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The relation between age, sex, comorbidity, and pharmacotherapy and the risk of syncope: a Danish nationwide study

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Aims Syncope is a common cause for hospitalization and may be related to comorbidity and concurrent medication. The objective of this study was to determine the incidence, comorbidity, and pharmacotherapy in a nationwide cohort of patients hospitalized with syncope.

Methods and results An observational study including patients with the diagnosis of syncope identified from the Danish National Patient Register in the period 1997–2009. All patients were matched on sex and age with five controls from the Danish population. We estimated the incidence of syncope and the association with comorbidities and pharmacotherapy by conditional logistic regression analyses. We identified 127 508 patients with a first-time diagnosis of syncope [median age 65 years (interquartile range 49–81), 52.6% female]. The age distribution of the patients showed three peaks around 20, 60, and 80 years of age with the third peak occurring 5–7 years earlier in males. Cardiovascular disease and cardiovascular drug therapy was present in 28 and 48% of the patients, respectively. We found significant association between cardiovascular disease and the risk of admission for syncope increasing with younger age; age 0–29 years [odds ratio (OR) = 5.8, confidence interval (CI): 5.2–6.4), age 30–49 (OR = 4.4, CI: 4.2–4.6), age 50–79 (OR = 2.9, CI: 2.8–3.0), and age above 80 (OR = 2.0, CI: 1.9–2.0). Cardiovascular pharmacotherapy associated with age and risk of syncope was similar.

Conclusion In a nationwide cohort of patients hospitalized for first syncope we found significant association between cardiovascular comorbidity and pharmacotherapy and the risk of syncope. The occurrence of syncope displayed an age distribution with important gender-specific differences and higher incidence rates than previously reported.

Keywords Syncope • Epidemiology

Introduction

Syncope comprises 1% of all attendances to European emergency departments (ED) and up to 6% of all hospital admissions.[1–4] The reported incidence is known to be distributed in a bimodal fashion with peaks in the young and the elderly with incidence rates ranging from 2.6 to 19.5 per 1000 person-years,[5–7] but these incidence rates are based on findings in selected cohorts.

Previous studies have shown that patients with cardiac syncope have a higher mortality than patients with non-cardiac syncope.[6,8] The main risk of non-cardiac syncope seems related to physical harm that may occur especially if the patient has recurrent syncope[9,10] and most of the deaths and poor outcomes are associated with the severity of the underlying disease rather than with syncope *per se*.[11] Differentiation between benign and malignant causes remains challenging and numerous previous studies are limited by small cohorts and by the setting of either tertiary

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syncope clinics or EDs introducing selection bias. Despite the high incidence of syncope, very few studies have evaluated the characteristics of morbidity and pharmacotherapy in patients with syncope and little is known about the relationship between syncope and underlying conditions. Many drugs are associated with orthostatic hypotension and a hypothesized increased risk of syncope needs to be further explored.

The aim of this study was to determine the incidence of medically reported syncope in a large unselected population and establish relations to age, gender, comorbidity, and pharmacotherapy. To accomplish this aim, we identified all patients with a registered hospitalization for syncope in the entire population of Denmark.

Methods

A personal and unique civil registration number is assigned to all residents in Denmark, which enables linkage of nationwide administrative registers on an individual level. We obtained information on hospitalization and comorbidities from the Danish National Patient Register, where information on all hospital admissions in Denmark has been stored since 1978.[12] At discharge, each hospital admission is coded with one primary diagnosis and if appropriate one or more secondary diagnoses according to the International Classification of Diseases (ICD), before 1994 the 8th revision and since 1994 the 10th revision (ICD-10). Information on all dispensed prescriptions from Danish pharmacies since 1995 is registered according to the Anatomical Therapeutic Chemical (ATC) system in The Danish Register of Medicinal Products.[13] Demographic information on date of birth, age, sex, and vital status was obtained from the Danish Civil Register.

Study population

From the Danish National Patient Register we identified all Danish residents with a first-time admission to hospital or ED visit for syncope when classified as the primary discharge diagnosis (ICD-10 code R55.9) between 1 January 1997 and 31 December 2009. All hospital admissions, ED contacts and non-acute referrals, that is, outpatients were included but each unique patient was only recorded once. R55.9 refers to 'syncope and collapse'. Patients seen in the ED, given the discharge diagnosis of R55.9 and in the same visit admitted were included if they retained the diagnosis of R55.9 during the hospital admission and were discharged with that diagnosis. To assess differences in comorbidity, hospital admissions, and pharmacotherapy between syncope patients and the general population, every syncope patient was matched on age and sex with five random controls from the Danish population. The controls were assigned the same date of syncope as the case they were matched upon. The 'greedy macro match' algorithm was used to identify the matched control population.[14]

The matching was unable to reach 100% because of a few very old cases, which could not be matched by five controls. The complete matching reached 99.73%.

Validation population

In order to ensure the validity of the R55.9 diagnosis we reviewed a random selection of 150 charts from three different EDs in the Capital Region of Copenhagen and a random selection of 601 charts from hospital admissions in three different hospitals [representing 50% of the hospitalized patients in the period 1 January 2007 to 31 December 2010 due to syncope (ICD-10 R55.9)]. For each patient, we determined if the hospital chart documentation satisfied the definition and diagnosis of syncope according to the European Society of Cardiology.[15]

Comorbidity and pharmacotherapy

Identification and information on major comorbidities related to syncope up to 5 years prior to index date for syncope admission or ED visit was based on hospital discharge diagnosis codes according to the Charlsons Comorbidity Index.[16,17] We obtained information through the Danish National Patient Register based on primary or secondary diagnosis for the following ICD-10 codes: peripheral vascular disease (I70, I74), cerebral vascular disease (I60–I69), ischaemic heart disease (I20–I25), previous myocardial infarction (I21–I22), cardiac conduction disorders (I44–I45), atrial fibrillation (I48–I49), other cardiac arrhythmias (I46–I47), heart failure (I50, I42), chronic renal failure (N18, I12, I13), acute renal failure (N17, N19, R34), peptic ulcer (K25–K28), diabetes with or without complications (E10–E14), pulmonary oedema (J81), shock (R57, A41), chronic obstructive pulmonary disease (J42–J44), dementia (G30), and malignancies and metastatic cancer (C00–C97).

Information on concomitant drug use up to 1 year prior to syncope was provided through The Register of Medicinal Product Statistics using the following ATC codes: statins (C10A), beta-blockers (C07), angiotensin-converting enzyme inhibitors (ACEi) (C09), loop diuretics (C03C), spironolactone (C03D), thiazides (C03A), calcium channel blockers (C08), digoxin (C01AA05), class I antiarrhythmic drugs (C01BC), class III antiarrhythmic drugs (C01BD and C07AA) class IV antiarrhythmic drugs (C08DA), morphine (N02AA), glucose-lowering medication (A10), clopidogrel (B01AC04), acetylsalicylic acid (B01AA0), vitamin K antagonists (VKA) (B01AA0), antiepileptic drugs (N03), antiparkinson drugs (N04), antidepressants (N06A), sedatives and anxiolytics (N05B, N05C), antipsychotic agents (N05A), bronchodilators (R04), and alpha-blockers (C02C).

We stratified patients according to comorbidity, pharmacotherapy, and age. Patients with one of the following diseases were grouped as having cardiovascular disease; ischaemic heart disease, cerebral vascular disease, previous myocardial infarction, cardiac arrhythmias, electrical conduction disorders, pulmonary oedema, congestive heart failure, cardiogenic shock, peripheral vascular disease, diabetes, and atrial fibrillation. Patients not included in this group were categorized as having non-cardiovascular-specific disease. Prescriptions claimed for the following agents were categorized as cardiovascular-specific medication; antiangina medication, ACEi, digoxin, class I antiarrhythmic drugs, class III antiarrhythmic drugs, class IV antiarrhythmic drugs, calcium channel blockers, beta-blockers, cholesterol-lowering agents, VKA, clopidogrel, glucose-lowering medication, and diuretics. Prescriptions claimed for the residual medications were categorized as non-cardiovascular medication.

Statistical analyses

Data are presented as numbers and percentages or means with standard deviation. Data without normal distribution are presented as medians with interquartile range (IQR). Differences between categorical variables were analysed with χ^2 test and differences between continual variables with the Wilcoxon ranked sum test or the Kruskall–Wallis test. The crude incidence rate of syncope was calculated by dividing the number of patients with syncope by the total number of 1000 person-years in the Danish population in the period 1997–2009.

Multivariable conditional logistic regression models were constructed to analyse odds ratios (ORs) for admission with syncope according to age, gender, comorbidity, and pharmacotherapy (*Table 1*). Three models were applied. In the first model (*Table 2*)

we adjusted for sex and age. In the second (*Table 3*) we adjusted for the types of hospital admissions as listed in *Table 1* and in the third (*Table 4*) we adjusted for concomitant pharmacotherapy as listed in *Table 1*. Association is given as ORs. All models were tested for linearity of continuous variables and lack of interactions. We choose the three different models to test the robustness of the individual covariates consecutively added to the models. In the first model we test the effect of either cardiovascular disease or use of cardiovascular pharmacotherapy across different age groups. The second model analyses the effect of more specific comorbid conditions on admission for syncope across age groups and the third model analyses the effect of specific cardiovascular and non-cardiovascular pharmacotherapy. The rationale for using this approach was to gain information on covariates of significance after testing in univariate models. All analyses were done using Statistical Analysis System (SAS) statistical software package, version 9.2 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Danish Data Protection Agency (ref. 2007-58-0015, int. ref: GEH-2010-001). Ethical approval is not required for register-based studies in Denmark.

Results

In the period from 1997 to 2009, a total of 127 508 patients were either seen in the ED, hospitalized, or handled as outpatients due to syncope according to the Danish National Patient Register. Women comprised 52.6% of the population, and were on average older than men at the time of diagnosis, 66 and 63 years, respectively. The median age was 65 years (IQR 49–81). The number of hospital contacts remained stable throughout the period with a median of 9791 per year (IQR: 9460–10 188). Admissions accounted for 43.0% (54 965 patients) of the total population, leaving 45.3% (57 855 patients) as ED contacts and 11.7% (14 885 patients) as ambulatory referrals.

The age-and-gender-matched control population comprised a total of 635 836 individuals (*Table 1*).

The positive predictive value of the diagnosis in validation substudy was 93 and 95% in admitted and ED visits, respectively.

Age and gender distribution of syncope

The age distribution of the patients showed three peaks (*Figure 1*). The first peak was represented primarily by females around 20 years of age, a second and quite smaller peak in older patients around 60 years of age and a third peak around 80 years of age. The third peak was left shifted in males compared with females; peaking 5–7 years earlier. The age distribution in men showed a steady increase in frequency with rising age peaking around 75 years. The largest proportion of syncope occurred in the age group 50–79 years (35.7%).

Age and gender incidence rates of syncope

The overall incidence rate of a first-time episode of syncope was 17.2 per 1000 person-years, women accounting for 17.8 and men for 16.5. The incidence rates showed a bimodal distribution being higher in the youngest and highest in the elderly, with a distinct rise at 70 years to 40.2 per 1000 person-years increasing to 81.2 in the age group above 80 years (shown in *Figure 2*).

Syncope accounted for 0.9% of the total admissions in the period and 0.6% of the total ED visits.

During the study period there was an overall increase in the incidence rates of syncope from 13.8 to 19.4 per 1000 person-years in 1997 and 2009, respectively.

Pharmacotherapy and comorbidity

As shown in *Table 1* cardiovascular disease was common in the syncope population, 11% had previously diagnosed ischaemic heart disease and 9.4% had cardiac arrhythmias. A total of 20% were treated with ACE inhibitors, 16% beta-blockers, 29% diuretics, and 11% statins, respectively. Anxiolytics and antidepressants were also commonly used, particularly in the elderly and females where women accounted for 62 and 61%, respectively (data not shown). *Figure 3* demonstrates the distribution and increased proportion of selected comorbidity in syncope patients compared with the control population. *Figure 4* shows the distribution of cardiovascular pharmacotherapy and cardiovascular disease in relation to the type of patient contact with the hospital.

Multivariate logistic regression analyses

Wide differences were seen when comparing comorbidities and pharmacotherapy between the syncope population and the control population (*Table 1*). *Table 2* shows the age-and-sex-adjusted ORs for syncope in patients in presence of concomitant cardiovascular disease and specific cardiovascular medication. *Table 3* shows the overall adjusted ORs from the conditional logistic regression analyses for syncope according to selected comorbidities and age. Ischaemic heart disease, cerebrovascular disease, cardiac arrhythmias, electrical conduction disorders, and previous myocardial infarction were strongly associated with the risk of syncope in all age groups, with the strongest association in the younger age groups. *Table 4* shows the adjusted ORs for selected pharmacotherapy and exhibiting the same trend the association with syncope was strongest in the younger age groups.

Discussion

We studied the epidemiology of syncope in a nationwide cohort of patients and the relation with age, gender, pharmacotherapy, and comorbidity.

The major four new findings of our study were that the incidence rates of syncope were found significantly higher than previously reported; that the age distribution for first syncope showed three peaks suggestive of a tri-modal distribution instead of bi-modal as previously described and that syncope was associated with marked cardiovascular comorbidity and use of cardiovascular pharmacotherapy across all age groups when compared with a control population. Furthermore, we found significant differences in the distribution of cardiovascular medication and cardiovascular disease according to the type of hospital contact. This has not previously been described and suggests a large number of patients are discharged from the ED despite considerable cardiovascular comorbidity and medication.

Table 1 Baseline characteristics of 5-year previous hospital admission and concomitant pharmacotherapy for syncope patients and the age-and-sex-matched control population

	Syncope	Age (IQR)	Controls	Age (IQR)	
N	127 508		635 836		
Men	60 445 (47.4%)	63 (49–77)	301 451 (47.4%)	63 (49–77)	
Women	67 063 (52.6%)	66 (48–84)	334 385 (52.6%)	66 (48–84)	
	Syncope		Controls		
Comorbidity	*N*	Per cent	*N*	Per cent	*P* value
Cardiovascular disease	35 670	28.0	90 687	14.3	<0.0001
Ischaemic heart disease	13 874	10.9	29 850	4.7	<0.0001
Cerebral vascular disease	9359	7.3	25 037	3.9	<0.0001
Previous myocardial infarction	4892	3.8	12 527	2.0	<0.0001
Cardiac conduction disorder	2581	2.0	2995	0.5	<0.0001
Cardiac arrhythmia	12 026	9.4	26 341	4.1	<0.0001
Previous atrial fibrillation	8842	6.9	21 799	3.4	<0.0001
Heart failure or pulmonary oedema	6941	5.4	21 769	3.4	<0.0001
Peripheral vascular disease	1656	1.3	6451	1.0	<0.0001
Diabetes	10 123	7.9	27 191	4.3	<0.0001
Acute or chronic renal failure	3216	2.5	4840	0.8	<0.0001
Chronic obstructive pulmonary disease	4532	3.6	19 414	3.1	<0.0001
Dementia	238	0.2	576	0.1	<0.0001
Cancer	4153	3.3	24 499	3.9	<0.0001
Liver disease mild to severe	1161	0.9	2479	0.4	<0.0001
Rheumatologic disease	1194	0.9	4497	0.7	<0.0001
Peptic ulcer	3952	3.1	11 987	1.9	<0.0001
Concomitant pharmacotherapy					
Cardiovascular pharmacotherapy	61 244	48.0	240 856	37.9	<0.0001
Statins	14 343	11.3	46 207	7.3	<0.0001
Beta-blockers	19 702	15.5	60 219	9.5	<0.0001
ACEi/ARB	25 352	19.9	83 398	13.1	<0.0001
Diuretics	36 846	28.9	146 218	23.0	<0.0001
Loop diuretics	15 960	12.5	69 149	10.9	<0.0001
Spironolactone	4125	3.2	13 586	2.1	<0.0001
Thiazide	16 761	13.2	63 483	10.0	<0.0001
Both thiazide and loop diuretics	1985	1.6	6805	1.1	<0.0001
Calcium channel block	16 663	13.1	61 127	9.6	<0.0001
Antiangina	10 370	8.1	25 999	4.1	<0.0001
Digoxin	6744	5.3	30 663	4.8	<0.0001
Class I antiarrhythmic	391	0.3	826	0.1	<0.0001
Class III antiarrhythmic	3903	3.1	11 921	1.9	<0.0001
Class IV antiarrhythmic	2657	2.1	10 169	1.6	<0.0001
Clopidogrel	1724	1.4	3163	0.5	<0.0001
ASA	21 038	16.5	70 368	11.1	<0.0001
VKA	5261	4.1	16 331	2.6	<0.0001
Glucose-lowering drugs	7350	5.8	31 526	5.0	<0.0001
Antidepressants	19 049	14.9	63 819	10.0	<0.0001
Antiepileptica	5087	4.0	13 816	2.2	<0.0001
Anti-Parkinson	2233	1.8	8066	1.3	<0.0001
Anxiolytics	30 887	24.2	120 219	18.9	<0.0001
Antipsychotics	6284	4.9	24 673	3.9	<0.0001
Alpha-blockers	1049	0.8	2915	0.5	<0.0001
Bronchoinhalers	10 903	8.6	55 525	8.7	0.04

Continued

Table 1 *Continued*

	Syncope	Age (IQR)	Controls	Age (IQR)	
Morphine	5046	4.0	22 896	3.6	<0.0001
Steroids	6242	4.9	30 185	4.8	0.02

Dichotomous variables are given in numbers and percentages. Continuous variables are given in medians; IQR, interquartile range; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; VKA, vitamin K antagonist, class I antiarrhythmic drugs, flecainide and propafenone; class III antiarrhythmic drugs, dronaderone, amiodarone and sotalol; class IV antiarrhythmic drugs, verapamil.

Table 2 Age-and-sex-adjusted odds ratio for cardiovascular disease and pharmacotherapy associated with syncope patients compared with controls

Age group	Odds ratio	95% Confidence interval
Cardiovascular disease		
[0–29]	5.8	5.2–6.4
[30–49]	4.4	4.2–4.6
[50–79]	2.9	2.8–3.0
[80+]	2.0	1.9–2.0
Cardiovascular medication		
[0–29]	2.4	2.2–2.6
[30–49]	2.2	2.1–2.2
[50–79]	1.9	1.8–1.9
[80+]	1.4	1.3–1.4

Table 3 Adjusted odds ratio for selected cardiovascular disease associated with syncope patients compared with controls

Age group	Odds ratio	95% Confidence interval
Myocardial infarction		
[11–29]	1.7	0.9–3.3
[30–49]	1.2	1.1–1.4
[50–79]	1.1	1.1–1.1
[80+]	1.1	1.1–1.2
Ischaemic heart disease		
[11–29]	4.0	2.8–5.8
[30–49]	2.8	2.6–3.0
[50–79]	2.1	2.0–2.2
[80+]	1.8	1.7–1.8
Cardiac arrhythmias		
[11–29]	6.6	5.3–8.3
[30–49]	4.3	3.8–5.0
[50–79]	2.7	2.5–2.9
[80+]	2.3	2.2–2.6
Conduction disorder		
[11–29]	12.1	8.5–17.2
[30–49]	7.7	6.1–9.7
[50–79]	3.3	3.0–3.6
[80+]	2.6	2.4–2.8
Heart failure		
[11–29]	4.3	2.7–6.9
[30–49]	1.7	1.5–2.0
[50–79]	0.9	0.9–0.9
[80+]	0.9	0.8–0.9
Dementia		
[11–29]	2.0	0.8–5.0
[30–49]	2.2	1.3–3.7
[50–79]	2.4	1.9–3.0
[80+]	1.5	1.2–1.9
Cerebral vascular disease		
[11–29]	8.2	6.2–10.8
[30–49]	3.6	3.3–4.0
[50–79]	1.9	1.8–2.0
[80+]	1.2	1.2–1.2

Incidence and distribution

We found a gender-related parallel shift in the third peak, where the distribution of men suffering syncope peaks 5 years earlier than the women, representing an age difference in the disease burden (*Figure 1*). The noticed second peak in the age distribution around the age of 60 as depicted in *Figure 1* is not readily explained, as comorbidities as well as pharmacotherapy increases steadily with age without any obvious plateau phases. We note an apparent total tri-modal distribution but this is not evident and the female peak is not as suggestive as the male peak. As noted, we found significantly higher incidence rates of first syncope than previously reported. The incidence discrepancy in our study probably represents underreporting in the selected population of the Framingham Study where the healthy participants, particular the elderly, were also subjected to recollection bias. Our study probably even underestimates the incidence, as our population is hospital based and it is only a small fraction of patients from the general population that presents in a clinical setting.[6,18]

Compared with previous findings[1–3,19] we find in our study a lower proportion of ED visits and admissions with syncope accounting for a total of 1 and 0.6% of all admissions and ED visits, respectively. Alshekhlee *et al.*[20] found in a large-scale study similar proportions (0.6%) of admissions in the United States.

Table 4 Adjusted odds ratio for selected pharmacotherapy associated with syncope patients compared with controls

Age group	Odds ratio	95% Confidence interval
Class I antiarrhythmic		
[11–29]	5.9	1.9–18.4
[30–49]	2.5	1.8–3.5
[50–79]	1.7	1.5–2.1
[80+]	2.1	1.7–2.7
Beta-blockers		
[11–29]	1.9	1.7–2.2
[30–49]	1.4	1.3–1.5
[50–79]	1.3	1.3–1.3
[80+]	1.2	1.2–1.3
Class III antiarrhythmic		
[11–29]	5.2	0.9–28.1
[30–49]	1.8	1.3–2.6
[50–79]	1.6	1.4–1.8
[80+]	1.9	1.6–2.2
Class IV antiarrhythmic		
[11–29]	1.5	0.8–2.6
[30–49]	1.2	1.0–1.4
[50–79]	1.1	1.0–1.2
[80+]	1.0	1.0–1.1
Loop diuretics		
[11–29]	1.6	1.3–2.0
[30–49]	1.4	1.3–1.5
[50–79]	1.0	0.9–1.0
[80+]	0.8	0.7–0.8
Antiepileptica		
[11–29]	1.5	1.4–1.7
[30–49]	1.8	1.6–1.9
[50–79]	1.5	1.4–1.6
[80+]	1.3	1.2–1.4
Anxiolytics		
[11–29]	2.5	2.3–2.7
[30–49]	1.6	1.5–1.7
[50–79]	1.1	1.1–1.2
[80+]	1.1	1.0–1.1

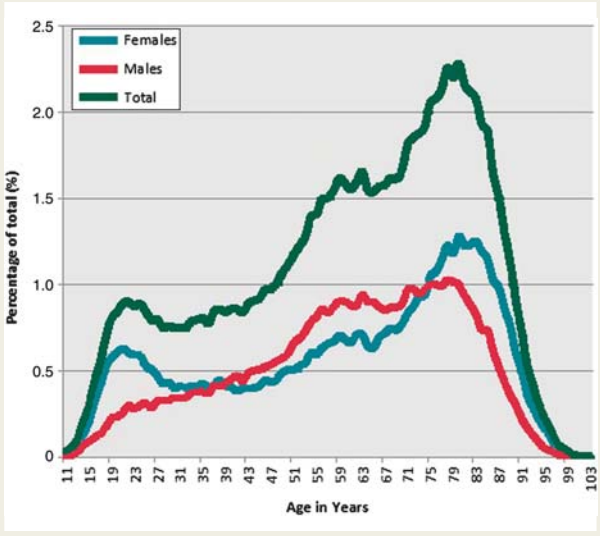

Figure 1 Distribution of syncope according to gender and age. Line chart type with age in years and distribution among women and men in percentage of total syncope cases.

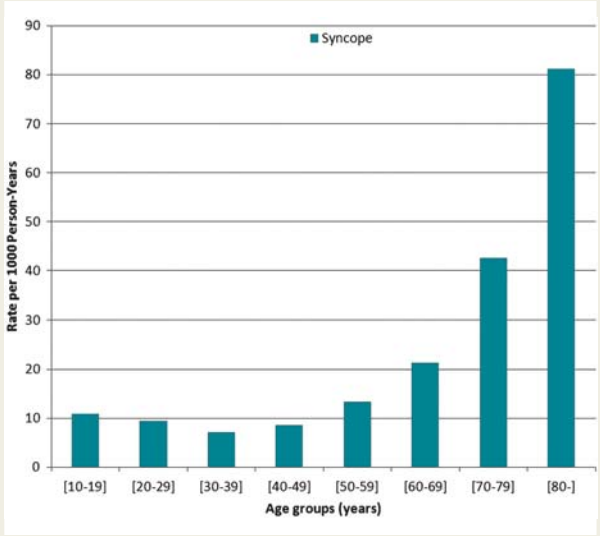

Figure 2 Incidence rates of syncope according to age. Stacked column bar chart. The incidence rates of syncope per 1000 person-years increased with age and the increase was steeper at the age of 70 years.

The actual numbers of admissions, ED visits, and incidence rates are presumably higher because of the nature of the code of diagnosis, R55.9, excluding some syncope of cardiac origin and we also excluded recurrent syncope in our data.

Validity of the diagnosis

We made a full journal audit including 751 randomly selected charts from three hospitals in the Capital Region of Denmark and found a very high positive predictive value of the diagnosis. The discharge coding diagnosis of syncope constituted all aetiological classes of syncope including reflex, orthostatic hypotension, carotid sinus syndrome, all types of cardiac causes, and syncope of unknown cause. Therefore, our study population is a mixed population in terms of aetiology of the syncope. This is consistent with the findings of Getchell *et al.*[21] who performed a study, revising the admission diagnosis of the ICD-9-CM code 780.2 (similar to R55.9). Sun *et al.*[22] validated the discharge diagnosis of ICD-9-CM code 780.2 and found a positive predictive value of 92% of identifying patients with syncope or near syncope, which is similar to our findings of the ICD-10 code.

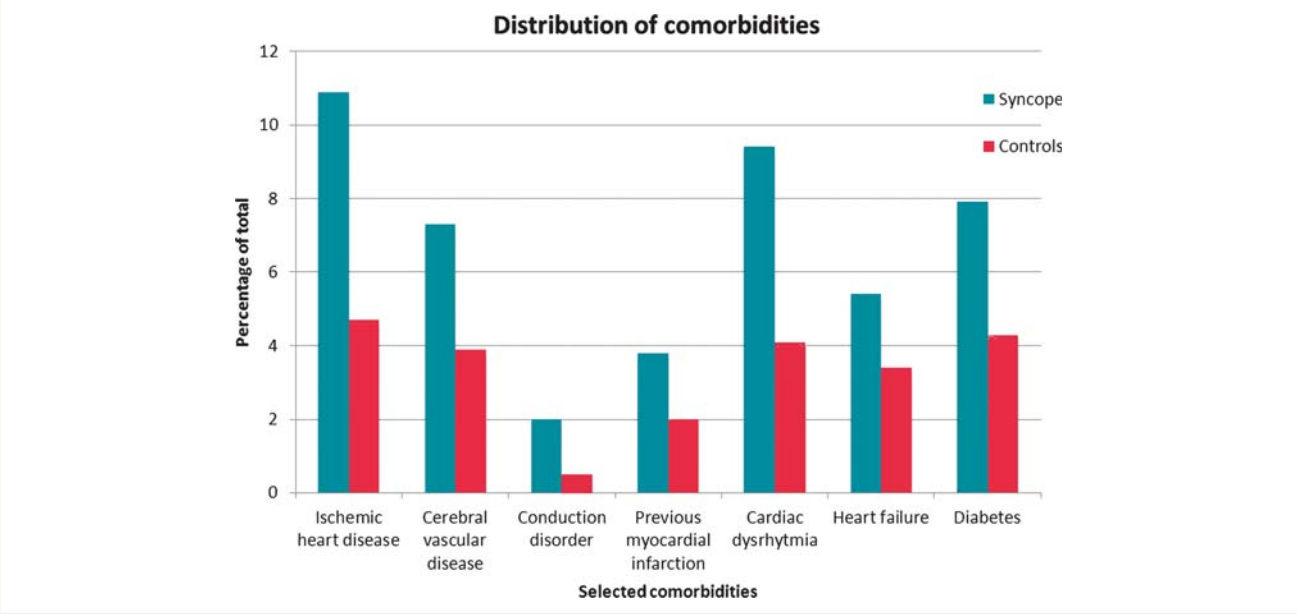

Figure 3 Distribution of selected comorbidities among syncope and controls. Clustered column bar chart with syncope and controls in percentages of total.

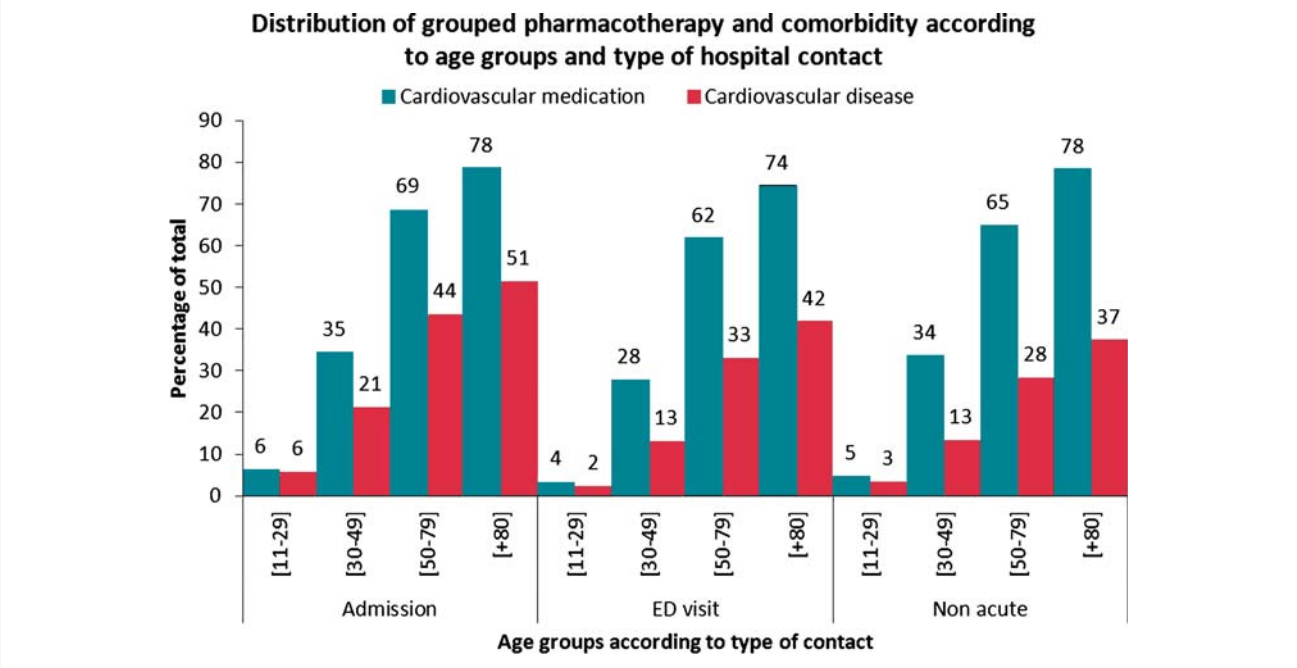

Figure 4 Distribution of grouped pharmacotherapy and comorbidity according to age and type of hospital contact. Stacked column bar chart in percentage of total and age groups divided into the following age groups 0–29, 30–49, 50–79, and above 80 years of age. Admission to hospital for more than 24 h. ED visit: Short-term stay in emergency department. Non-acute referral: Outpatients.

Association between syncope and cardiovascular disease and medication

One major finding in this nationwide study was the marked association between cardiovascular medication and comorbidities and the risk of syncope across age groups. This association is of concern and may reflect more serious underlying cardiovascular disease or progress in existing cardiovascular condition, eventually leading to recurrent syncope or sudden death.

Previous studies have shown that cardiac aetiologies of syncope are common and can result in increased mortality, but these studies are limited by cohort size (2;4;5). We found our study population to have a relatively high rate of comorbidities and a markedly higher use of drugs than an age-and-sex-matched control population. A total of 28% had cardiovascular disease compared with 14% in the control population and 47 vs. 31% in the age group above 80 years. Nearly half (48%) of the syncope population were medicated with one or more types of cardiovascular-specific medication as compared with 38% of our control population. This difference was even more pronounced in the age group 50–79 years, 66 vs. 51%, respectively. Furthermore, we found the use of antidepressants and anxiolytics to be markedly higher in our syncope population than in our control population and markedly higher in women than in men. This is new information to the risk assessment of syncope and provides detailed information on important associated factors. The increased use of medication in our syncope population is representative of a sick population, not only in increased risk of recurrent syncope but also as a potential marker of identification and risk stratification in the ED.

Differences between admissions and emergency departments visits

When comparing the morbidity and pharmacotherapy between ED visits and admissions according to age groups (*Figure 4*), we found a significant difference in the burden of cardiovascular disease and cardiovascular-specific medication in the higher age groups. There was no marked difference in the youngest age groups except for a higher proportion of cardiovascular disease among those being admitted. We interpret this finding as an indication that the patients at highest risk of adverse outcome are those being admitted to exclude cardiac causes according to general guidelines. However, the relatively high proportion of cardiovascular disease and the use of cardiovascular medication in the elderly age groups sent home from the ED with a diagnosis of syncope require apprehension and prognostic implications need to be studied.

Implications

The Framingham Heart Study disclosed that the proportion of vasovagal syncope diminished whenever cardiovascular disease was present, that the proportion of cardiac syncope increased equivalently and that syncope without an identifiable cause had a higher mortality compared with the general population.[6] This is a cause of concern, when pooled data from electrophysiological and electrocardiographic studies in selected subgroups revealed that one-third of the syncope due to unknown cause could be assigned an arrhythmic cause.[15] Older studies revealed 45–80% could be assigned a cardiac cause,[23–25] whereas most investigators agree that at least 40% of patients with unexplained syncope have reflex syncope.[26]

We found a strong association between cardiovascular disease and cardiovascular-specific medications and the risk of syncope. We cannot, however, state anything about causality in this study. This potentially helps to identify patients at increased risk and subsequently questions the importance of establishing an immediate aetiological diagnosis. Rather it seems, and supported by an older study by Kapoor *et al.*[11] that focus should be on important comorbidities, especially cardiovascular and relevant concomitant pharmacotherapy, when evaluating the patient with syncope.

Strength and limitations

Important strengths of the study include the large size of our study sample and the fact that it was based on a nationwide unselected cohort of patients with syncope in a clinical setting. The Danish National Patient Register contains representative data set that provides descriptive information about ED visits and admissions. By including information from nationwide registers we minimize the risk of selection bias. This study includes patients independent of sex, socioeconomic status, age, ethnicity and participation in insurance or health programmes, and importantly includes patients independent of participation in the labour market.

The main limitation is inherited in the observational nature of the study and the lack of clinical data. However, validity of the diagnosis was ensured by undertaking a representative journal audit. Our case ascertainment strategy could not identify individuals with syncope who had an alternative discharge diagnosis and did not have syncope coded as the principal ICD-10 discharge diagnosis. Particularly, it should be noted that the current definition of syncope was not precisely made by the European Society of Cardiology task force before 2001,[27] which may increase the risk of misdiagnosis.

We cannot determine the true aetiology of the syncope but we rely on the validity of the registered data and our chart reviews and are confident that R55.9 consists as noted of an etiologic mixture of patients suffering from syncope.

Conclusion

In this nationwide study of patients admitted with syncope we were able to demonstrate a significant association between cardiovascular comorbidity and pharmacotherapy and the risk of syncope. The incidence rates presented in this study are markedly higher than previously reported and the age distribution of syncope is widely different according to gender. Syncope is more common in the elderly, females and is generally a diagnosis associated with considerable comorbidity that was unrelated to the chance of hospital admission, suggesting insufficient risk stratification. Further implications of these findings need to be studied in relation to the prognostic impact of syncope in the general population.

Conflict of interest: None declared.

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