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Clinical Paper

Hospital admissions and pharmacotherapy before out-of-hospital cardiac arrest according to age☆

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ABSTRACT

Background: The underlying etiology of sudden cardiac death varies with age and is likely to be reflected in type and number of healthcare contacts. We aimed to determine the specific type of healthcare contact shortly before out-of-hospital cardiac arrest (OHCA) across ages.
Methods: OHCA patients were identified in the nationwide Danish Cardiac Arrest Register and Copenhagen Medical Emergency Care Unit (2001–2006). We matched every OHCA patients with 10 controls on sex and age. Healthcare contacts were evaluated 30 days before event by individual-level-linkage of nationwide registers.
Results: We identified 16,924 OHCA patients, median age 70.0 years (Q1–Q3: 59–80). OHCA patients had a higher number of hospitalizations and received more pharmacotherapy compared to the control population across all ages (p for difference <0.001). OHCA patients aged 70–79 and 80–89 years had the highest proportion of hospitalizations (70%) and pharmacotherapy (73%), respectively. In general, the association between OHCA and hospitalizations and pharmacotherapy was more pronounced among the youngest OHCA patients compared to controls. OHCA patients in age groups 14–19, 20–29, 30–39 were ~5 times more likely to be in contact with the healthcare service than the control population (p for difference <0.001). Similarly, OHCA patients in the oldest age groups (60–69, 70–79, 80–89, >89) were <2 times more likely to be in contact with the healthcare services shortly before OHCA compared to the control population (p for difference <0.001).
Conclusion: Young OHCA patients are more likely to be in contact with the healthcare services compared with an age and sex matched control population suggestive of traits that make them stand out from the general population.

1. Introduction

Sudden cardiac death (SCD) comprise 18.5% of deaths in the western world and underlines the need for effective preventive strategies.[1] The etiology of SCD varies with age and if preventive strategies are to become more successful in predicting and identifying SCD before an event it is important to examine how age influences the underlying causes of SCD which is likely to be reflected in the type of healthcare contacts (hospital admissions or pharmacotherapy) experienced imminently before an event. For instance atherosclerosis is the primary cause of cardiovascular disease among the elderly ultimately leading to SCD, whereas hypertrophic cardiomyopathy is one of the predominant causes of SCD among young individuals and athletes.[2,3] Predicting and identifying patients at risk of SCD is difficult and is highlighted by the fact that ~50% of all coronary heart disease related deaths have SCD as the first symptom of underlying cardiovascular disease.[3] We have previously been able to demonstrate how the majority of out-of-hospital cardiac arrest (OHCA) patients are in contact with the healthcare services shortly before OHCA which makes them

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eligible for early identification and risk stratification.[4] However, little is known about how age influences the likelihood of being in contact with the healthcare services shortly before OHCA.

The aim of the present nationwide study is to investigate how the type of healthcare contact (hospital admissions and pharmacotherapy) shortly before OHCA is correlated with age. Combining information on age, the number and type of healthcare contact imminently prior to OHCA in relation to current risk stratification tests and knowledge, our findings could alert the attention of physicians towards patient characteristics associated with OHCA across differences in age.

2. Methods

2.1. Databases

All Danish citizens are assigned a permanent, personal, and unique civil registration number which enables individual-level-linkage of nationwide registers. The registers used for the present study include: the National Prescription Register, the Danish National Patient Register, the Danish Cardiac Arrest Register, and the Copenhagen Mobile Emergency Care Unit (MECU). Information on all dispensed prescriptions from Danish pharmacies since 1995 is registered in the National Prescription Register, where drugs are classified according to the Anatomical Therapeutic Chemical (ATC) system. Because the government-financed healthcare system partially reimburse drug expenses, all Danish pharmacies are obliged to register all dispensed drug prescriptions which ensures a valid and accurate register.[5] Included in the Danish National Patient Register is information on all hospital admissions in Denmark since 1978.[6] Each hospital admission is recorded and registered according to the International Classification of Diseases—before 1994 the 8th revision (ICD-8) and from 1994 and onwards the 10th revision (ICD-10).With data from the Integrated Database for the Danish Labour Market we defined socioeconomic status by the individual average annual gross income during the five-year period before OHCA and divided patients into quintiles accordingly.

2.2. Study population

We identified all patients (aged ≥14 years) suffering an OHCA according to the Danish Cardiac Arrest Register and the Copenhagen MECU (2001–2006). Included in both registers are information on time, date, and occurrence of all incidences where an ambulance was dispatched to an OHCA. The Copenhagen MECU covers the central part of Copenhagen (approximately 600,000 inhabitants) where physician manned ambulances systematically records data from all OHCA responses.[7,8] Patients who did not receive cardiopulmonary resuscitation or defibrillation (by the responding ambulance personnel or bystanders) were not classified as OHCA. Furthermore, patients with obvious signs of death were also not classified as an OHCA. In order to evaluate pharmacotherapy and hospital admissions shortly before OHCA to the general Danish population, we matched 10 controls to every OHCA patient on sex and age. Every control was given the same index date as the case they were matched upon. We used a matched case-control study design and applied conditional multivariable logistic regression analyses to determine the association of covariates to OHCA. The control group was identified and matched (1:10) on age and sex using the "Greedy match algorithm".[9] Lastly, parts of the OHCA population (2001–2005) used in the present study have been interrogated previously.[4]

2.3. Pharmacotherapy

From the National Prescription Register we obtained information on the following pharmacotherapy 30 days before OHCA (ATC codes): antidepressants (N06A), sedatives and anxiolytics (N05B, N05C), anti-psychotic agents (N05A), analgesics (including morphine) (N02), bronchial dilators (R02), corticosteroids (systemic) (H02A), antithrombotic agents (B01), cholesterol-lowering agents (C10), anti-angina medication (C01D), angiotensin converting enzyme inhibitors or angiotensin-2 receptor blockers (C09), beta-blockers (C07), diuretics (C03), and digoxin (C01A). Further, patients who claimed at least one prescription for glucose lowering medication up to 30 days before event (ATC:A10) were identified as patients with diabetes requiring medical therapy.

2.4. Hospital admissions

Information on all hospital admissions before the time of OHCA was obtained from the Danish National Patient Register (primary or secondary discharge diagnoses according to ICD-10). We used the discharge diagnoses previously defined in the Charlsons Comorbidity Index, modified for use with ICD-10 to identify hospital admissions.[10,11] We also included information on the following discharge diagnoses: trauma, psychiatric illness (including substance abuse), and any cardiovascular disease(CVD), as done previously.[4] The Charlson Comorbidity Index score presented in Table 1 is calculated with information from hospital discharge diagnoses up to one-year before OHCA.

In order to examine the relationship between very recent healthcare contacts (hospital admissions or pharmacotherapy) and OHCA across age groups, we investigated periods of 30 days before OHCA in the following age groups: 14–39, 40–49, 50–59, 60–69, 70–79, and ≥80.

2.5. Prioritized groups

All patients were divided into four prioritized groups according to the type of healthcare system contact they experienced before OHCA (1–4) with descending priority: (1) cardiovascular hospital admissions, (2) non-cardiovascular hospital admissions, (3) cardiovascular related pharmacotherapy, and (4) non-cardiovascular related pharmacotherapy. Cardiovascular hospital admissions include patients who were admitted to hospital with any CVD or diabetes. Non-cardiovascular hospital admissions include patients admitted with peptic ulcer, trauma, psychiatric illness, liver disease, malignancy, or chronic obstructive pulmonary disease (COPD). Patients without any immediate hospital admissions but with at least one claimed prescription for a cardiovascular related drug (cholesterol-lowering agents, anti-thrombotic agents, anti-angina medication, calcium inhibitors, beta-blockers, digoxin, diuretics, angiotensin converting enzyme inhibitors/angiotensin-II-receptor blockers) were assigned to the cardiovascular related pharmacotherapy group. Patients without any immediate hospital admissions or claimed prescriptions for cardiovascular related pharmacotherapy, but a claimed prescription for one of the following drugs: antidepressants, anxiolytics and sedatives, antipsychotics, analgesics (incl. morphine), bronchial dilators, or corticosteroids, were assigned to the non-cardiovascular related pharmacotherapy group.

2.6. Statistics

We compared binary variables with a chi-square test and continuous variables with the non-parametric Kruskal–Wallis test. Association of covariates to OHCA was investigated by conditional multivariable logistic regression analyses. Association is given as

Table 1
Hospital admissions and pharmacotherapy 30 days before out-of-hospital cardiac arrest for cases and controls.

	OHCA	Control population
N (%)	16,924	169,240
Male, *N* (%)	11,138 (65.8%)	111,380 (65.8%)
Mens age, years (Q1–Q3)	69.0 (58–78)	69.0 (58–78)
Women's age, years (Q1–Q3)	73.0 (62–85)	73.0 (62–85)
Income group (%)		
0 (lowest income quintile)	4092 (24.2)	33,141 (19.6)
1	3991 (23.6)	33,241 (19.6)
2	3781 (22.3)	33,451 (19.8)
3	2919 (17.3)	34,316 (20.3)
4 (highest income quintile)	2141 (12.7)	35,091(20.7)
Mean Charlson Comorbidity Index Score (±SD)	0.6 (±1.0)	0.2 (±0.5)
Hospital admissions		
30 days before OHCA (%)		
Peripheral vascular disease	50 (0.3)	153 (0.1)
Cerebral vascular disease	131 (0.8)	404 (0.2)
Ischemic heart disease	357 (2.1)	653 (0.4)
Myocardial infarction	174 (1.0)	134 (0.1)
Cardiac dysrhythmia	280 (1.7)	507 (0.3)
Heart failure	346 (2.0)	336 (0.2)
Diabetes	968 (5.7)	5193 (3.1)
Peptic ulcer	59 (0.4)	149 (0.1)
Trauma	298 (1.8)	1366 (0.8)
Psychiatric illness	239 (1.4)	337 (0.2)
Liver disease mild/severe	288 (1.7)	45 (0.03)
Malignancy	526 (3.1)	848 (0.5)
COPD	417 (2.5)	411 (0.2)
Pharmacotherapy		
30 days before OHCA (%)		
Antithrombotic agents	1945 (11.5)	12144 (7.2)
Cholesterol lowering drugs	846 (5.0)	5947 (3.5)
Calcium inhibitors	975 (5.8)	7375 (4.4)
Beta-blockers	1357 (8.0)	8185 (4.8)
ACEi/ARB	1930 (11.4)	11791 (7.0)
Diuretics	3150 (18.6)	14443 (8.5)
Digoxin	1065 (6.3)	3598 (2.1)
Anti-angina medication	893 (5.3)	2991 (1.8)
Antidepressants	1526 (9.0)	7730 (4.6)
Sedatives/anxiolytics	2642 (15.6)	12273 (7.3)
Anti-psychotic medication	845 (5.0)	2800 (1.7)
Analgesics(incl. morphine)	3360 (19.9)	16653 (9.8)
Bronchial dilators	2314 (13.7)	7718 (4.6)
Corticosteroids(systemic)	992 (5.9)	2634 (1.4)

Q1–Q3 = inter-quartile range; ±SD = standard deviation; COPD = chronic obstructive pulmonary disease; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker. *p*-value for difference between groups was in all instances <0.05.

odds ratios (OR) and 95% confidence intervals (CI). The predictive power of each model used to determine OHCA and healthcare association was assessed by the *c*-statistic value. Model assumptions were fulfilled unless otherwise specified. All analyses were done using SAS, version 9.1 (SAS institute Inc., Cary, NC, USA). A two-sided *p*-value <0.05 was considered statistically significant.

2.7. Ethics

The Danish Data Protection Agency approved the present study (No. 2008-41-2685). Register-based retrospective studies do not require ethical approval in Denmark.

3. Results

In the period 2001–2006, we identified 16,924 patients who experienced an OHCA according to the Danish Cardiac Arrest Register and the Copenhagen MECU and matched 169,240 controls on age and sex. The median age was 70.0 years (Q1–Q3: 59–80) and men comprised 65.8%. Of the 16,924 OHCA patients we identified 6225 (36.8%) who were not admitted to hospital nor received treatment with the investigated types of concomitant pharmacotherapy 30 days before OHCA.

Shown in Table 1 are characteristics for the OHCA cases and age and sex matched controls. Table 2 shows the basic characteristics including hospital admissions and pharmacotherapy for the case population 30 days before OHCA stratified by age. Among the youngest age groups (14–39 and 40–49 years) we found the highest proportion of patients being admitted to hospital 30 days before OHCA with a psychiatric illness (3.1% and 2.9%, respectively) as well as the highest proportion of patients using antipsychotic medication (8.3% and 8.2%, respectively) (Table 2).

Results from the conditional logistic regression analyses for being admitted to hospital 30 days before OHCA according to age group are shown in Table 3. We found significant associations across all ages between OHCA and a hospital admission for heart failure, psychiatric illness, diabetes, malignancy and COPD. Due to the low number of hospital admissions among the youngest age group (14–39 years) we were mostly unable to evaluate the association between OHCA and hospital admissions, but some associations were found although with wide CI's (Table 3).

The results from the conditional logistic regression analyses on the association between OHCA and pharmacotherapy 30 days before OHCA are shown in Table 4. The strongest associations were found among the younger age groups (14–39 years and 40–49 years). In particular we saw high associations in the youngest group (14–39 years) for: antidepressants (OR = 4.0, CI: 2.7–5.8), sedatives and anxiolytics (OR = 11.6, CI: 8.2–18.5), anti-psychotic medication (OR = 5.2, CI: 3.2–8.4), bronchial dilators (OR = 2.9,CI: 1.9–4.5), and corticosteroids (OR = 4.5, CI: 1.9–10.6). Similar to Table 3 we identified the highest associations with OHCA among the younger age groups and saw a decrease in association with increasing age (Tables 3 and 4).

Depicted in Fig. 1 are the proportion of healthcare contacts and the correlation with age for both cases and controls according to the prioritized groups. We found an age related increase in the proportion of healthcare contacts 30 days before OHCA for both cases and controls. However, there was a marked difference in the number of healthcare contacts between cases and controls in favour of the OHCA cases across all age groups (*p* for difference <0.05) (Fig. 1). However, with older age the relative difference in proportions between cases and controls (proportion of healthcare contacts for cases divided by the proportion of healthcare contacts for controls) is reduced. This relationship between the proportions of healthcare contacts among cases vs. controls is presented in Fig. 2 together with the absolute numbers of OHCA patients according to age. Younger OHCA cases (age groups: 14–19, 20–29, and 30–39 years) are ~5 times as likely to be in contact with the healthcare services compared with the age and sex matched control population in spite of comprising only a small proportion of all 16,924 OHCA cases (Fig. 2). In comparison, the older patients comprised the majority of all OHCA cases but were <2 times as likely to be in contact with the healthcare services 30 days before an event compared with the age and sex matched control population (Fig. 2).

The discriminatory power of the model to predict OHCA (*c*-statistics from analysis including all healthcare contacts) improved from 0.65 in the oldest age group to 0.69 in the younger age groups.

4. Discussion

The present study demonstrates how younger OHCA patients are ~5times as likely to be in contact with the healthcare services compared with an age and sex matched control population, suggestive of traits that distinguish them from the general population.

Table 2
Baseline characteristics for out-of-hospital cardiac arrest individuals stratified by age.

Age group, years	14–39	40–49	50–59	50–69	70–79	>80	*p*-value
N (%)	796 (4.7)	1188 (7.0)	2369 (14.0)	3739 (22.1)	4573 (27.0)	4259 (25.2)	
Male, *N* (%)	597 (75.0)	845 (71.1)	1683 (71.0)	2663 (71.2)	3000 (26.9)	2350 (55.2)	
Mens age, years (Q1–Q3)	32 (26–36)	46 (13–48)	55 (53–58)	65 (62–67)	75 (72–77)	84 (81–87)	
Women's age, years (Q1–Q3)	33 (26–37)	46 (43–48)	55 (53–58)	65 (62–67)	74 (72–77)	85 (82–89)	
Hospital admissions							
30 days before OHCA (%)							
Peripheral vascular disease	0	2 (0.2)	4 (0.2)	9 (0.2)	23 (0.5)	12 (0.3)	0.04
Cerebral vascular disease	0	4 (0.3)	11 (0.5)	29 (0.8)	41 (0.9)	46 (1.1)	0.003
Ischemic heart disease	2 (0.3)	8 (0.7)	33 (1.4)	94 (2.5)	120 (2.6)	100 (2.4)	<0.001
Myocardial infarction	2 (0.3)	4 (0.3)	22 (0.9)	37 (1.0)	53 (1.2)	56 (1.3)	0.01
Cardiac dysrhythmia	3 (0.4)	10 (0.8)	35 (1.5)	71 (1.9)	110 (2.4)	117 (2.8)	<0.001
Heart failure	3 (0.4)	4 (0.3)	20 (0.8)	43 (1.2)	89 (2.0)	121 (2.8)	<0.001
Diabetes	14 (1.8)	38 (3.2)	153 (6.5)	265 (7.1)	298 (6.5)	200 (4.7)	<0.001
Peptic ulcer	0	3 (0.3)	11 (0.5)	14 (0.4)	17 (0.4)	14 (0.3)	0.52
Trauma	28 (3.5)	29 (2.4)	36 (1.5)	39 (1.0)	60 (1.3)	106 (2.5)	<0.001
Psychiatric illness	25 (3.1)	34 (2.9)	50 (2.1)	57 (1.5)	34 (0.7)	29 (0.9)	<0.001
Liver disease mild/severe	1 (0.1)	4 (0.3)	11 (0.5)	7 (0.2)	3 (0.1)	2 (0.1)	<0.001
Malignancy	6 (0.8)	26 (2.2)	105 (4.4)	147 (3.9)	156 (3.4)	86 (2.0)	<0.001
COPD	1 (0.1)	7 (0.6)	33 (1.4)	94 (2.5)	166 (3.6)	116 (2.7)	<0.001
Pharmacotherapy							
30 days before OHCA (%)							
Antithrombotic agents	7 (0.9)	42 (3.5)	158 (6.7)	389 (10.4)	651 (14.2)	698 (16.4)	<0.001
Cholesterol lowering drugs	5 (0.6)	32 (2.7)	108 (4.6)	263 (7.0)	309 (6.8)	129 (3.0)	<0.001
Calcium inhibitors	5 (0.6)	27 (2.3)	104 (4.4)	211 (5.6)	305 (6.7)	323 (7.6)	<0.001
Beta-blockers	11 (1.4)	55 (4.6)	172 (7.3)	338 (9.0)	390 (8.5)	391 (9.2)	<0.001
ACEi/ARB	4 (0.5)	55 (4.6)	231 (9.8)	458 (12.3)	668 (14.6)	514 (12.1)	<0.001
Diuretics	17 (2.1)	84 (7.1)	267 (11.3)	616 (16.5)	1004 (22.0)	1162 (27.3)	<0.001
Digoxin	4 (0.5)	14 (1.2)	54 (2.3)	173 (4.6)	351 (7.7)	469 (11.0)	<0.001
Anti-angina medication	2 (0.3)	9 (0.8)	73 (3.1)	161 (4.3)	300 (6.6)	348 (8.2)	<0.001
Antidepressants	73 (9.2)	120 (10.1)	205 (8.7)	305 (8.2)	407 (8.9)	416 (9.8)	0.13
Sedatives/anxiolytics	113 (14.2)	207 (17.4)	382 (16.1)	620 (16.6)	721 (15.8)	599 (14.1)	0.01
Anti-psychotic medication	66 (8.3)	97 (8.2)	141 (6.0)	182 (4.9)	169 (3.7)	190 (4.5)	<0.001
Analgesics (incl. morphine)	42 (5.3)	157 (13.2)	385 (16.3)	713 (19.1)	989 (21.6)	1074 (25.2)	<0.001
Bronchial dilators	34 (4.3)	75 (6.3)	212 (9.0)	552 (14.8)	883 (19.3)	558 (13.1)	<0.001
Corticosteroids (systemic)	9 (1.1)	29 (2.4)	95 (4.0)	234 (6.3)	360 (7.9)	265 (6.2)	<0.001

Discrete variables are given in numbers and percentages. Continuous variables are given in medians and Q1–Q3 = inter-quartile range. COPD = chronic obstructive pulmonary disease; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

The overall risk of SCD increases with age and peaks among individuals aged 75–84 years which is concordant with the OHCA population used in the present study (Table 2).[12] Not surprisingly, individuals of older age are more likely to suffer from disease compared with younger individuals which is reflected in Fig. 1 where the number of healthcare contacts increased with age from 30 to 45% in juveniles and adolescents, to almost 75% in the older age groups. However, despite the high proportion of healthcare contacts among the older age groups, the associations between healthcare contacts and OHCA were mostly low, which suggests that the older OHCA patients resembles the general population to a large extent in terms of healthcare contacts (Tables 3 and 4). In contrast, we generally found high associations between OHCA and recent healthcare contacts 30 days before an event among the younger age groups despite the younger age groups comprised less in absolute numbers (Table 2). This important inverse relationship between having the highest likelihood of being in contact with the healthcare services compared with the control population, but comprising the fewest in absolute numbers are depicted in Fig. 2. In terms of healthcare contacts our results suggests that younger OHCA individuals have certain characteristics that make them get into contact with the healthcare services prior to their

Table 3
Odds ratio for a hospital admission 30 days before to out-of-hospital cardiac arrest by age group compared with an age and gender matched control group (reference).

Age groups, years	14–39	40–49	50–59	50–69	70–79	>80
Reason for hospital admission						
Peripheralvasculardisease	NA	NA	NA	0.5 (0.2–1.5)	**2.5 (1.4–3.7)**	1.4 (0.7–2.6)
Cerebral vasculardisease	NA	4.1 (0.6–26.1)	2.3 (0.9–6.1)	1.1 (0.6–1.9)	**1.4 (1.0–2.1)**	**1.4 (1.0–2.0)**
Ischemicheartdisease	NA	**5.6 (1.3–23.7)**	**3.2 (1.6–6.1)**	**3.2 (2.3–4.5)**	**1.8 (1.3–2.3)**	**1.7 (1.3–2.2)**
Myocardialinfarction	NA	4.9 (0.5–48.7)	**10.7 (4.0–29.1)**	**5.5 (3.0–10.1)**	**4.1 (2.7–6.5)**	**4.0 (2.7–6.0)**
Cardiacdysrhythmia	**7.8 (1.4–43.8)**	0.8 (0.1–4.7)	1.6 (0.7–3.8)	**1.6 (1.0–2.6)**	**2.0 (1.4–2.7)**	**2.3 (1.7–2.9)**
Heart failure	**11.9 (1.8–78.1)**	**13.0 (3.2–53.0)**	**20.1 (8.6–47.2)**	**8.7 (5.5–13.7)**	**3.9 (2.9–5.3)**	**2.7 (2.1–3.6)**
Diabetes	**5.7 (2.9–11.1)**	**3.6 (2.4–5.3)**	**3.6 (3.0–4.4)**	**2.1 (1.8–2.4)**	**1.6 (1.4–1.8)**	**1.4 (1.2–1.6)**
Pepticulcer	NA	2.2 (0.3–18.1)	**2.0 (0.6–6.7)**	**1.5 (0.6–3.5)**	2.0 (1.1–3.6)	1.0 (0.6–2.0)
Trauma	**2.6 (1.7–4.1)**	**2.0 (1.3–3.2)**	**1.6 (1.1–2.4)**	**1.2 (0.8–1.8)**	**1.7 (1.3–2.3)**	**1.9 (1.5–2.4)**
Psychiatricillness	**70.5 (21.0–237.0)**	**13.7 (7.5–25.0)**	**8.7 (5.4–14.0)**	**8.6 (5.6–13.3)**	**1.8 (1.2–2.9)**	**1.6 (1.0–2.2)**
Liver disease mild/severe	NA	1.0 (0.2–5.9)	0.9 (0.3–2.7)	0.3 (0.1–1.2)	2.0 (0.8–4.8)	3.2 (0.7–15.2)
Malignancy	**16.3 (4.6–57.7)**	**19.1 (9.5–38.1)**	**21.4 (14.9–30.6)**	**8.1 (6.4–10.2)**	**4.0 (3.3–4.9)**	**2.7 (2.1–3.4)**
COPD	NA	**14.9 (3.2–69.3)**	**7.8 (4.1–15.1)**	**7.8 (5.6–11.0)**	**5.9 (4.7–7.4)**	**5.2 (4.0–6.7)**

All values are presented as odds ratio and 95% confidence interval; statistically significant findings are highlighted in bold; NA = not available; COPD = chronic obstructive pulmonary disease.

Table 4
Likelihood for specific pharmacotherapy 30 days prior to out-of-hospital cardiac arrest by age group compared with an age and gender matched control group (reference).

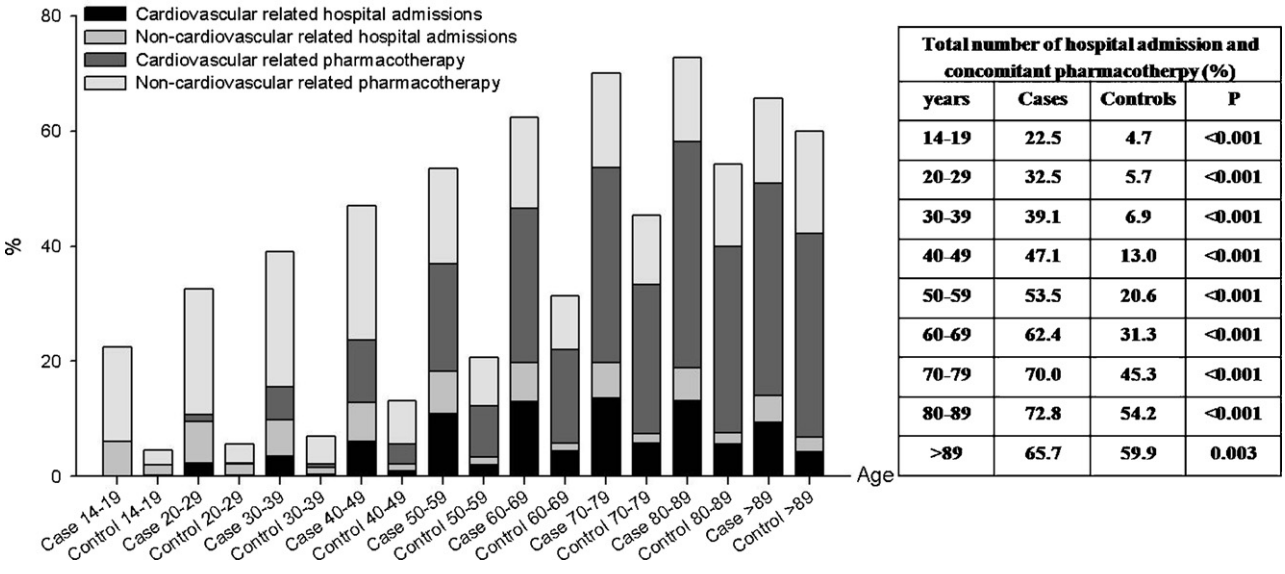
Age groups, years	14–39	40–49	50–59	50–69	70–79	>80
Concomitant pharmacotherapy						
Antithrombotic agents	**6.3 (1.6–24.7)**	**2.7 (1.7–4.4)**	**1.8 (1.4–2.2)**	**1.2 (1.0–1.3)**	**1.1 (1.0–1.2)**	**1.1 (1.0–1.2)**
Cholesterollowering drugs	5.4 (0.9–31.0)	1.1 (0.7–1.8)	0.9 (0.7–1.2)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	1.0 (0.8–1.2)
Calcium inhibitors	3.3 (0.8–13.6)	1.6 (1.0–2.8)	1.2 (0.9–1.5)	0.9 (0.8–1.1)	0.8 (0.7–0.9)	0.9 (0.8–1.0)
Beta-blockers	1.3 (0.4–4.0)	**1.9 (1.3–2.9)**	**1.3 (1.1–1.6)**	**1.3 (1.1–1.5)**	1.0 (0.9–1.1)	1.1 (1.0–1.2)
ACEi/ARB	2.1 (0.4–11.2)	1.4 (0.9–2.1)	**1.3 (1.1–1.5)**	**1.2 (1.0–1.3)**	**1.3 (1.2–1.4)**	**1.1 (1.0–1.3)**
Diuretics	**10.5 (3.9–28.2)**	**3.9 (2.8–5.5)**	**2.4 (2.0–2.8)**	**2.1 (1.9–2.4)**	**1.7 (1.6–1.9)**	**1.4 (1.3–1.5)**
Digoxin	NA	**4.4 (1.7–11.4)**	**5.9 (3.8–9.2)**	**3.7 (3.0–4.6)**	**2.3 (2.0–2.6)**	**1.8 (1.6–2.0)**
Anti-angina medication	NA	**2.0 (0.7–5.4)**	**6.1 (4.1–9.0)**	**3.0 (2.4–3.7)**	**2.2 (1.9–2.6)**	**1.8 (1.6–2.0)**
Antidepressants	**4.0 (2.7–5.8)**	**2.0 (1.5–2.6)**	**1.4 (1.2–1.8)**	**1.3 (1.1–1.5)**	**1.3 (1.2–1.5)**	**1.0 (0.9–1.1)**
Sedatives and anxiolytics	**11.6 (8.2–18.5)**	**4.2 (3.4–5.3)**	**2.5 (2.2–2.9)**	**2.0 (1.8–2.3)**	**1.4 (1.3–1.5)**	1.0 (0.9–1.1)
Anti-psychoticmedication	**5.2 (3.2–8.4)**	**4.3 (3.0–6.0)**	**3.2 (2.5–4.0)**	**2.1 (1.7–2.6)**	**1.7 (1.5–2.1)**	**1.5 (1.2–1.7)**
Analgesics (incl. morphine)	**2.5 (1.5–4.1)**	**2.2 (1.7–2.8)**	**2.2 (1.9–2.6)**	**1.9 (1.7–2.1)**	**1.5 (1.4–1.6)**	**1.3 (1.2–1.4)**
Bronchialdilators	**2.9 (1.9–4.5)**	**2.3 (1.7–3.2)**	**2.8 (2.6–3.4)**	**1.7 (2.4–3.0)**	**2.4 (2.2–2.6)**	**2.2 (2.0–2.4)**
Corticosteroids (systemic)	**4.5 (1.9–10.6)**	**6.0 (3.3–10.8)**	**4.3 (3.1–5.8)**	**3.2 (2.7–3.9)**	**2.2 (1.9–2.5)**	**2.0 (1.7–2.3)**

All values are presented as odds ratio and 95% confidence interval; statistically significant findings are highlighted in bold; ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

OHCA and hereby eligible for potential identification and early SCD risk stratification (Fig. 2).

In agreement with an age related risk of SCD, we found that especially cardiovascular hospital admissions rose with higher age for both cases and controls (Fig. 1 and Table 2). These findings were also reflected in our association models where the associations decreased for cardiovascular specific hospital admissions which suggest that these diseases are more common with older age among both cases and controls (Table 3). Interestingly, Bardai and colleagues interrogated the causes of paediatric OHCA cases showed how the majority of naturally occurring OHCA had cardiovascular disease as the underlying etiology.[13] Keeping that in mind it was somewhat surprising that we did not see a higher number of hospital admissions for cardiac related matters among the youngest age group. (Table 2). In fact less than 1% of the OHCA patients in the youngest age group were hospitalised with ischemic heart disease, myocardial infarction, cardiac dysrhythmia, or heart failure within 30 days of their OHCA (Table 2). However, in spite of comprising less than 1% we did still see high OR associated with both cardiac dysrhythmia and heart failure in the young group compared to the older age groups where the OR approached one which suggest a higher degree of abnormality in being young and admitted for the interrogated reasons whereas it is less abnormal among older patients (Table 3).

Atherosclerosis (clinical and subclinical) has been recognized as one of the key risk factors in the development of coronary artery disease which accounts for an estimated 80% of all SCD.[3,14] Atherosclerosis is an age related disease which is supported by our findings where we found that a larger number of the older population were admitted for diseases potentially related to atherosclerosis such as ischemic heart disease, peripheral vascular disease, and heart failure (Table 2). Importantly, the coronary artery risk development in young adults (CARDIA) study demonstrated how subclinical atherosclerosis (coronary calcium) is present even in young adults and how this is associated with risk of CVD including high body mass index, high systolic blood pressure, diabetes, and high cholesterol levels.[15] However, it is less likely that subclinical atherosclerosis is the direct cause leading to SCD among the younger OHCA individuals. Albeit we had no way to interrogate this notion in the present study (autopsies were not routinely performed) we did see that the majority of OHCA patients were of older age which could support the possibility of age induced atherosclerosis being the underlying cause leading to cardiac arrest (Fig. 2).



Total number of hospital admission and concomitant pharmacotherpy (%)			
years	Cases	Controls	P
14-19	22.5	4.7	<0.001
20-29	32.5	5.7	<0.001
30-39	39.1	6.9	<0.001
40-49	47.1	13.0	<0.001
50-59	53.5	20.6	<0.001
60-69	62.4	31.3	<0.001
70-79	70.0	45.3	<0.001
80-89	72.8	54.2	<0.001
>89	65.7	59.9	0.003

Fig. 1. Pharmacotherapy and hospital admissions 30 days before out-of-hospital cardiac arrest by age.

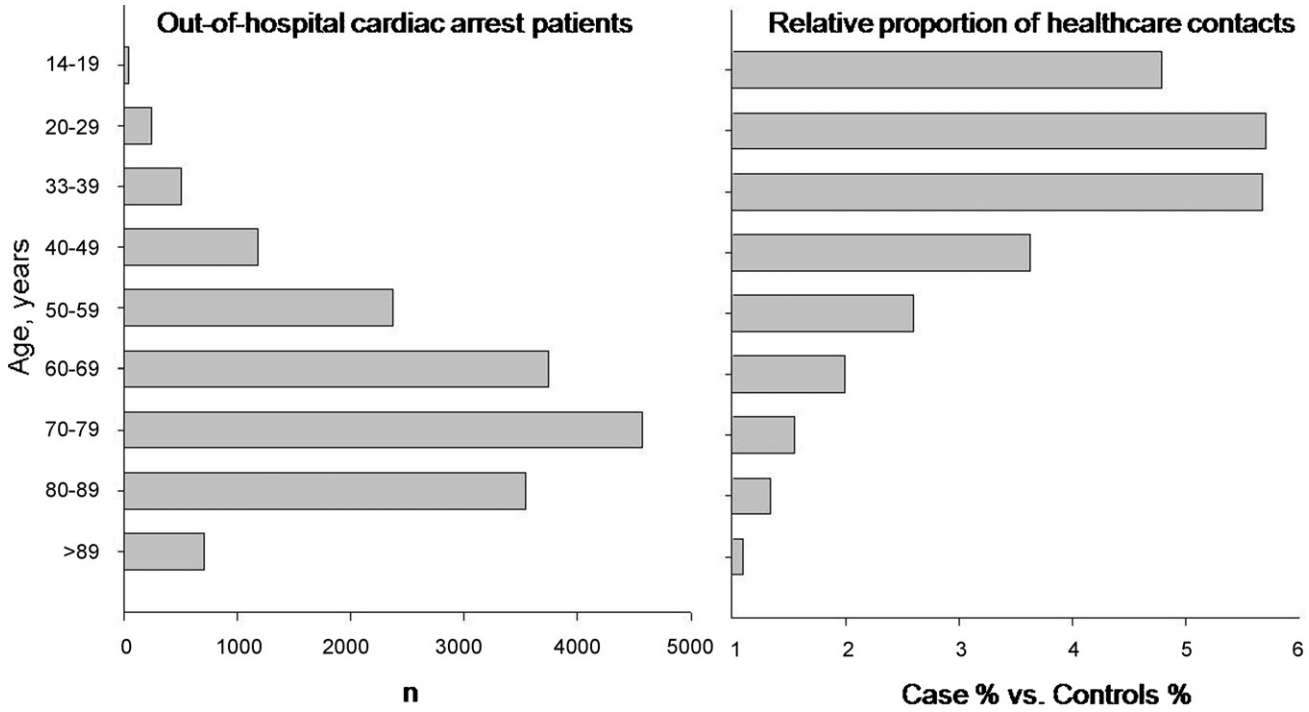


Fig. 2. The total number of out-of-hospital cardiac arrests by age groups (2001–2006) and the relationship between the proportions of healthcare contacts 30 days before OHCA (cases vs. controls).

Diabetes is tightly linked to cardiovascular disease with increased morbidity and mortality rates.[16] Previous studies have shown how patients with diabetes have more than a four-fold increase in the incidence of coronary heart disease and more than a two-fold increase in the risk of having a cardiovascular event compared with the general population.[17,18] In agreement with these findings our results demonstrated how diabetes was associated with OHCA across all age groups although the association approached one with higher age (Table 3). Despite being a well established risk factor for CVD it is recommended that diabetes is not used as an independent risk factor, but is used in combination with of risk factors predisposing SCD in terms of risk profile evaluation.[19] For these reasons we included diabetes as a cardiovascular risk factor and grouped patients with diabetes in the cardiovascular group accordingly.

Individuals at high risk of a cardiovascular event with recognized risk factors only comprise a small fraction of the total number of SCD individuals.[20] Misclassification and inability to identify individuals at risk are in part due to the failure of current tests to recognize important risk factors of SCD including genetic predispositions before an event. Moreover, the fact that well established risk factors such as MI and impaired left ventricular function can be asymptomatic and unrecognized adds further to this notion.[21,22] Currently, there are no well established risk factors for detecting high risk coronary artery disease patients in the early stages of their disease.[23]

Individuals with a psychiatric illness have a high risk of SCD, which was reflected in our results on the high association between OHCA and hospital admissions for psychiatric illnesses or consumption of antidepressants and antipsychotics (Tables 3 and 4). In particular, we found the risk to be more pronounced among the younger part of the OHCA population. Notably, previous studies have shown that individuals with severe mental illness have a twofold increase in the prevalence of cardiovascular risk factors such as dyslipidemia, hypertension, obesity, and diabetes.[24,25] Adding further to the risk profile is the possibility of behavioural risk factors such as smoking and substance abuse which is more predominant in this population.[26] Importantly, antidepressants and antipsychotic medication have been associated with prolongation of the QT interval which is associated with the risk of torsades de pointes and SCD, why an accession of risk factors is important before treatment is initiated.[27] Our findings could suggest a high risk associated with these drugs, however, the results on the increased association between OHCA and antidepressants and antipsychotics, is most likely confounded by the indication for initiating the medication in itself (Tables 3 and 4).

4.1. Strengths and limitations

The main strength of this study is the ability to evaluate healthcare contacts on a nationwide level shortly before OHCA by combining national registers holding information on hospital admissions and concomitant pharmacotherapy. By including information from nationwide registers we minimized the risk of selection bias. Thus, our final study population comprised citizens both in and out of the labour market, independent of sex, socioeconomic status, age, ethnicity and, participation in health or insurance programs.

One of the main limitations to the present observational study is the lack of clinical data with information being obtained from national administrative registers only—only associations are reported. Albeit we tried to eliminate potential confounders from our analyses we acknowledge the possibility of residual confounding including pre-existing conditions. Notably, the indication for being in treatment with a certain type of pharmacotherapy 30 days before OHCA was not available why these results should be interpreted with caution and not readily be associated with a certain comorbidity (i.e. beta-blockers is not solely used for cardiac related causes). We are not able to fully determine of patients actually took the claimed medication, but because medical expenses are only partially reimbursed by the government financed healthcare system we assumed that patients who claimed a prescription were also likely to the take it as they would also have an economic incentive. Lastly, as the Danish government financed healthcare system

is highly available and accessible, we acknowledge that extrapolating results from the present study to other countries or healthcare systems should be done with caution.

5. Conclusion

Young individuals (<40 years) who experience an OHCA are far more likely to be in contact with the healthcare services shortly before their OHCA compared with an age and gender matched control population. We were able to show that the type and number of hospital admissions are different from the older OHCA patients and how psychiatric related illnesses and concomitant use of antidepressants and antipsychotics 30 days before OHCA was frequent among young OHCA patients. Our results also show how young OHCA patients have traits that make them stand out from the general population in terms of hospital admissions and concomitant pharmacotherapy.

Conflicts of interest statement

None.

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