Original research

Sex differences in sudden cardiac death in a nationwide study of 54 028 deaths

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ABSTRACT

Objective Sudden cardiac death (SCD) is a leading cause of death and is more common among males than females. Epidemiological studies of sex differences in SCD cases of all ages are sparse. The aim of this study was to examine differences in incidence rates, clinical characteristics, comorbidities and autopsy findings between male and female SCD cases.

Methods All deaths in Denmark in 2010 (54 028) were reviewed. Autopsy reports, death certificates, discharge summaries and nationwide health registries were reviewed to identify cases of SCD. Based on the available information, all deaths were subcategorised into definite, probable and possible SCD.

Results A total of 6867 SCD cases were identified, of which 3859 (56%) were males and 3008 (44%) were females. Incidence rates increased with age and were higher for male population across all age groups in the adult population. Average age at time of SCD was 71 years among males compared with 79 among females (p<0.01). The greatest difference in SCD incidence between males and females was found among the 35–50 years group with an incidence rate ratio of 3.7 (95% CI: 2.8 to 4.8). Compared with female SCD victims, male SCD victims more often had cardiovascular diseases and diabetes mellitus (p<0.01).

Conclusion This is the first nationwide study of sex differences in SCD across all ages. Differences in incidence rates between males and females were greatest among young adults and the middle-aged. Incidence rates of SCD among older female population approached that of the male population, despite having significantly more cardiovascular disease and diabetes in male SCD cases.

INTRODUCTION

Sudden cardiac death (SCD) is a substantial public health problem and a major cause of death,[1 2] despite increased awareness and focus on prevention throughout recent decades. The incidence of SCD among males (SCDm) is higher than the incidence of SCD among females (SCDf).[1 3] The incidence of SCD in all age groups has most likely declined in recent years.[4–6] Previous studies have shown that SCD in females often occurs at an older age compared with males.[5 7] Additionally, both the causes and symptoms prior to SCD in females are more heterogenous.[8] Furthermore, studies have shown that SCDf is more likely to occur in the absence of manifest coronary artery disease (CAD), and that females have a greater tendency to have unrecognised myocardial infarctions.[7 9 10] In addition, prospective studies of SCD have reported differences in heart rhythm preceding death with females, more likely to present with asystole and pulseless electrical activity.[10] Therefore, prediction and prevention of SCD is likely more challenging in the female population. Although SCDf is less common than SCDm, it is still a substantial cause of death among females,[5 7 8] thus warranting further investigation.

There have been few studies examining the differences in incidence, underlying causes and clinical characteristics of SCD between the male and female sex across all age groups,[8 10 11] and none of these has been nationwide. In regional studies, demographic variations may be a barrier to provide the true estimate of the burden of SCD in an unselected population. We have, in a recently published study, characterised and identified all cases of SCD in Denmark in 2010.[2] For all cases of SCD in 2010, we have comprehensive health information, including information of cause of death, previous diseases and autopsy findings. For this study, we aimed to examine differences in the epidemiology of SCD among female and male cases focusing on the cause of death, comorbidities and clinical characteristics.

METHODS

Study design and population

This nationwide study includes all persons deceased in Denmark from 1 January 2010 to 31 December 2010. Comprehensive information was retrieved from death certificates, autopsy reports and discharge summaries. All deaths were reviewed by one physician to exclude deaths that were obviously non-sudden and non-natural (eg, non-natural deaths and deaths in patients with terminal cancer). On any indication the death was sudden and unexpected (SD), the case was reviewed independently by two physicians to identify all SD cases. In cases where the two physicians disagreed, they re-evaluated all available information to reach consensus. Subsequently, SD with an underlying cardiac cause (ie, SCD) were identified through a comprehensive review of autopsy records, the Danish National Patient Register and the National Causes of Death Registry.

Danish healthcare system

The Danish government provides tax-financed healthcare for all permanent residents. Residents of Denmark have a unique Civil Registration Number,

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making interactions between patient and medical professionals traceable. Consequently, national registries of patients' diagnoses and treatment can be traced back to an individual through their Civil Registration Number.

Medical history can be retrieved from the Danish National Patient Register. This register contains information on all inpatient and outpatient activities at Danish hospitals and emergency departments since 1977 (and outpatient contacts since 1994) using International Classification of Diseases (ICD), Eighth Revision for 1977–1994 and ICD, Tenth Revision (ICD-10) from 1995 and onwards) diagnosis codes for each visit.[12] Contacts with general practitioners and pharmacies are not included in this register.

Information on the cause of death can be obtained from the Danish Cause of Death Register, in which immediate, contributory and underlying causes of death are recorded using ICD-10 codes.[13]

Death certificates and autopsy

Danish law requires that a death certificate must always be issued by a medical doctor, who based on the available information, determines the most likely cause of death. In the case of sudden and unexpected death, contacting the police is mandatory. The police decide if there should be performed a medicolegal external examination in cooperation with a public health medical officer. The public health officer has access to first responder records, all medical records relating to the deceased, police reports including eyewitness statements and interviews with general practitioners and the body of the deceased. The information from these sources are included in the supplementary information field of the death certificate. Even in the absence of an external examination, information on circumstances of death is often included in the supplementary information field, which makes Danish death certificates a useful tool for identifying SD.[3 14]

A forensic autopsy is conducted in cases with an unknown or uncertain manner of death. If forensic autopsy is not conducted, physicians and/or relatives of the deceased can request a hospital autopsy, which is performed at local pathology departments.

Definitions

SD was defined as a sudden, natural, unexpected death. Cases of SD presumed to be of cardiac origin were classified as SCD and further subcategorised based on the criteria provided in table 1.[2]

Statistical methods

Statistical analysis was performed with the use of SAS Enterprise V.7.15 as well as R studio 1.2.5001. Population data for incidence calculations were retrieved via Statistics Denmark, using the population on 1 January 2010 as reference. CIs for incidence rates were based on a normal distribution. Fisher's exact test was used to compare categorical data and a Student's t-test was used to compare continuous data. Sex differences were also evaluated using logistic regression, applying age as a covariate. A p value <0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in any way in the study design, conduct, reporting, dissemination of results or evaluation of the study since all cases are deceased participants.

RESULTS

Study population

The population of Denmark on 1 January 2010 was 5.5 million (50.4% females). There was a total of 54 028 deaths. Of these, 7627 (14.1%) were classified SDs. Of all deaths, 6867 (12.7%) deaths were SCD. All SCD cases were subdivided into definite (n=591), probable (n=1568) and possible (n=4708) SCD according to the definitions described in the 'Methods' section (figure 1). SCDm accounted for most cases (n=3859, 56.2%), and there were proportionally more SCDm cases in the definite and probable SCD groups (10.8% vs 5.9% and 25.1% vs 19.9%, respectively, p<0.01).

SCDm victims were significantly younger than SCDf victims with a mean age of 71.3±14.3 and 79.4±13.3 years (mean age±SD, p<0.01), respectively. Male victims were also significantly younger on average than their female counterparts in each SCD subcategory. Male victims died at the hospital more often than female victims (22.8% vs 16.8%, p<0.01), while female victims more often died at home (80.5% vs 69.7%, p<0.01). In total, 458 SCD cases were autopsied, giving an overall autopsy rate of 6.7%, and more male victims were autopsied, with 329 SCDm cases (8.5%) and 129 SCDf cases (4.3%) autopsied (p<0.01). External examinations were performed on 916 (23.7%) SCDm cases and 463 (15.4%) SCDf cases. After age adjustment, however, the difference between male and female victims in autopsy rates and rates of external examinations was insignificant (p=0.07 and p=0.62, respectively).

Table 1 Definitions of sudden death (SD) and sudden cardiac death (SCD)

Term	Definition
SD	A sudden, natural and unexpected death.
Definite SD	An SD with established time frame from change in cardiovascular status to death: ► In witnessed cases: an acute change in cardiovascular status with time to death <1 hour; ► In unwitnessed cases: the deceased seen alive and functioning normally <24 hours before being found dead.
Probable SD	Death in a person without fully established time frame from change in cardiovascular status to death with cause of death likely to be SD in an otherwise healthy person free of any chronic and/or severe diseases expected to lead to a non-SD.
SCD	
Definite SCD	Autopsied definite SD of unknown or cardiac cause. OR SD with documented ventricular arrhythmia immediately preceding death.
Probable SCD	Non-autopsied definite SD presumed to be of cardiac origin after review of all available information.
Possible SCD	Non-autopsied probable SD presumed to be of cardiac origin after review of all available information.

Comorbidities

When adjusting for age, male SCD cases had significantly more cardiovascular diagnoses in the 10 years prior to SCD (51.4% vs 50.7%, p<0.01). In addition, when examining the individual cardiovascular diseases, significantly more male population suffered from CAD (19.8% vs 12.5%, p<0.01), acute myocardial infarctions (13.3% vs 11.0%, p<0.01), congestive heart failure (13.5% vs 10.6%, p<0.01), cardiac arrhythmia (15.2% vs 15.4%, p<0.01) and peripheral artery disease (12.3% vs 10.0%, p<0.01) (table 2). Furthermore, more male patients were diagnosed with a ventricular arrhythmia prior to death (2.3% vs 0.9%, p<0.01). Finally, more male patients suffered from diabetes mellitus (11.1% vs 7.5%, p<0.01), kidney disease

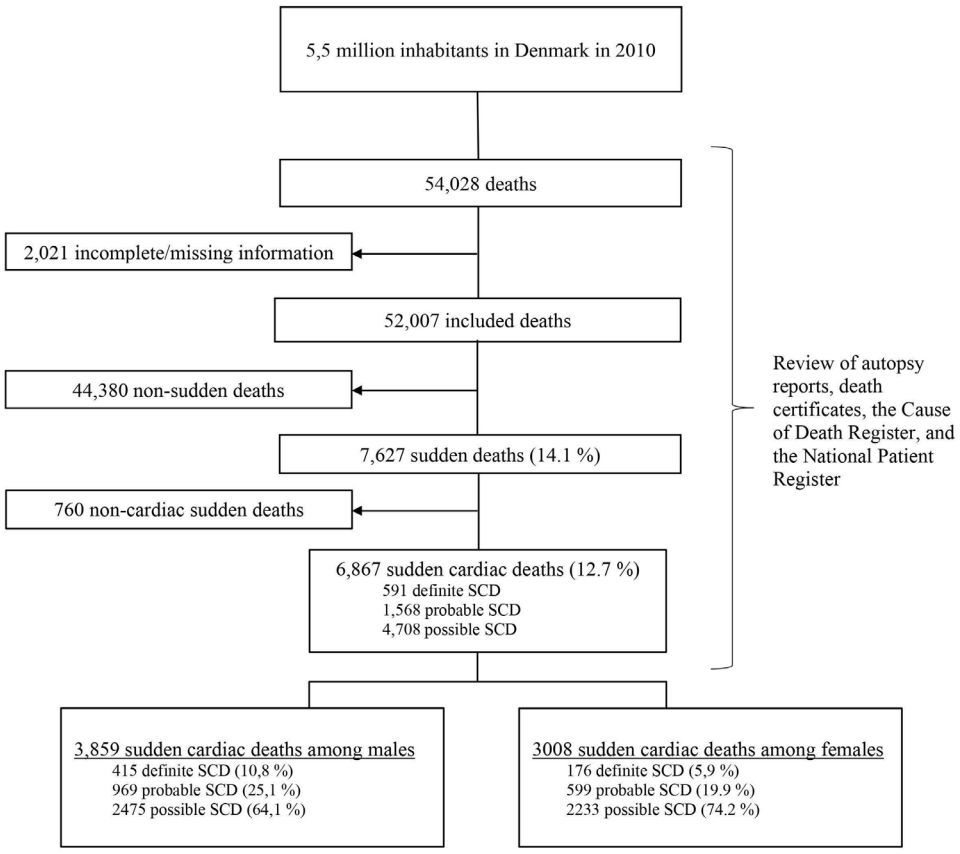

Figure 1 Flow chart of population. SCD, sudden cardiac death.

(5.1% vs 3.5%, p<0.01) and cancer (10.8% vs 9.6%, p<0.01), while more female patients suffered from cerebrovascular disease (15.1% vs 14.4%, p=0.03) and connective tissue disease (4.6% vs 1.7%, p<0.01).

Incidence of SCDm and SCDf

For both male and female cases, incidence rates of SCD increased with age, across all SCD categories (figure 2 and online supplemental figure 5). Incidence rates of SCD were higher for male cases in all age groups, with exception of the 10–19 years group where there was no difference between male and female cases (table 2). The sex differences in incidence rates were most pronounced in the middle-aged population. Incidence rate ratios (IRR) of SCD comparing male and female cases are shown in table 3.

Causes of SCDm and SCDf

Ischaemic heart disease was the leading cause of death among male and female population according to the Danish Cause of Death Register accounting for 40.1% and 40.5% of deaths, respectively (figure 3). A large proportion of male and female SCD cases were categorised as unknown cause of death (24.1% and 24.1%) (figure 3).

Among the autopsied population, CAD was the most common cause of death in both sexes, contributing to 60.2% of all SCDm and 47.3% of SCDf (figure 4). Other structural heart diseases, such as dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, hypertrophy, fibrosis and myocarditis, constituted a greater proportion of SCD among female sex in all age groups compared with male sex (figure 4).

DISCUSSION

In this nationwide study of SCDm and SCDf of all ages in 2010, we found that the incidence rates of SCDm were higher in all adult age groups and that male victims were on average, >8 years younger at time of SCD than their female counterparts. The lowest SCD incidence in this study was observed among male (0.56 per 100 000 person-years) and female population (0.59 per 100 000 person-years) aged between 10 and 19 years. Sudden infant death syndrome and congenital heart disease is the driver of the higher incidence in the 0–9 years group, which coincides with findings from previous studies.[15] Previous studies have suggested that SD among female victims lags about 10–20 years behind that of the male victims.[5 7 11 16] The age disparity between male and female population is also illustrated in our incidence data, with the incidence rate of SCD in middle-aged to older male patients corresponding to the incidence of SCD in female patients aged 10 years older (figure 2 and table 2). The lower cardiovascular mortality among young and middle-aged female patients has been described by the protective effects of oestrogen on both vascular tonus and development of atherosclerosis before menopause.[17] It follows that the diminishing protective effect of oestrogen in postmenopausal female patients could explain why SCD incidence rates among female patients increase later in life compared with their male counterparts (tables 2 and 4). In addition, inherited arrhythmias such as Brugada syndrome and long QT syndrome both display sex differences in the occurrence of arrhythmic events and SCD.[18 19] Brugada syndrome causes arrhythmic events such as SCD more frequently in males, the opposite is true for long QT syndrome where females are at higher risk of fatal arrhythmias. In conclusion, hormonal and genetic factors, among others, are thought

Table 2 Clinical characteristics of all sudden cardiac death (SCD) cases in 2010 according to sex

Cases of SCD in 2010	Total n=6867	Female SCD cases n=3008	Male SCD cases n=3859	P value	P value (age-adjusted*)
Average age, years (SD)	74.8 (14.5)	79.4 (13.3)	71.3 (14.3)	<0.01	–
Place of death†	n=5443	n=2297	n=3146		
Hospital	1102 (20.2)	385 (16.8)	717 (22.8)		
Home	4043 (74.3)	1849 (80.5)	2194 (69.7)	<0.01	–
Other	298 (5.5)	63 (2.7)	235 (7.5)		
External examination performed	1379 (20.1)	463 (15.4)	916 (23.7)	<0.01	0.62
Autopsy performed	458 (6.7)	129 (4.3)	329 (8.5)	<0.01	0.07
Forensic autopsy	243 (3.5)	60 (2.0)	183 (4.7)	<0.01	0.07
Hospital autopsy	215 (3.1)	69 (2.3)	146 (3.8)	<0.01	0.11
Comorbidities					
Cardiovascular diagnosis	3508 (51.1)	1524 (50.7)	1984 (51.4)	0.54	<0.01
Coronary artery disease	1142 (16.6)	376 (12.5)	766 (19.8)	<0.01	<0.01
Acute myocardial infarction	846 (12.3)	331 (11.0)	515 (13.3)	<0.01	<0.01
Arrhythmia	1050 (15.3)	463 (15.4)	587 (15.2)	0.84	<0.01
Atrial arrhythmia	950 (13.8)	441 (14.7)	509 (13.2)	0.08	0.06
Ventricular arrhythmia	114 (1.7)	26 (0.9)	88 (2.3)	<0.01	<0.01
Other arrhythmia	42 (0.6)	10 (0.3)	32 (0.8)	0.01	<0.01
Congestive heart failure	839 (12.2)	318 (10.6)	521 (13.5)	<0.01	<0.01
Peripheral arterial disease	776 (11.3)	300 (10.0)	476 (12.3)	<0.01	<0.01
Diabetes mellitus	657 (9.6)	227 (7.5)	430 (11.1)	<0.01	<0.01
Cerebrovascular disease	1009 (14.7)	454 (15.1)	555 (14.4)	0.41	0.03
Neurological disease	1023 (14.9)	413 (13.7)	610 (15.8)	0.02	0.50
Psychiatric illness	757 (11.0)	332 (11.0)	425 (11.0)	0.98	0.06
Chronic obstructive pulmonary disease	701 (10.2)	325 (10.8)	376 (9.7)	0.15	0.07
Kidney disease	304 (4.4)	106 (3.5)	198 (5.1)	<0.01	<0.01
Connective tissue disease	206 (3.0)	139 (4.6)	67 (1.7)	<0.01	<0.01
Cancers	704 (10.3)	288 (9.6)	416 (10.8)	0.10	<0.01

All values in the table are counts with percentages in parenthesis, unless stated otherwise.
*Age-adjusted p values calculated by logistic regression.
†Information on place of death not available for all cases.

to contribute to differing incidence rates of SCD among male and female patients.[1]

As cases of SCD of all ages were included in this study, the available data regarding the circumstances surrounding death were less detailed compared with previous studies of young SCD victims.[3] Consequently, it was necessary to divide the SCD population into the subcategories: definite, probable and possible. All three SCD subcategories showed similar patterns of incidence

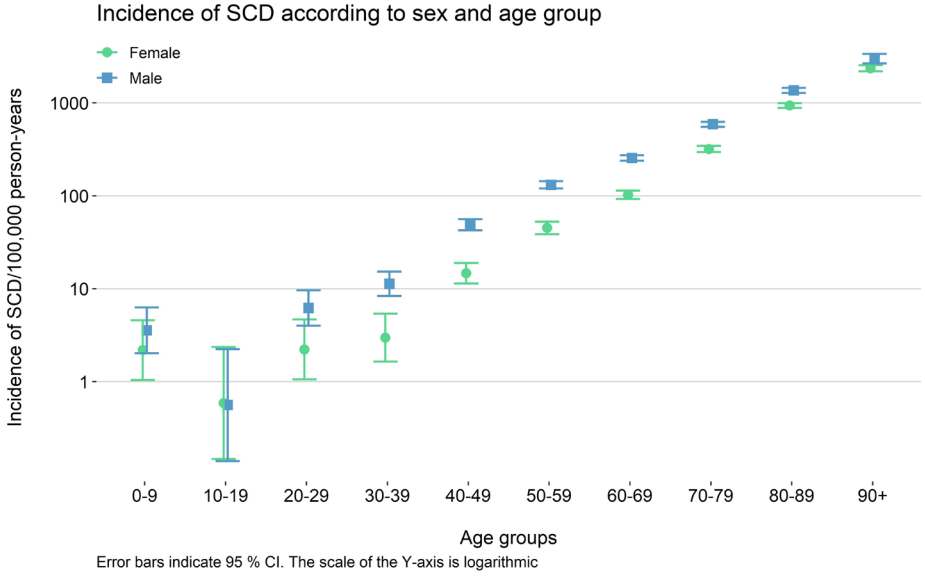

Figure 2 Incidence rates according to sex and age group. SCD, sudden cardiac death.

Table 3 Sudden cardiac death (SCD) incidence rates and incidence rate ratios (IRR) for selected age groups

	Incidence of SCD/100 000 person-years					
Age group (years)	Total	Female SCD cases	Male SCD cases	IRR	95% CI for IRR	P value
<35	2.90	2.00	3.77	1.89	1.14 to 3.12	0.01
35–50	27.29	11.61	42.62	3.67	2.8 to 4.8	<0.01
>50	325.21	278.60	376.92	1.35	1.3 to 1.4	<0.01

differences between male and female patients (online supplemental figure 5). An inherent limitation to the possible SCD group was that the time from change in cardiovascular status to death was not fully established. This may have led to misclassification of deaths that were in fact, non-sudden. In contrast, all victims found >24 hours after death were all classified as non-sudden, although some of cases almost certainly had a cause of death suggestive of SCD (ie, aortic dissection, myocardial infarction). Studies of SCD examining solely autopsied cohorts, where cause of death is certain, do not give precise estimates on the burden of SCD in the general population, as autopsy rates decrease with increasing age and comorbidity.[20] Therefore, it was paramount for this study to be able to compare unbiased and unselected SCD cases in order to provide a precise estimate of the burden of SCDm and SCDf in a nationwide setting, as well as uncovering sex differences in autopsy rates, age and comorbidity.

An interesting finding in this population is the distribution of male and female cases. Among all the cases of SCD, 56.2% were males and 43.8% were females. In contrast, previous studies have found a substantially higher proportion of male cases,[10 21] suggesting that the sex gap in SCD is narrowing. A possible explanation to diminishing differences in rates of SCD between the sexes is greater decreases in cardiovascular mortality among males compared with females.[1 10] In addition, our study finds that despite male victims dying on average 8 years before female victims, they had significantly more cardiovascular diagnoses after adjusting for age. In a previous study among the young Danish population, comorbidity was evenly distributed between male and female patients.[4] The higher percentage of comorbidity among the SCDm population despite them being significantly younger, raises the question of whether SCD is more common among previously healthy females or if cardiovascular disease is underdiagnosed among females?

In the 10 years prior to death, 19.8% of males were diagnosed with CAD, in contrast to females where only 12.5% had such a diagnosis. Under-recognition of CAD among female patients, despite CAD being the leading cause of SCD, may be explained by multiple factors. First, physicians may take a less aggressive approach in managing CAD among female patients.[22] Second, assessment of traditional risk factors are known to underestimate risk of CAD in females, and assessment of symptoms of CAD is often based on knowledge derived from male population, which is not necessarily transferable to female population.[23] Finally, microvascular CAD, as opposed to epicardial CAD, is more common among female further complicating the diagnosis.[24]

Our study also showed that female patients were less thoroughly examined post mortem. After adjustment for age, however, the differences were no longer significant. Nevertheless, fewer females were externally examined and autopsied in this study, which could suggest under-reporting of SCDf . Furthermore, a recent study showed that female patients had lower chance of resuscitation after out-of-hospital cardiac arrest.[25] These findings combined underline the need for increased focus pre mortem and post mortem on cardiac arrest in female patients.

The overall autopsy rate among SCD cases in this study was 7% with autopsy rates declining with increasing age. If age is the most important determinant of who is autopsied, this might be a structural barrier in furthering our knowledge of the underlying causes of SCDf. Despite the relatively low autopsy rates in our SCD population, our findings are comparable to the Fingesture study of 5869 autopsied SCDs in Finland. Both studies find non-ischaemic causes of death to be more common among female patients, while an ischaemic causes of death was more common among male patients.[11] Identification of cause of death in non-autopsied SCD was based on information from death certificates and nationwide health registries. Although Danish death certificates are highly suitable for identification of sudden and unexpected death, we know from previous studies that death certificate information on cause of death is often inaccurate.[26] It follows that our estimates of cause of death in non-autopsied SCD carry large uncertainties. Furthermore, previous studies

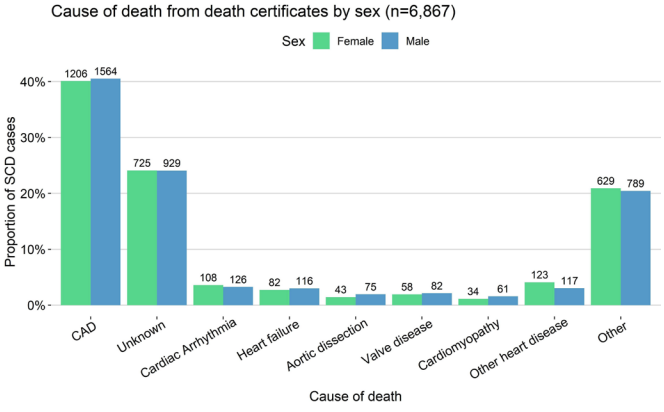

Figure 3 Causes of death in all cases of SCD according to sex. CAD, coronary artery disease; SCD, sudden cardiac death.

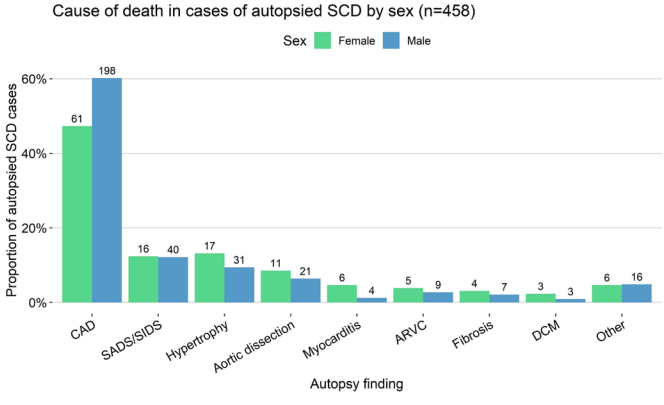

Figure 4 Causes of death in autopsied SCD cases according to sex. ARVC, arrhythmogenic right ventricle cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; SADS, sudden arrthythmic death syndrome; SCD, sudden cardiac death; SIDS, sudden infant ddeath syndrome.

Table 4 Sex-specific and age-specific sudden cardiac death incidence rates per 100 000 person-years

	Female SCD cases		Male SCD cases	
Age group (years)	Incidence/100 000 person-years	95% CI	Incidence/100 000 person-years	95% CI
0–9	**2.19**	1.04 to 4.59	**3.57**	2.03 to 6.29
10–19	**0.59**	0.15 to 2.46	**0.56**	0.14 to 2.24
20–29	**2.22**	1.09 to 4.60	**6.20**	4.00 to 9.62
30–39	**2.98**	1.65 to 5.38	**11.29**	9.35 to 15.28
40–49	**14.69**	11.38 to 18.97	**48.92**	42.62 to 56.16
50–59	**45.18**	38.72 to 52.73	**131.30**	119.95 to 143.72
60–69	**102.35**	92.14 to 113.68	**254.91**	238.29 to 272.69
70–79	**318.84**	295.23 to 344.44	**588.00**	552.95 to 625.28
80–89	**936.45**	883.11 to 993.01	**1361.52**	1278.69 to 1449.72
90+	**2355.30**	2180.62 to 2543.96	**2994.86**	2660.44 to 3371.33

on causes of SCD have predominantly included autopsied cases making comparison with our results difficult.[27] In general, with declining autopsy rates we lack information on changes in patterns of overall cause of death and causes of SCD.

Studying the differences in the epidemiology of SCDm and SCDf raises the question of whether the underlying mechanism of SCD differs between the two sexes. In an American retrospective analysis of mortality after sudden cardiac arrest, left ventricular ejection fraction <40% and CAD were the most powerful predictors of mortality among male and female patients, respectively.[9] Multiple studies have found sudden cardiac arrest and SCD more common in females without prior CAD or left ventricle dysfunction,[7 10 28] underlining the need for further research into sex-specific cardiac pathophysiology among females. In addition, gender differences in cultural, psychosocial, behavioural and socioeconomic factors also affect the risk of SCD among male and female population.[29] Further research is needed to illuminate how both sex-specific and gender-specific risk factors of cardiovascular disease affect the risk of SCD.

Prevention

There have been major advances in the prevention of SCD in persons with known cardiac disease and high risk of SCD.[1] In line with previous findings, approximately half of the male and female SCD population did not have a cardiovascular diagnosis preceding SCD.[1 8 16 30] Current risk models have not been successful in discriminating between SCD and all-cause mortality.[30] Understanding the sex differences in the epidemiology of SCD is crucial to ensure future risk models are equally successful in predicting the risk of SCD in both sexes. Less comorbidity and lower autopsy rates among the female population underline the importance of further premortem and postmortem research of cardiac arrest in female SCD cases.

Limitations

The primary limitation of this study was its retrospective design. A prospective study would allow a more standardised data collection. Furthermore, retrospective studies tend to overestimate the burden of SCD.[26] Some cases of SCD included in this study were possibly non-sudden but misclassified due to inadequate information in the death certificate. Conversely, some SCD victims were also likely missed due to them being found >24 hours after death. In addition, data were obtained in a single calendar year, 2010, and it was not possible to report on changes in SCD incidence and causes in recent years.

CONCLUSIONS

In this nationwide study of all SCD in persons of all ages in Denmark in 2010, male population had a higher incidence rate of SCD in all adult age groups. Differences in incidence rates of SCD between male and female cases were greatest among young adults and the middle-aged. Female SCD cases were less often diagnosed with cardiovascular disease prior to death, which could complicate SCD prevention.

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Contributors THL and JT-H have reviewed the death certificates and are joint senior authors of this manuscript. TS wrote the first draft of this manuscript. All authors have been involved in the further development of the manuscript, discussed

Key messages

What is already known on this subject?

⇒ Sudden cardiac death (SCD) is a leading cause of death and accounts for a large proportion of all deaths globally.

⇒ Despite SCD incidence rates being higher for male population of all age groups, it is still a leading cause of death in both male and female population.

What might this study add?

⇒ This is the largest nationwide study of sex differences in SCD among all age groups.

⇒ Differences in SCD incidence rates were greatest in the young and middle-aged population.

⇒ The female SCD cases were on average >8 years older than the male SCD cases.

⇒ Even though the female patients were older at the time of SCD, they had less cardiovascular diagnoses in the 10 years prior to SCD.

How might this impact on clinical practice?

⇒ SCD is an important contributor to overall mortality in the general population, also among persons without known cardiovascular disease.

⇒ Future research on this topic should be focused on early identification of persons at risk of SCD.

⇒ Understanding how male and female population differ in regard to SCD is important to ensure that future preventive strategies are equally effective for both sexes.

the data and prepared the manuscript for submission. TS acted as gaurantor of this manuscript. All authors have approved the final draft of the manuscript before submission.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study complies with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (2015-41-4510) and the Danish Patient Safety Authority (3-3013-2262/1). Patient consent was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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