

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the study sample from some general population. For example, subjects derived from groups likely to contain exposed people are likely to be representative of exposed individuals, while they are not representative of all people the community.

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3) Ascertainment of Exposure

Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

A maximum of 2 stars can be allotted in this category.

OUTCOME

2) Assessment of Outcome

For some outcomes, reference to the medical record is sufficient to satisfy the requirement for confirmation. This may not be adequate for other outcomes where reference to specific tests or measures would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (health records, etc.) ☆
b) Record linkage (e.g. identified through ICD codes on database records) ☆
c) Self-report (i.e. no reference to original health records or documented source to confirm the outcome)
d) No description.

3) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins.

4) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet

Appendix 8-5

Table 8-1 Studies reported the type of bystander CPR

Author	Total	Conventional		Compression only		Rescue breathing	
	N	N	%	N	%	N	%
Kitamura 2010	2439	1551	30	888	17	nr[a]	nr
Abe 2012	2461	1463*	50.4	nr	nr	988	40.6
Akahane 2012	758	397	22.3	304	17.1	57	3.2
Goto 2014	2019	855	31.7	1101	40.8	63	2.3
Goto 2016	6722	3122	46.4	3250	48.3	350	5.2
Fukuda 2016	1150	417	36.2	733	63.8	nr	nr
Naim 2017	1411	697	49.3	714	50.7	nr	nr

[a]Not reported

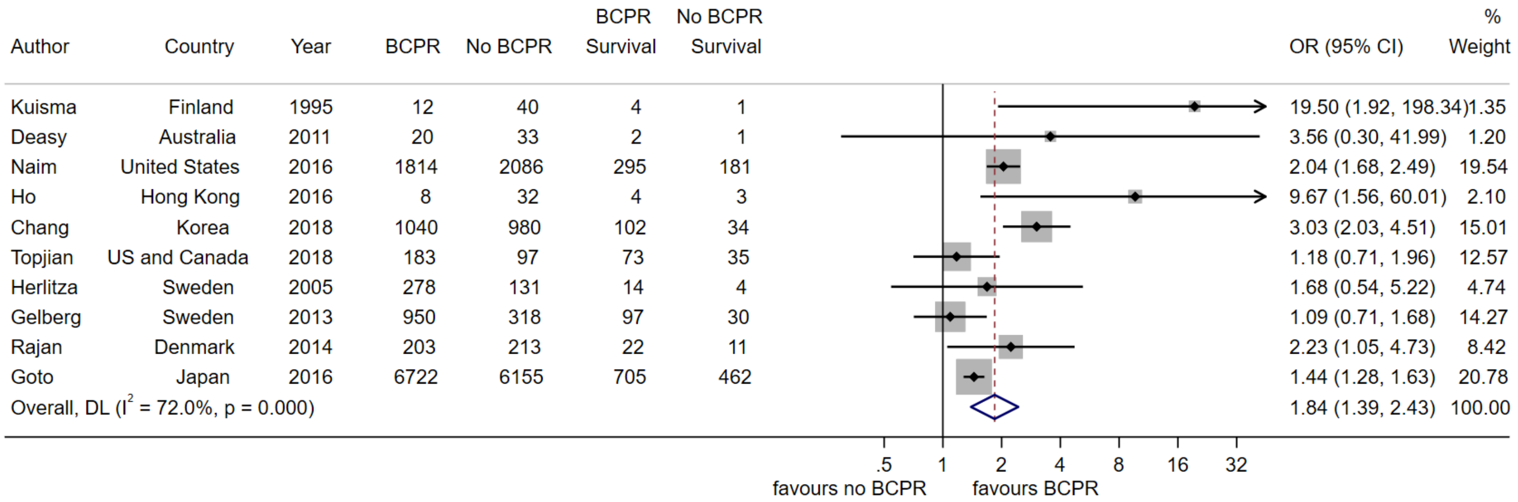


Figure 8-1 Pooled analysis of odds of survival to one month and survival to hospital discharge combined

Appendix 8-7

Variables	Code	Justification of adjusting data	Definition	Data missing	Format of data analysis
age	Clg_Age	Type of cardiac arrest different by age, Younger children are more likel to have parent/guardian with them, so a witness to the CA and potentially Bystander CPR compared to teenager with friends	Patient age : Age is firstly calculated using date of birth and then EMS estimated age was used if DOB is missing. The value is truncated to 1 decimal place. The actual age in years needs to be calculated using clg_AgeUnit. For example, if clg_Age=6 and clg_AgeUnit=2 (2=month), then the age=0.5 year. Note: Any derived age in years out of a reasonable range (0-120) is recoded as missing.	No data missing - Create a graph show the distribution of age by the year of arrest. - A graph show the distribution of age by bystander CPR status and survival outcome. What test am I going to use. Mean and ST or median and IQR. Why I choose one over the other eg. Create histogram or plot	Continuous If grouped in analysis, then what would be grouping e.g. <1 year, > 1year? Categorical Utstein age: 0-1yr, >1yr to 4 yrs, >4yrs to 8yrs, >8-12 yrs, 12-18yrs
Aetiology	clg_InitAetiology	Infant patients are prone to SIDS compare to older age group	Initial aetiology of cardiac arrest	Data missing: 6% Create a graph showing the distribustion of aetiology by age,sex and bystander CPR rate	If grouped in analysis. Type of aetiology e.g. Medical, trauma, drowning, drug overdose, asphyxia,Exsanguination,Electrocution and non-cardiac Catagorical : Medical or Trauma Medical include: drug overdose,asphyxia
bystander	clg_CPRLay	bystander CPR associated with better outcome	Bystander commenced CPR	9% missing create graph showing distribution of bystander CPR with survival outcome	categorical :bystander cpr vs no bcpr
Witnessed	clg_Wit	Witnessed patient more likely to receive bystander CPR compared to unwitnessed	Occurrence witnessed by a layperson	9% missing data Create a graph showing the distribution of witness status by bystander rate and survival	Categorical: Witnessed, Unwitnessed
Rhythm	clg_InitRhythm	younger children more likely to have asystole compare to older children	Initial cardiac arrest rhythm	15% missing data - Create a graph showing the distribution of rhythm by bastander rate and survival	If grouped in analysis: - shockable including (VF/VT,VF,Pulseless VT,AED shockable) -

					Nonshockable including (Asystole,PEA,AED nonshockable) -other including Bradycardia,other)
Sex	clg_Sex	Female children receive bystander cpr more than male	Patient sex	2.6% missing data - Create graph showing the distribution of sex by bystander rate and survival outcome - Create a graph showing the distribution of sex by age	catagorical: Male or Female - keep
Arrest location	clg_EMSLoc	Children get cardiac arrest in home more than public places - Bystander resus is low in areas where the level of education is low	location where the arrest occur	Data missing is unknown Create a graph showing the distribution of arrest location by bystander rate and survival	Categorical : Low, High socioeconomic level
EMS date	clg_EMSDate	OHCA is common in winter compare to other seasons and survival are is low	Date of EMS call	No missing data - Create a graph showing the distribution of ems date by bystander rate - Create a graph showing the distribution of ems date by survival outcome - Create a graph showing the distribution of ems date by Aetiology	Categorical: Winter ,autumn, Spring, summer
EMSTime	clg_EMSTime	Survival rate is lower during night	Time of EMS call	4.3 missing data - Create a graph showing the distribution of ems time by bystander rate and survival - Create a graph showing the distribution of ems time by ems date and survival	Categorical : Night and daytime based on EMS shift or hospital shift ? continous : 24 hrs eg. 01:23:18,12:10:18
PADUsed	clg_PADUsed		Public access defibrillator used by the public	45% missing data	Categorical: yes /no
ROSCPreEMS	clg_ROSCPreEMS		Was a ROSC noted on arrival of EMS staff	48% missing data	Categorical: yes, no

DNAR	clg_DNAR		Do not attempt resuscitation order in place	60% missing data	Categorical: yes, no
Defib	clg_Defib		Attempted defibrillation of the patient	44% missing data	Categorical: yes, no
ROSCPeriEMS	clg_ROSCPeriEMS		ROSC at any time	33% missing data	Categorical: yes, no
ROSCHosp	clg_ROSCHosp		ROSC at hospital handover	10% missing data	Categorical: yes, no
ROLE	clg_ROLE		Death confirmed by EMS	38% missing data	Categorical: yes, no or
Discharged	clg_Discharged		Survival to discharge	17% missing data	Categorical: yes, no
DischargedDate	clg_DischargedDate		Date discharged	96% missing data	
ArrestTime	clg_ArrestTime		Time of witnessed cardiac arrest by bystander or EMS	93% missing data	Continuous
ROSCTime	clg_ROSCTime		Time of ROSC	91% missing data	Continuous

EMS; Emergency medical services ; PAD; public access defibrillation;ROSC; return to spontaneous circulation ;DNAR; Do not attempt resuscitation; ROLE; recognition of life extinct

Appendix 8-8

Table 8-2 Sensitivity analysis of survival to hospital discharge for total group and EMS regions

			Sensitivity Analysis 1: All missing data reported as 'survived'					Sensitivity Analysis 2: All missing data reported as 'died'				
	Total	N (%) of cases missing survival outcome	Survived		Died		p-value	Survived		Died		P value[b]
	N		N	%	N	%		N	%	N	%	
Total[a]	2862	490(17.1)	750	26.2	2112	73.8		260	9.0	2602	91%	
EMS regions							<0.001					0.056
EMS1	164	95(58.0)	110	67.1	54	32.9		15	9.1	149	90.9	
EMS2	244	27(11.0)	47	19.3	197	80.7		20	8.2	224	91.8	
EMS3	590	35(6.0)	90	15.3	500	84.7		55	9.3	535	90.7	
EMS4	199	93 (46.7)	109	54.8	90	45.2		16	8.0	183	92.0	
EMS5	405	20(5.0)	58	14.3	347	85.7		38	9.4	367	90.6	
EMS6	121	95(78.5)	100	82.6	21	17.4		5	4.1	116	95.9	
EMS7	250	50((20)	63	25.2	187	74.8		13	5.2	237	94.8	
EMS8	296	24(8.1)	49	16.6	247	83.4		25	8.4	271	91.6	
EMS9	402	41(10.1)	92	22.9	310	77.1		51	12.7	351	87.3	
EMS10	191	10(5.2)	32	16.8	159	83.2		22	11.5	169	88.5	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Appendix 8-9

Table 8-3 Sensitivity analysis of ROSC at anytime for total group and EMS regions

			Sensitivity Analysis 1: All missing data reported as 'achieved ROSC at anytime'					**Sensitivity Analysis 2: All missing data reported as 'did not achieve ROSC at anytime'**				
	Total	**N (%) of cases missing ROSC at anytime**	**ROSC at anytime**		**Did not achieve ROSC at anytime**		**p-value**	**ROSC at anytime**		**Did not achieve ROSC at anytime**		**P value[b]**
	N		**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Total[a]	2862	274(9.5)	921	32.2	1941	67.8		647	22.6	2215	77.4	
EMS regions												
EMS1	164	2(1.2)	44	26.8	120	73.2		42	25.6	122	74.4	
EMS2	244	0(0)	49	20.1	195	79.9		49	20.1	195	79.9	
EMS3	590	4(0.6)	137	23.2	453	76.8		133	22.5	457	77.5	
EMS4	199	76(38.2)	147	73.9	52	26.1	<0.001	71	35.7	128	64.3	<0.001
EMS5	405	0(0)	76	18.8	329	81.2		76	18.8	329	81.2	
EMS6	121	41(33.8)	55	45.5	66	54.5		14	11.6	107	88.4	
EMS7	250	27(10.8)	109	43.6	141	56.4		82	32.8	168	67.2	
EMS8	296	6(2.0)	73	24.7	223	75.3		67	22.6	229	77.4	
EMS9	402	0(0)	90	22.4	312	77.6		90	22.4	312	77.6	
EMS10	191	118(61.7)	141	73.8	50	26.2		23	12.0	168	88.0	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Appendix 8-10

Table 8-4 Sensitivity analysis of hospital ROSC for total group and EMS regions

			Sensitivity Analysis 1: All missing data reported as 'Hospital ROSC"					**Sensitivity Analysis 2: All missing data reported as 'did not achieve Hospital ROSC**				
	Total	**N (%) of cases missing Hospital ROSC**	**Hospital ROSC**		**Did not achieve Hospital ROSC**		**p-value**	**Hospital ROSC**		**Did not achieve Hospital ROSC**		**P value[b]**
	N		**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Total[a]	2862	284(9.9)	797	27.9	2065	72.1		513	17.9	2349	82.1	
EMS regions												
EMS1	164	7(4.2)	47	28.7	117	71.3		40	24.4	124	75.6	
EMS2	244	0(0)	40	16.4	204	83.6		40	16.4	204	83.6	
EMS3	590	4(0.6)	123	20.8	467	79.2	<0.001	119	20.2	471	79.8	
EMS4	199	76(38.2)	97	48.7	102	51.3		21	10.6	178	89.4	<0.001
EMS5	405	0(0)	71	17.5	334	82.5		71	17.5	334	82.5	
EMS6	121	43(35.5)	48	39.7	73	60.3		5	4.1	116	95.9	
EMS7	250	44(17.6)	100	40.0	150	60.0		56	22.4	194	77.6	
EMS8	296	8(2.7)	68	23.0	228	77.0		60	20.3	236	79.7	
EMS9	402	1(0.2)	81	20.1	321	79.9		80	19.9	233	80.1	
EMS10	191	101(52.8)	122	63.9	69	36.1		21	11.0	170	89.0	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Appendix 8-11

Table 8-5 Demographic of paediatric OHCA association with witness status

	Total		**Witnessed**		**Unwitnessed**		**p-value[b]**
	N	**%**	**N**	**%**	**N**	**%**	
Total[a]	2270	100	776		1494		
Age	2270	100					
(median, IQR)			5.3 (1, 13.3)		2.3 (.3, 10.2)		<0.001
0-1 year	761	33.5	195/776	25.1	566/1494	37.9	
1-4 years	486	21.5	161/776	20.7	325/1494	21.8	
4-8 years	260	11.4	100/776	12.9	160/1494	10.7	
8-12 years	229	10.1	104/776	13.4	125/1494	8.4	
12-18 years	534	23.5	216/776	27.8	318/1494	21.3	
Sex[c]							
Male	1305	57.5	455/772	58.9	850/1458	58.3	0.77
Female	925	40.7	317/772	41.1	608/1458	41.7	
Aetiology[d]							
Medical	1796	79.1	607/750	80.9	1189/1423	83.6	<0.001
Trauma	143	6.3	83/750	11.1	60/1423	4.2	
Drowning	38	1.7	6/750	0.8	32/1423	2.2	
Drug overdose	24	1.1	11/750	1.5	13/1423	0.9	
Asphyxia	172	7.5	43/750	5.7	129/1423	9.1	
Initial rhythm[e]							
Shockable	136	6.0	103/673	15.3	33/1356	2.4	<0.001
AED[f]							
AED use	35	1.5	19/518	3.7	16/880	1.8	0.033
Time of day[g]							
Daytime	728	32.1	291/720	40.4	437/1410	31.0	<0.001
Season							
Spring	610	26.9	184/776	23.7	426/1494	28.5	0.043
Summer	549	24.2	195/776	25.1	354/1494	23.7	
Autumn	575	25.3	217/776	28.0	358/1494	24.0	
Winter	536	23.6	180/776	23.2	356/1494	23.8	

Table 8-5 (continued) Demographic of paediatric OHCA association with witness status

	Total		Witnessed		Unwitnessed		p-value
	N	**%**	**N**	**%**	**N**	**%**	
Year							
2014	457	20.1	147/776	18.9	310/1494	20.7	0.040
2015	454	20.0	136/776	17.5	318/1494	21.3	
2016	412	18.1	160/776	20.6	252/1494	16.9	
2017	438	19.3	146/776	18.8	292/1494	19.5	
2018	509	22.4	187/776	24.1	322/1494	21.6	
Outcomes[h]							
Survival to hospital discharge	215	9.5	138/687	20.1	77/1302	5.9	<0.001
Any ROSC	510	22.5	290/765	37.9	220/1454	15.1	<0.001
Hospital ROSC	422	18.6	250/755	33.1	172/1433	12.0	<0.001
Pre-hospital ROSC	400	17.6	230/638	36.1	170/1193	14.2	<0.001

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Missing data:

c Sex (n=40)

d Aetiology (n=97)

e Initial rhythm (n=241)

f AED (n=872)

g Time of the day (n=140)

h Survival to hospital discharge (n=281) , any ROSC (n=51),hospital ROSC (n=82),pre-hospital ROSC(n=439)

Appendix 8-12

Table 8-6 Demographic of paediatric OHCA association with initial rhythm

	Total		**Shockable**		**Non-shockable**		**p-value[b]**
	N	**%**	**N**	**%**	**N**	**%**	
Total[a]	2095	100	144		1951		
Age			12.85 (5.6,15.6)		2.9 (.4, 11)		<0.001
(median, IQR)							<0.001
0-1 year	699	33.4	21/144	14.6	678/1951	34.8	
1-4 years	442	21.1	14/144	9.7	428/1951	21.9	
4-8 years	233	11.1	7/144	4.9	226/1951	11.6	
8-12 years	209	10.0	22/144	15.3	187/1951	9.6	
12-18 years	512	24.4	80/144	55.6	432/1951	22.1	
Sex[c]							
Male	1206	58.1	81/142	57.0	1125/1934	58.2	0.79
Female	870	41.9	61/142	43.0	809/1934	41.8	
Aetiology[d]							
Medical	1637	82.0	123/139	88.5	1514/1859	81.4	0.27
Trauma	134	6.7	6/139	4.3	128/1859	6.9	
Drowning	36	1.8	2/139	1.4	34/1859	1.8	
Drug overdose	24	1.2	2/139	1.4	22/1859	1.2	
Asphyxia	167	8.3	6/139	4.3	161/1859	8.7	
AED[e]							
AED use	33	2.5	13/99	13.1	20/1203	1.7	<0.001
Time of day[f]							
Daytime	661	33.6	65/138	47.1	596/1830	32.6	<0.001
Season							
Spring	574	27.4	35/144	24.3	539/1951	27.6	0.31
Summer	485	23.2	31/144	21.5	454/1951	23.3	
Autumn	532	25.4	46/144	31.9	486/1951	24.9	
Winter	504	24.0	32/144	22.2	472/1951	24.2	
Year							
2014	400	19.1	32/144	22.2	368/1951	18.9	0.57
2015	392	18.7	31/144	21.5	361/1951	18.5	
2016	403	19.2	27/144	18.8	376/1951	19.3	
2017	422	20.1	23/144	16.0	399/1951	20.5	
2018	478	22.9	31/144	21.5	447/1951	22.9	

Table 8-6 (continued) Demographic of paediatric OHCA association with initial rhythm

	Total		Shockable		Non-shockable		p-value
	N	**%**	**N**	**%**	**N**	**%**	
Outcomes[g]							
Survival to hospital discharge	161	7.7	56/120	46.7	105/1712	6.1	<0.001
Any ROSC	431	20.5	85/143	59.4	346/1940	17.8	<0.001
Hospital ROSC	342	16.3	76/141	53.9	266/1909	13.9	<0.001
Pre-hospital ROSC	349	16.6	66/114	57.9	283/1627	17.3	<0.001

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.
Missing data:
c Sex (n=19)
d Aetiology (n=97)
e AED (n=793)
f Time of the day (n=127)
g Survival to hospital discharge (n=263) , any ROSC (n=12),hospital ROSC (n=45),pre-hospital ROSC(n=354)

Appendix 8-13

Table 8-7 Association of paediatric OHCA outcomes with age

	Total		<1 year		1-4 years		4-8 years		8-12 years		12-18 years		p-value[b]
	N	%	N	%	N	%	N	%	N	%	N	%	
Total[a]	2363	100	790	33.4	502	21.2	276	11.6	242	10.2	553	23.4	
Outcomes													
Survival to hospital discharge	225	100	61/681	9.0	49/428	11.4	30/245	12.2	24/217	11.1	61/495	12.3	0.37
Any ROSC	523	100	116/779	14.9	97/483	20.1	64/259	24.7	63/229	27.5	183/539	34.0	<0.001
Hospital ROSC	431	100	108/773	14.0	71/473	15.0	47/252	18.7	52/226	23.0	153/530	28.9	<0.001
Pre-hospital ROSC	412	100	91/612	14.9	78/411	19.0	49/217	22.6	51/194	26.3	143/455	31.4	<0.001

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Appendix 8-14

Table 8-8 Association of BCPR and survival outcome by the status of witness and initial rhythm

	BCPR					no-BCPR				
	Survive to discharge				p-value	Survive to discharge				p-value[b]
	Yes		No			Yes		No		
Total[a]	N	%	N	%		N	%	N	%	
Status of witness										
Witnessed	100	20.7	382	79.2	<0.001	38	18.5	167	81.4	<0.001
Unwitnessed	49	5.4	862	94.6		28	7.2	363	92.8	
Initial rhythm										
Shockable	43	46.2	50	53.8	<0.001	13	48.1	14	51.9	<0.001
Nonshockable	73	6.0	1138	94.0		32	6.4	469	93.6	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

Appendix 8-15

Table 8-9 Association of BCPR and ROSC at anytime by the status of witness

	BCPR					**no-BCPR**				
	ROSC at anytime				**p-value**	**ROSC at anytime**				**p-value[b]**
	Yes		**No**			**Yes**		**No**		
Total[a]	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Status of witness										
Witnessed	218	40.3	323	59.7	<0.001	72	32.1	152	67.9	<0.001
Unwitnessed	163	16.3	835	83.7		57	12.5	399	87.5	
Initial rhythm										
Shockable	72	63.7	41	36.3	<0.001	13	43.3	17	56.7	<0.001
Non-shockable	259	19.1	1097	80.9		87	14.9	497	85.1	

[a]Results expressed as number (percent). [b]Chi2 or Fisher exact test was used for categorical variable.

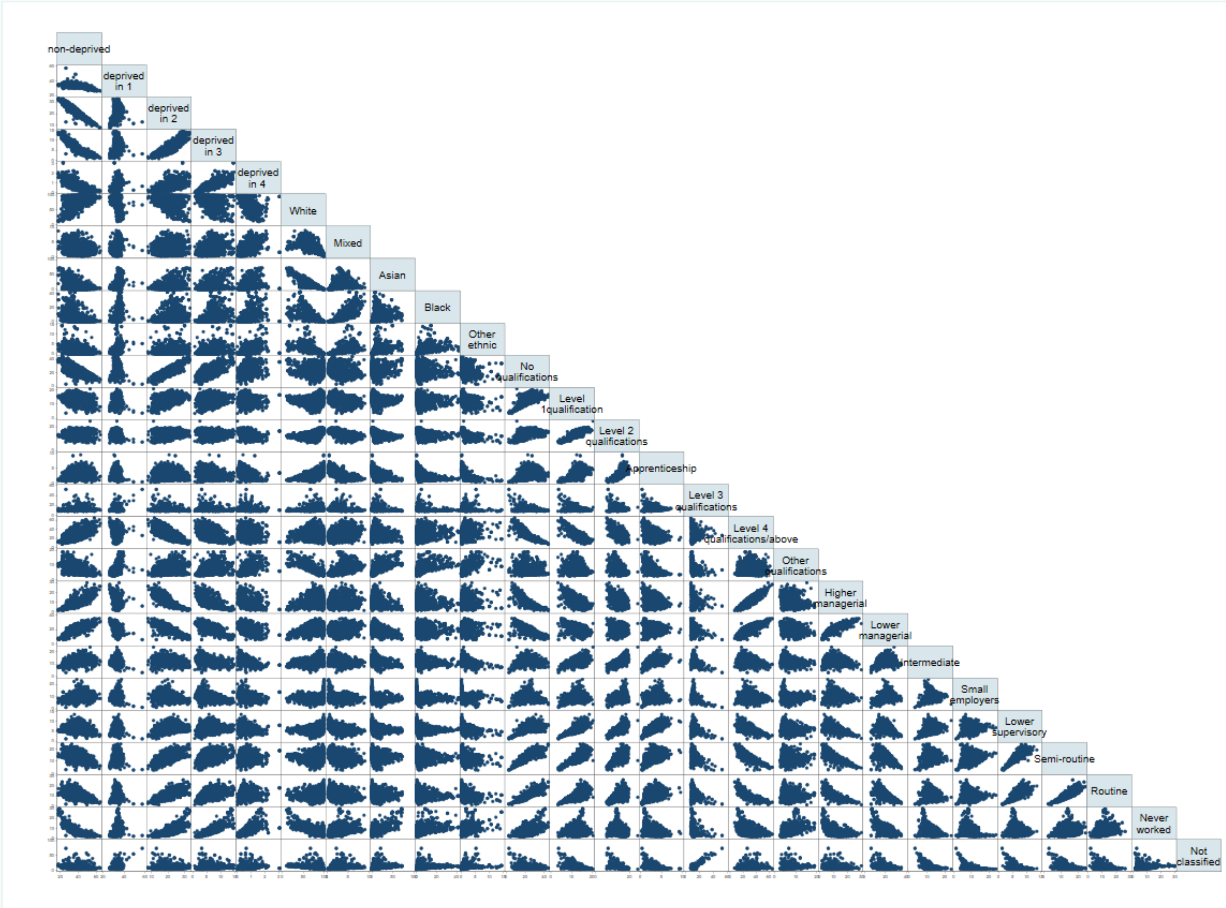


Figure 8-2 Correlation between deprivation, ethnicity, qualification and work level

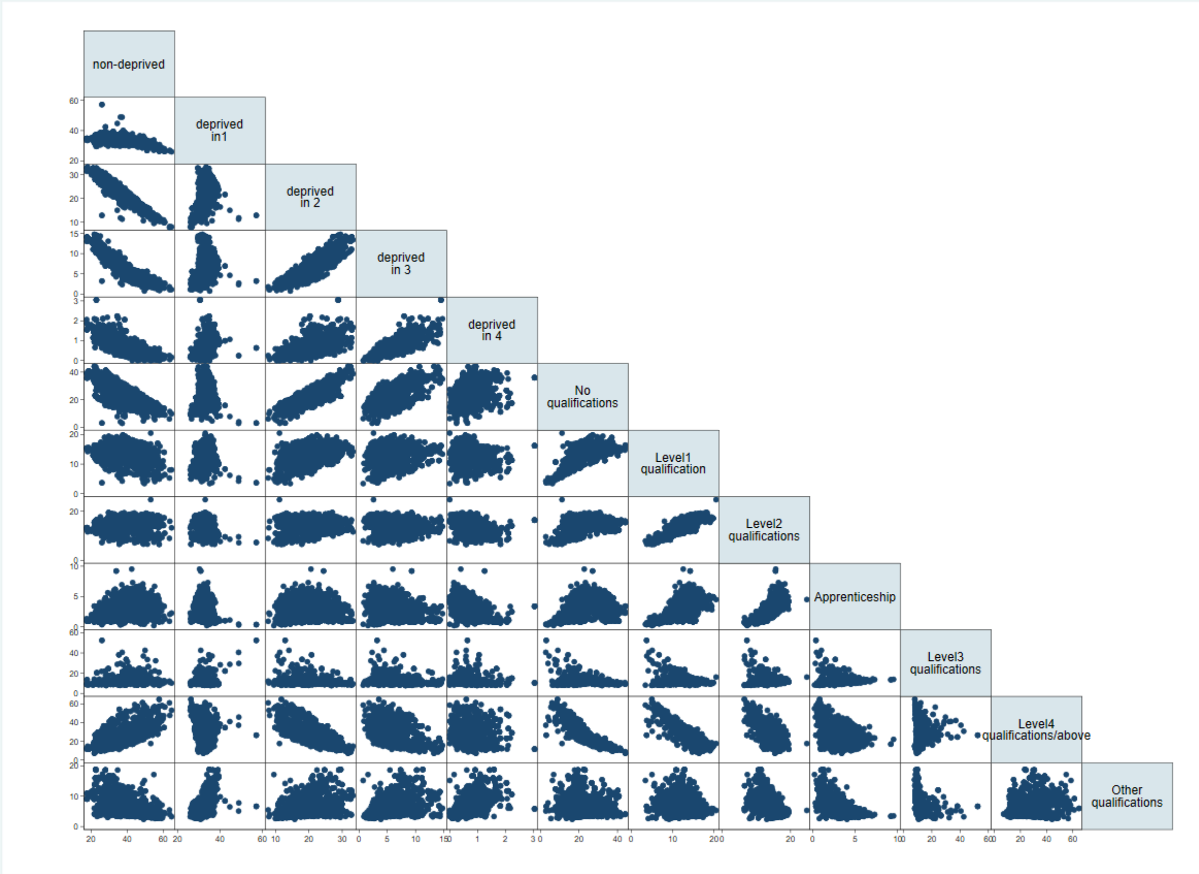


Figure 8-3 Correlation between deprivation dimensions and qualification

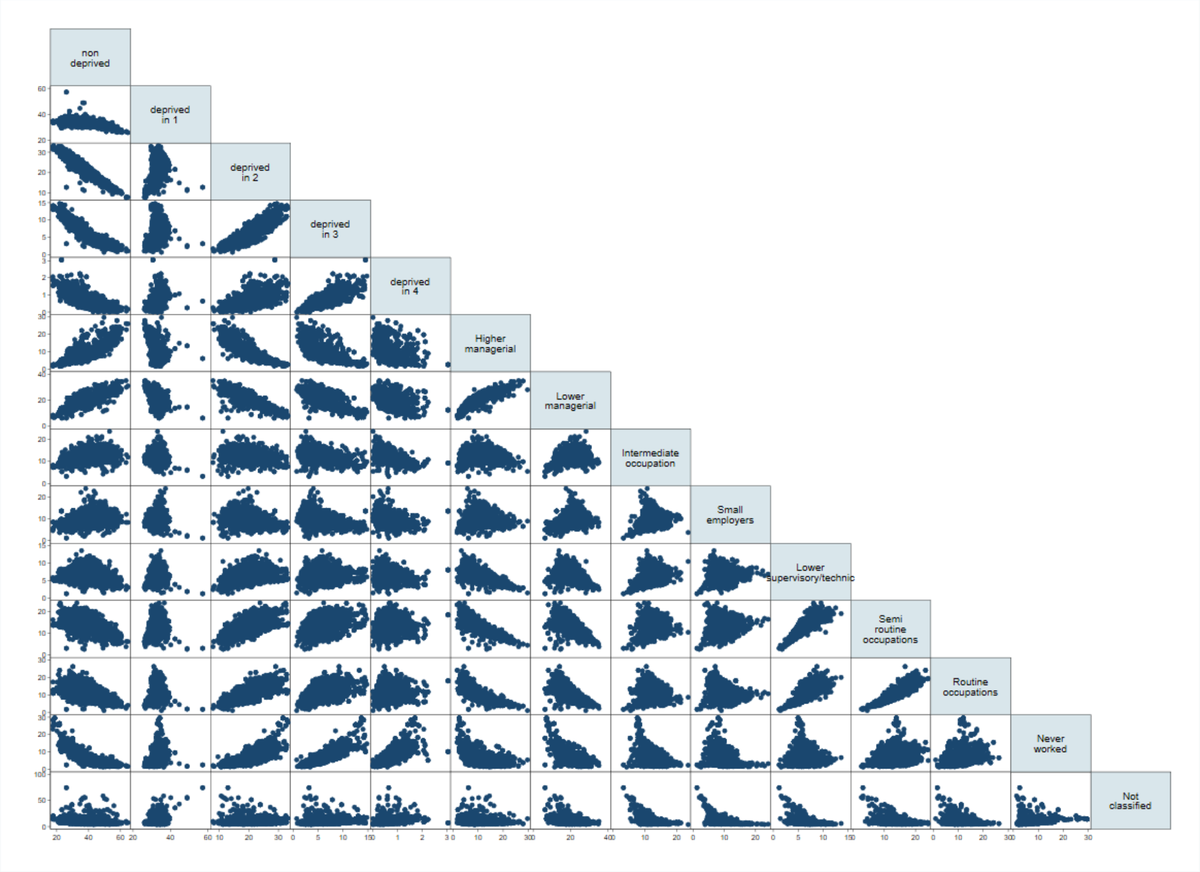


Figure 8-4 Correlation between deprivation dimensions and work level

Table 8-10 Correlation between the deprivation dimensions and qualification level

	Non-deprived		Deprived in 1		Deprived in 2		Deprived in 3		Deprived in 4	
	Correlation	P value	Correlation	P value	Correlation	P value	Correlation	P value	Correlation	P value
No qualification	-0.66	0.0001	0.00	0.97	0.83	0.0001	0.63	0.0001	0.24	0.0001
Qualification 1	-.026	0.0001	-0.03	0.13	0.42	0.0001	0.15	0.0001	-0.14	0.0001
Qualification 2	0.20	0.0001	-0.30	0.0001	-0.0008	0.68	-028	0.0001	-0.52	0.0001
Apprenticeship	0.33	0.0001	-0.37	0.0001	-0.14	0.0001	-0.39	0.0001	-0.60	0.0001
Qualification 3	0.21	0.0001	0.02	0.26	-0.25	0.0001	-0.23	0.0001	-0.19	0.0001
Qualification 4	0.53	0.0001	-0.07	0.0005	-0.69	0.0001	-0.42	0.0001	-0.05	0.0001
Other qualification	-0.52	0.0001	0.63	0.0001	0.32	0.0001	0.45	0.0001	0.64	0.0001

Table 8-11 Correlation between the deprivation dimensions and Work level

	Non-deprived		Deprived in 1		Deprived in 2		Deprived in 3		Deprived in 4	
	Correlation	P value	Correlation	P value	Correlation	P value	Correlation	P value	Correlation	P value
Higher managerial	0.75	0.0001	-0.30	0.0001	-0.83	0.0001	-0.63	0.0001	-0.32	0.0001
Low managerial	0.83	0.0001	-0.36	0.0001	-0.86	0.0001	-0.75	0.0001	-0.46	0.0001
Intermediate	0.42	0.0001	-0.27	0.0001	-0.31	0.68	-0.49	0.0001	-0.56	0.0001
Small employers	0.31	0.0001	0.02	0.27	-0.32	0.0001	-0.41	0.0001	-0.25	0.0001
Lower supervisory/technic	-0.14	0.0001	-0.12	0.0001	0.32	0.0001	0.04	0.04	-0.26	0.0001
Semi routine	-0.14	0.0001	-0.02	0.21	0.63	0.0001	0.36	0.0001	-0.001	0.94
Routine	-0.54	0.0001	-0.03	0.08	0.71	0.0001	0.50	0.0001	0.12	0.0001
Never worked	-0.82	0.0001	0.37	0.0001	0.75	0.0001	0.86	0.0001	0.77	0.0001
Not classified	-0.27	0.0001	0.44	0.0001	0.09	0.0001	0.25	0.0001	0.38	0.0001

Appendix 8-17

Table 8-12 Odds ratio of BCPR in socioeconomic (Model 1)

Total n=2343	**OR (95% CI)**	**P value**
Socioeconomic factors		
Non-deprived	1.01 (0.99-1.02)	0.12
White ethnicity	1.01 (1.001-1.02)	0.0001

Appendix 8-18

Table 8-13 Odds ratio of BCPR in socioeconomic and prehospital factors (Model 2)

Total n=1856	**OR (95% CI)**	**P value**
Pre-hospital factors		
Age	0.99 (0.97-1.01)	0.58
Sex	0.99 (0.81-1.22)	0.96
Aetiology		
Medical	**Reference**	
Trauma	0.60 (0.41-0.88)	0.009
Drowning	0.81 (0.37-1.74)	0.59
Drug overdose	0.62 (0.37-1.43)	0.26
Asphyxia	1.01 (0.69-1.49)	0.92
EMS region		
EMS 1	**Reference**	
EMS 2	0.82 (0.47-1.42)	0.48
EMS 3	0.77 (0.48-1.22)	0.27
EMS 4	1.25 (0.66-2.33)	0.48
EMS 5	1.20 (0.83-1.73)	0.31
EMS 6	1.78 (0.36-8.75)	0.47
EMS 7	5.61 (1.95-16.14)	0.001
EMS 8	1.23 (0.77-1.95)	0.37
EMS 9	0.63 (0.45-0.87)	0.006
EMS 10	0.99 (0.49-2.00)	0.99

Witnessed	0.65 (0.52-0.80)	0.0001
Shockable rhythm	1.58 (1.02-2.45)	0.04
Time of the day	0.91 (0.73-1.2)	0.40
Seasons		
Spring		
Summer	0.87 (0.99-1.03)	0.07
Autumn	1.03 (1.001-1.01)	0.01
Winter	0.92 (0.41-1.31)	0.30
Year of incidence		
2014		
2015	0.97 (0.70-1.35)	0.90
2016	1.31 (0.93-1.83)	0.11
2017	1.06 (0.76-1.48)	0.70
2018	1.36 (0.96-1.92)	0.07
Socioeconomic factors		
Non-deprived	1.01 (0.99-1.03)	0.07
White ethnicity	1.01 (1.01-1.02)	0.0001

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