Sudden cardiac death among persons with diabetes aged 1-49 years

a 10-year nationwide study of 14 294 deaths in Denmark

Lynge, Thomas Hadberg; Svane, Jesper; Pedersen-Bjergaard, Ulrik; Gislason, Gunnar; Torp-Pedersen, Christian; Banner, Jytte; Risgaard, Bjarke; Winkel, Bo Gregers; Tfelt-Hansen, Jacob; ESCAPE-NET

Published in:
European Heart Journal

DOI (link to publication from Publisher):
10.1093/eurheartj/ehz891

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

ESC European Society of Cardiology

European Heart Journal (2019) **41**, 2699–2706
doi:10.1093/eurheartj/ehz891

CLINICAL RESEARCH
Prevention and epidemiology

Sudden cardiac death among persons with diabetes aged 1–49 years: a 10-year nationwide study of 14 294 deaths in Denmark

Thomas Hadberg Lynge [1†], Jesper Svane [1*†], Ulrik Pedersen-Bjergaard [2], Gunnar Gislason [3,4,5], Christian Torp-Pedersen[6,7], Jytte Banner[8], Bjarke Risgaard[1], Bo Gregers Winkel [1], and Jacob Tfelt-Hansen[1,8] for ESCAPE-NET

[1]The Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Section 2142, Blegdamsvej 9, 2100 Copenhagen, Denmark; [2]Department of Cardiology, Nephrology and Endocrinology, Nordsjællands Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark; [3]Department of Cardiology, Copenhagen University Hospital, Gentofte Hospitalsvej 1, 2900 Hellerup, Denmark; [4]The Danish Heart Foundation, Vognmagergade 7, 3., 1120 Copenhagen, Denmark; [5]The National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 Copenhagen, Denmark; [6]Department of Cardiology and Clinical Investigation, Nordsjaellands Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark; [7]Department of Cardiology, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark; and [8]Section of Forensic Pathology, Department of Forensic Medicine, Copenhagen University, Frederik V's Vej 11, 2100 Copenhagen, Denmark

Received 16 July 2019; revised 8 October 2019; editorial decision 28 November 2019; accepted 3 December 2019; online publish-ahead-of-print 17 December 2019

See page 2707 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa011)

Aims The aim of this study was to compare nationwide incidence rate (IR) of sudden cardiac death (SCD) in persons aged 1–49 years with and without diabetes mellitus (DM).

Methods and results The study population consisted of all persons in Denmark aged 1–49 years in 2000–09, which equals 27.1 million person-years. All 14 294 deaths in the 10-year period were included. By using the highly descriptive Danish death certificates, 1698 cases of sudden and unexpected death were identified. Through review of autopsy reports, discharge summaries, and the Danish registries, we identified 1363 cases of SCD. The Danish Register of Medicinal Product Statistics was used to identify persons with type 1 DM and type 2 DM. Among the 14 294 decedents, there were 669 with DM, of which 118 suffered SCD (9% of all SCD), making SCD the leading cause of death among young persons with DM. Among those aged 1–35 years, the IR of SCD-DM was 21.9 per 100 000 person-years compared to 2.6 per 100 000 person-years among persons without DM [IR ratio 8.6, 95% confidence interval (CI) 5.8–28.6]. Within the age range 36–49 years, the IR among persons with DM was 119.8 per 100 000 person-years compared to 19.7 per 100 000 person-years among persons without DM (IR ratio 6.1, 95% CI 4.7–7.8).

Conclusion We found that young persons with DM aged 1–35 years had >8-fold higher SCD IR compared to young persons without DM. Our study highlights the need for early cardiovascular risk monitoring and assessment in young persons with DM.

Keywords Sudden cardiac death • Diabetes • Children • Young

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases in the young.[1] Persons with DM have increased all-cause mortality compared to the general population.[1–5] The decreased life expectancy is in part explained by an increased risk of cardiovascular disease and sudden cardiac death (SCD) among patients with DM (SCD-DM).[1–3,5–9]

Diabetes mellitus is a well-established risk factor of SCD and several mechanisms have been proposed to account for the increased

* Corresponding author. Tel: +45 60 45 44 13, Fax: +45 35 45 65 00, Email: jespersvane@gmail.com

† The first two authors contributed equally to this work.

risk of SCD among persons with DM.[2,5,6] These include manifest and silent myocardial ischaemia, QT interval prolongation, hypoglycaemia, diabetic cardiomyopathy, and decreased ventilatory response to hypoxia and hypercapnia.[5] Increased arrhythmogenic potential, occurring as a result of diabetes-related autonomic neuropathy may be another contributing factor.[5] Previous studies report a two- to four-fold increased risk of SCD in persons with DM after adjustment for cardiovascular risk factors.[2,6,7,9] However, these studies do not include young persons or are based on findings from one region of a country with data almost exclusively obtained from autopsied decedents. As autopsy is far from always conducted, there is a potential bias in the reported results. Furthermore, information on differences in risk of SCD between persons with DM type 1 (DM1) and 2 (DM2) is scarce.[5]

We have previously identified and characterized all SCD cases in Denmark among persons aged 1–35 years in 2000–09 and 36–49 years in 2007–09.[10,11] The aim of this study was to use this unique dataset together with information from the Danish nationwide health registries to examine incidence rates (IRs) and underlying causes of SCD in persons with DM aged 1–49 years. Furthermore, we aimed to explore any differences between persons with DM1 and DM2.

Methods

In this Danish nationwide population-based study, we included all deaths in persons aged 1–35 years in 2000–09 and 36–49 years in 2007–09.[10,11] Autopsy reports, discharge summaries, death certificates, and information from nationwide Danish health registries were used to identify all persons with diabetes who suffered SCD.

The Danish health care system and Danish registries

All Danish residents are assigned a unique and personal Civil Registration Number, which can be linked to national registries on an individual level. Information on prior medicinal usage can be retrieved from the Danish Register of Medicinal Product Statistics, which holds information on all prescriptions dispensed from Danish pharmacies since 1995. Prescribed drugs are coded according to the international Anatomical Therapeutic Chemical (ATC) classification system. Drug expenses are partially reimbursed by health care authorities and therefore Danish pharmacies are required to register all dispensed prescriptions, which ensures complete registration.[12]

Information on prior medical history can be retrieved from the Danish National Patient Register which contains information on all inpatient activities at Danish hospitals and emergency departments since 1977 (and outpatient contacts since 1995) using ICD diagnosis codes for each visit.

Death certificates and forensic and clinical autopsy

Whenever a person dies in Denmark a death certificate is issued. The death certificate is always issued by a medical doctor, who on basis on all available information, including medical files, determines most likely cause of death. Police involvement is mandatory whenever a person is found dead and/or death is sudden and unexpected. The police decide whether a medicolegal external examination is performed. The police carry out this examination together with a Medical Doctor of Public Health who has access to first responder records, any medical files related to the deceased, the entire police record including eye witness statements, and the body of the deceased, which is always externally examined. Information from all of these sources is included in a *supplementary information field* on the death certificate, which makes Danish death certificates highly suitable for identification of sudden and unexpected death.[10,11]

Forensic autopsy is conducted if manner of death is not fully elucidated after medicolegal external examination. When indicated a toxicological examination is performed by the forensic toxicology department.[13] Furthermore, physicians and relatives of the deceased can request a hospital autopsy if it is decided not to perform a forensic autopsy.

Study population and data collection

We have previously used the highly informative Danish death certificates to identify sudden deaths in Denmark among all individuals aged 1–35 years in 2000–09 and 36–49 years in 2007–09.[10,11]

Cases of sudden and unexpected death due to cardiac causes, i.e. SCD, were subsequently identified using autopsy reports, the Danish National Patient Register, discharge summaries, and in selected cases medical records. Persons with DM requiring glucose-lowering pharmacotherapy were identified using information from the Danish Register of Medicinal Product Statistics.

Definitions

Sudden death was defined as a sudden, natural, unexpected death; in witnessed cases, as an acute change in cardiovascular status with time to death being <1 h and, in unwitnessed cases, as a person last seen alive and normally functioning <24 h before being found death.

Sudden cardiac death in autopsied cases was defined as a sudden death of unknown (sudden arrhythmic death syndrome, SADS) or cardiac cause and in non-autopsied cases as a sudden death presumed to be of cardiac origin after review of all available information. Non-SCD was defined as death of either confirmed or likely cardiac aetiology, where criteria of being sudden and unexpected were not fulfilled.

Among the deceased a person was defined as having DM if this person had claimed ≥1 prescription of glucose-lowering drugs (ATC A10) within 180 days of death. In the background study population, the proportion of persons with DM was identified on an annual basis as all persons claiming ≥1 prescription of glucose-lowering drugs within 180 days of January 1.[14] For both deceased and the background population, persons who at any point in their life redeemed prescriptions of oral antidiabetic agents (ATC A10B) ± insulin or insulin-analogues (ATC A10A) were defined as persons with DM2. Those who only claimed prescriptions of insulin or insulin-analogues were defined as persons with DM1. Due to very few events among children and young adults, mortality patterns among persons with DM2 were analysed only for persons aged 21–49 years. For DM1, all persons aged 1–49 years were included in the analyses.

Use of QT-prolonging medicine was identified as persons that claimed prescription ≤90 days before death of a drug that prolongs the QT interval according to the Credible Meds website.[15]

Statistical methods

Data analysis was performed using SAS software package 9.4. Incidence rate was stratified by age and sex or calculated by direct age- and sex-standardization. For direct standardization, 5-year age- and sex-specific mortality rates were applied to the equivalent age and sex strata from the general Danish population calculated as the average population in Denmark from 2000 to 2009. Incidence rate of SCD for persons with DM was calculated using the sex- and age-specific diabetic background population as denominator. Incidence rate for persons without DM were

Table 1 Clinical characteristics in sudden cardiac death cases among persons with and without diabetes mellitus aged 1–35 years in 2000–09 and 36–49 years in 2007–09

Clinical characteristics	SCD with DM ($n = 118$)	SCD without DM ($n = 1245$)	*P*-value[a]
Age (years), median (IQR)	43 (35–47)	37 (29–45)	<0.001
Males, *n* (%)	84 (71)	891 (72)	0.930
Previous medical history, *n* (%)			
Psychiatric disease	31 (26)	266 (21)	0.217
Cardiovascular disease	32 (27)	191 (15)	<0.001
Ischaemic heart disease	22 (19)	98 (8)	<0.001
Heart failure	25 (21)	89 (7)	<0.001
Cardiac arrhythmia	11 (9)	74 (6)	0.147
Neurological disorders	12 (10)	168 (13)	0.308
Gastrointestinal disease	10 (8)	59 (5)	0.077
Cerebrovascular disease	6 (5)	43 (3)	0.363
Medicolegal external examination[b], *n* (%)	55 (50)	912 (76)	<0.001
Witnessed deaths[c], *n* (%)	38 (40)	447 (40)	0.939
Autopsied SCD, *n* (%)	38 (32)	715 (57)	<0.001
Explained SCD	28 (74)	454 (63)	0.202
SADS	10 (26)	261 (37)	
Place of cardiac arrest, *n* (%)			
Home	72 (61)	773 (62)	0.086
Public place	19 (16)	278 (22)	
Hospital/ambulance	16 (14)	132 (11)	
Other	11 (9)	62 (5)	
Activity prior to cardiac arrest, *n* (%)			
Awake and relaxed	45 (38)	551 (44)	<0.001
Sleep	22 (19)	320 (26)	
Physical activity	3 (3)	93 (7)	
Other	48 (41)	281 (23)	

DM, diabetes mellitus; IQR, interquartile range; SADS, sudden arrhythmic death syndrome; SCD, sudden cardiac death.
[a]*P*-value for differences between sudden cardiac death cases with and without diabetes mellitus.
[b]Data missing in 4% of all sudden cardiac deaths.
[c]Data missing in 11% of all sudden cardiac deaths.

calculated with non-diabetic population of Danes as the reference population. Exact confidence intervals (CIs) for age- and sex-specific rates were calculated assuming Poisson distributed data. Directly standardized IRs of SCD were also computed. Differences in proportions were tested with the Fisher's exact test. Continuous variables were compared using medians and the Wilcoxon rank-sum test. Logistic regression was used to compare SCD in persons with and without DM and to examine associations between SCD-DM and prehospital factors, comorbidities, and post-mortem examination. Covariates for the multivariable model were selected on basis of the univariate analysis presented in *Table 1*.

Results

The mean population of Danish residents aged 1–35 years in 2000–09 and 36–49 years in 2007–09, were 2.37 and 1.11 million inhabitants, respectively. This corresponds to 27.1 million person-years in the 10-year period. There was a total of 14 294 deaths, of which 1363 (10%) suffered SCD (*Figure 1*). Among the 14 294 decedents, there were 669 (5% of all deaths) with DM, of which 118 suffered SCD (9% of all SCD); 71 (60%) with DM1 and 47 (40%) with DM2.

Clinical characteristics

A comparison of clinical characteristics between SCD cases with and without DM is shown in *Table 1*. Among persons who suffered SCD those with DM were older than persons without DM (median age 43 and 37, respectively, $P < 0.001$). The SCD-DM population had a significantly higher prevalence of cardiovascular diseases compared to the non-DM SCD population ($P < 0.001$). In total, 30 (25%) SCD-DM cases claimed prescriptions of proarrhythmic pharmacotherapy within 90 days of death.

Of all deaths in the study period, medicolegal external examination and autopsy were performed in 32% and 33%, respectively. Both medicolegal external examinations and autopsies were less frequently conducted among SCD cases with DM compared to SCD cases without DM (50% vs. 76% and 32% vs. 57%, respectively, $P < 0.001$). In a multivariable analysis comparing SCD in persons with and without DM, both medicolegal external examination and autopsy was

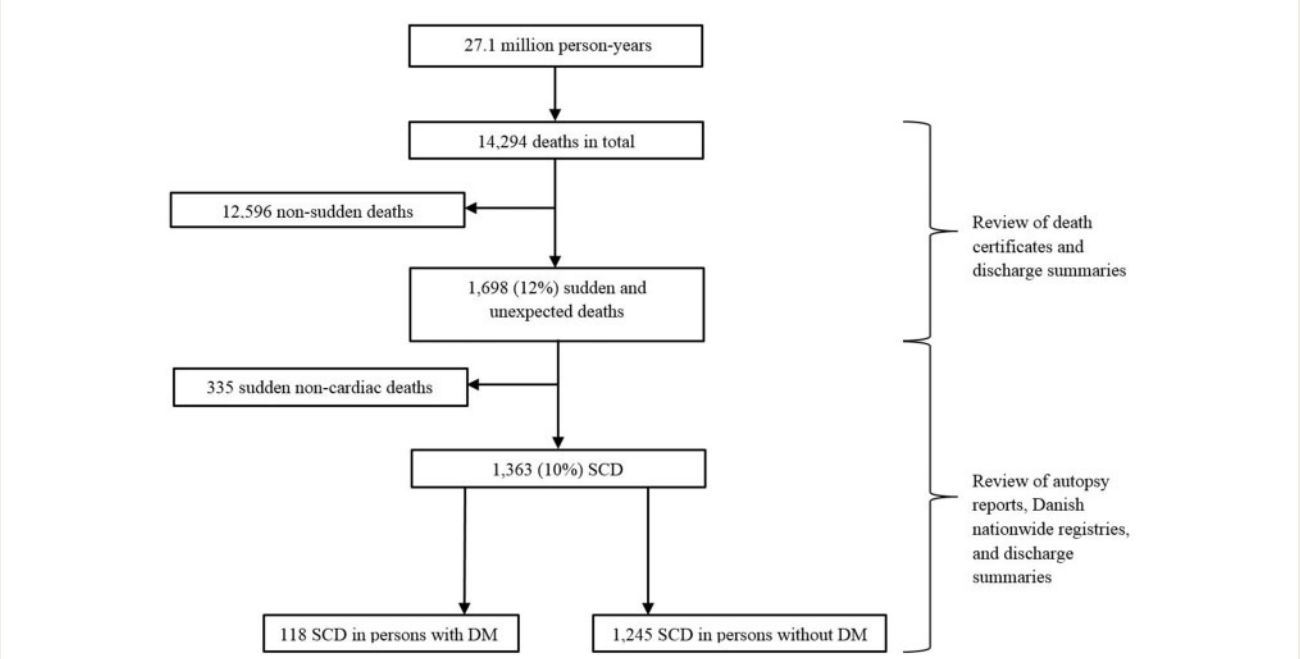


Figure 1 Flowchart of the identification of all sudden cardiac deaths among patients with diabetes mellitus aged 1–35 years in 2000–09 and 36–49 years in 2007–09. DM, diabetes mellitus; SCD, sudden cardiac death.

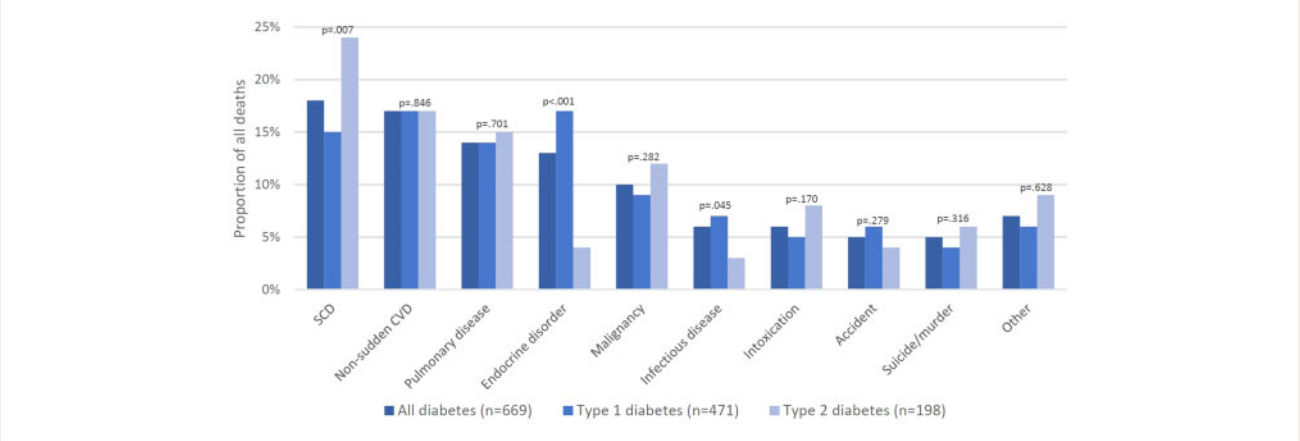


Figure 2 Causes of death among deceased persons with diabetes aged 1–35 years in 2000–09 and 36–49 years in 2007–09 ($n = 669$). CVD, cardiovascular disease; SCD, sudden cardiac death. *P*-values are for differences between persons with type 1 and 2 diabetes.

conducted less frequently among SCD-DM cases independent of age and cardiac comorbidity. Age and a diagnosis of heart failure were also independently associated with SCD-DM.

Cause of death among persons with diabetes mellitus

An overview of causes of death among the 669 deceased with DM is shown in *Figure 2*. The most common causes of death were SCD ($n = 118$, 18%), non-SCD ($n = 112$, 17%), pulmonary disease ($n = 96$, 14%), and endocrine disease ($n = 87$, 13%). Diabetic ketoacidosis was the most common underlying endocrine cause of death ($n = 24$, 28% of all endocrine causes of death) followed by diabetic nephropathy ($n = 10$, 11%) and hypoglycaemia ($n = 5$, 6%).

Of 38 autopsied SCD-DM cases the most frequent underlying causes of SCD were coronary artery disease ($n = 18$, 47%), SADS ($n = 10$, 26%), and hypertrophic heart ($n = 4$, 11%). Of the 10 SADS cases, 6 had DM1 and were found dead-in-bed. In 17 (45%) of the autopsied SCD-DM cases, cause of death was a potentially inherited heart disease (e.g. SADS and cardiomyopathy). Among SCD-DM

cases aged 1–35 years, SADS was the most frequent underlying cause of death ($n = 7$, 54%), while coronary artery disease ($n = 16$, 64%) was most common among cases aged 36–49 years. Of the 38 autopsied SCD-DM cases, 22 (58%) were examined toxicologically. In 2 of these 22 cases, findings of illicit drugs were reported (both cocaine).

Incidence rates

Sudden cardiac death IR according to age in persons with and without DM are shown in *Figure 3*, while age- and sex-stratified IR are shown in *Table 2*. The age- and sex-standardized IR of SCD in persons with DM aged 1–35 years was 21.9 (95% CI 14.9–72.5) per 100 000 person-years compared to 2.6 (95% CI 2.4–2.8) per 100 000 person-years in persons aged 1–35 years without DM. This corresponds to an IR ratio of 8.6 (95% CI 5.8–28.6). Among persons with DM aged 36–49 years, the IR of SCD was 119.8 (95% CI 93.7–152.1) per 100 000 person-years, while the IR of SCD among persons aged 36–49 years without DM was 19.7 (95% CI 18.2–21.2) corresponding to an IR ratio of 6.1 (95% CI 4.7–7.8).

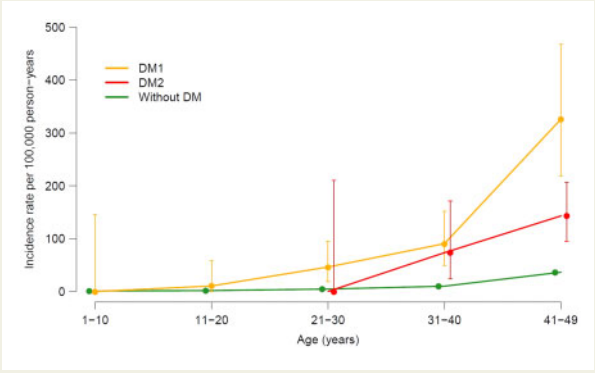


Figure 3 Incidence of sudden cardiac death according to age among persons with and without diabetes mellitus. Vertical bars represent 95% confidence intervals. DM, diabetes mellitus; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2.

Type 1 and 2 diabetes mellitus

Compared to persons with DM1, persons with DM2 were older at time of SCD ($P = 0.036$) and more often had psychiatric comorbidities ($P = 0.047$) (Supplementary material online, *Table S1*). Duration of antidiabetic therapy was calculated as time from first redeemed antidiabetic agent to time of death or end of observational period. According to information from The Danish National Patient Register (capturing 90% of the SCD-DM cases in the study) median duration of DM was 13.9 years for persons with DM1 and 3.9 years for persons with DM2.

Sudden cardiac death was the leading cause of death among persons with DM2, while the most common causes of death among persons with DM1 were endocrine disease ($n = 79$, 17%) and non-SCD ($n = 78$, 17%) (*Figure 2*). Most common cause of SCD in autopsied cases was coronary artery disease for both persons with DM1 and DM2, ($n = 11$, 42% and $n = 7$, 58%, respectively), while this was closely followed by SADS among persons with DM1 ($n = 7$, 31%).

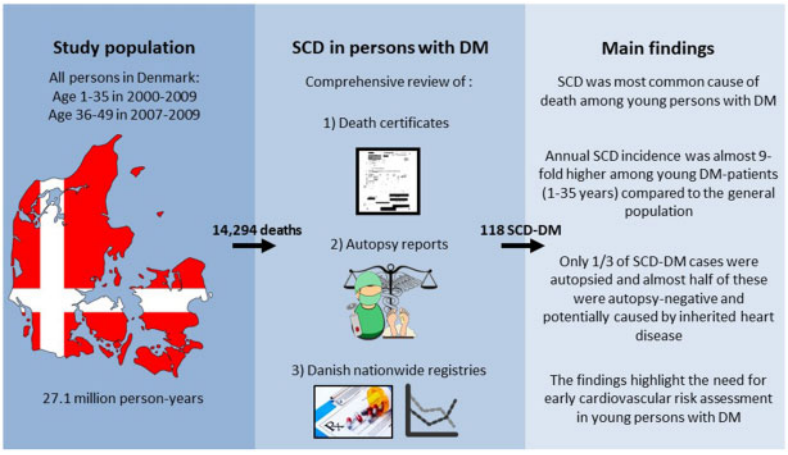
Age- and sex-standardized IR of SCD for persons with DM1 aged 1–35 years was 25.1 (16.3–76.1) per 100 000 person-years and 180.7 (95% CI 130.5–247.3) among persons aged 36–49 years. The IR ratios between persons with DM1 and without DM were 9.9 (95% CI 6.3–30) for persons aged 1–35 years and 9.2 (95% CI 6.6–12.7) for persons aged 36–49 years.

Age- and sex-standardized IR of SCD for persons with DM2 aged 21–35 years was 26.7 (95% CI 9.7–150.1) per 100 000 person-years and 92.4 (95% CI 62.7–135.2) among persons aged 36–49 years. The IR ratios between persons with DM2 and without DM were 6.1 (95%

Table 2 Annual incidence rates of sudden cardiac death per 100 000 person-years stratified by age and sex

	Age (years)	Non-DM		DM1				DM2			
		Number of deaths	IR/100 000 PY	Number of deaths	IR/100 000 PY	IR ratio[c] (95% CI)	*P*-value[a]	Number of deaths	IR/100 000 PY	IR ratio[d] (95% CI)	*P*-value[b]
Males	1–10	31	0.9	0	—	—	—	0	—	—	—
	11–20	57	1.8	<3	10.5	5.9 (0.1–34.4)	0.315	0	—	—	—
	21–30	154	4.6	7	46.3	10.2 (4–21.5)	<0.001	0	—	—	—
	31–40	258	10.1	14	90.5	9 (4.8–15.4)	<0.001	5	73.4	7.3 (2.3–17.2)	0.002
	41–49	391	36.5	29	325.9	8.9 (5.9–13)	<0.001	28	143	3.9 (2.6–5.7)	<0.001
Females	1–10	16	0.5	0	—	—	—	0	—	—	—
	11–20	34	1.1	<3	12.1	10.9 (0.3–65.1)	0.180	0	—	—	—
	21–30	72	2.2	7	61.1	28.2 (10.9–61.1)	<0.001	<3	12.8	5.9 (0.1–33.9)	0.315
	31–40	92	3.7	4	37.6	10.2 (2.7–27)	0.002	6	51.3	13.9 (5–31.5)	<0.001
	41–49	140	13.3	8	141.8	10.6 (4.5–21.5)	<0.001	7	48.7	3.6 (1.4–7.7)	0.008

DM, diabetes mellitus; IR, incidence rate; PY, person-years.
[a]*P*-value for differences between persons with DM1 and persons without DM.
[b]*P*-value for differences between persons with DM2 and persons without DM.
[c]Incidence rate ratio between persons with DM1 and persons without DM.
[d]Incidence rate ratio between persons with DM2 and persons without DM.



Take home figure Identification and characterization of young persons with diabetes mellitus suffering sudden cardiac death in Denmark. DM, diabetes mellitus; SCD, sudden cardiac death.

CI 2.2–34.5) for persons aged 21–35 years and 4.7 (95% CI 3.2–6.9) for persons aged 36–49 years.

Discussion

Using autopsy reports, death certificates, discharge summaries, and information from nationwide health registries, we have conducted a comprehensive nationwide study on SCD among persons with DM aged 1–49 years.

Autopsy of sudden cardiac death cases with diabetes

We found lower rates of both medicolegal external examination and autopsy among SCD-DM cases compared to non-DM SCD cases. A large proportion of autopsied SCD-DM was, however, caused by potentially inherited heart conditions such as SADS. Identification of inheritable SCD causes is important to reduce mortality in family members of SCD victims as appropriate investigations may identify living relatives with undiagnosed inherited heart disease.[16,17] Sudden arrhythmic death syndrome was found to be a common cause of SCD-DM. Postmortem genetic testing has been shown to identify a likely cause of death in 13–35% of SADS cases and detailed cardiac and genetic investigation of first-degree relatives of SADS victims have been shown to yield a diagnosis of inherited heart disease in up to 50% of affected families.[18–26] There is accumulating evidence that hypoglycaemia can cause cardiac dysfunction and sudden death by hypoglycaemia-induced cardiac arrhythmias and abnormal cardiac repolarization.[4] Since serum glucose level is greatly modified in the death process and after death, and not examined routinely in sudden death, we cannot exclude that the underlying mechanism in some of the autopsy-negative cases is caused by hypoglycaemia and not an inherited cardiac disease. However, most previous studies have not excluded DM in the studies of SADS and current literature within this area shows that in ≈40% of all SADS cases, there is a monogenetic cause or positive findings in the family for primary arrhythmias such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT).[19] The yield of cardiac and genetic investigation of relatives of SCD-DM victims is, however, not known.

Taken together this supports use of autopsy in all cases of sudden and unexpected death among young persons, including persons with DM.

Incidence rates of sudden cardiac death in persons with diabetes

Previous studies have shown that persons with DM have a two- to four-fold increased risk of SCD compared to persons without DM.[2,5,6]This finding is consistent across studies with different study design and/or geographical settings.[2,5,6] These studies have either been regional or been conducted in selected populations (e.g. only autopsied cases). Our study is the first to describe nationwide IR of SCD among persons with DM in an unselected and young population. We found that persons with DM had significantly higher SCD rates compared to persons without DM with IR ratios of ≈9 and ≈6 in persons aged 1–35 and 36–49 years, respectively.

The discrepancy in IR ratios is likely in part explained by age differences in the populations studied.[2,5,6] Sudden cardiac death IR in a young and presumably healthy background population is low and therefore the increased IR of SCD in persons with DM has a greater impact when examining younger age. Furthermore, this was a retrospective nationwide population-based study and we were not able to adjust for known risk factors for SCD, as done by previous prospective or case control studies in selected cohorts.[2] In the present study, non-autopsied cases of sudden death were also included, which naturally leads to higher IR compared to studies that only include autopsied SCD. Finally, the method we used to identify persons with DM has a high sensitivity, enabling us to capture most SCD-DM cases.[27,28]

Cause of death among persons with diabetes

In line with previous studies, we found cardiovascular disease to be the most common cause of death among persons with DM.[1,29,30]

In studies of causes of death among persons with DM, cardiovascular disease is rarely divided into SCD and non-SCD.

An Australian-based review of causes of death from 1914 coronial postmortem examinations in young Australians with DM1, found the three predominant causes of death among persons <40 years to be unnatural death (28%), acute complications of diabetes (27%), and sudden unexpected death (22%).[31] Two-thirds of the sudden unexpected deaths were attributed to the so-called 'dead-in-bed' syndrome. Dead-in-bed was defined as a death in a generally well individual with DM1 that suffers unwitnessed sudden unexpected death in an undisturbed bed and where autopsy provides no clear anatomical cause of death.[31]

The underlying mechanism leading to dead-in-bed syndrome remains largely unknown, although growing evidence points towards autonomic neuropathy and nocturnal hypoglycaemia as contributory causes. Autonomic neuropathy among persons with DM can cause reduced parasympathetic activity and, in some cases, eventually lead to sympathetic predominance. Normally at night, the sympathetic response is low and parasympathetic activity is relatively high. With chronic hyperglycaemia resulting in damage to the parasympathetic system, persons with DM can develop increased mean heart rate and reduction in diurnal heart rate variation.[31] Furthermore, the dead-in-bed syndrome is believed to be caused by nocturnal arrhythmia promoted by hypoglycaemia, which causes QTc lengthening. Hypokalaemia due to over-insulinization and adrenaline response may also play a role.[31,32]

In the present study, we found 10 SADS cases of which 6 had DM1 and was found dead-in-bed. This corresponds to a dead-in-bed IR of 6.7 (95% CI 3.0–14.8) per 100 000 person-years. These cases could potentially be dead-in-bed cases, although information regarding whether the bed was undisturbed was not available.

Duration of DM among SCD-DM cases was remarkable short, both among DM1 and DM2. The Danish Register of Medicinal Product Statistics was, however, established in 1995. Furthermore, the Danish National Patient Register did not include outpatient contacts until 1995. As many DM patients only have outpatient contact with the health care system, we likely underestimate DM duration in some patients.

Cardiovascular mortality in persons with DM1 and DM2 is often due to accelerated atherosclerosis, ischaemic heart disease, and heart failure, which are all important risk factors for SCD, independent of other risk factors.[33] However, other mechanisms are also likely in play.[4] As in the background population, persons with DM1 may have a variety of subclinical cardiac diseases. In these patients, arrhythmia/cardiac arrest may be triggered by severe metabolic decompensation (e.g. severe diabetic ketoacidosis, hypoglycaemia, and/or out-of-range potassium). In addition, cardiac autonomic neuropathy (CAN) might explain the increased incidence of SCD among diabetes patients. CAN is a serious complication of DM which is associated with five-fold increased risk of cardiovascular mortality, and an increased frequency of SCD among persons with CAN has been reported in multiple studies. Cardiac autonomic neuropathy has been found both among individuals with DM1 and DM2 and in children and adults. Risk markers for CAN are age, DM duration, glycaemic control, hypertension, and dyslipidemia.[5] The study population in this study is relatively young and consequently we find more individuals with DM1 than DM2. The duration of DM among persons with DM1 is more than three times as long compared to persons with DM2, presumably, leading to a higher prevalence of CAN among the DM1 group.

Increased prevalence of manifest and silent myocardial ischaemia and QT interval prolongation have been found among persons with DM with CAN and this partly explains the increased mortality and higher proportion of deaths attributed to SCD among persons with DM.[5,33]

We found that a high proportion of SCD-DM cases claimed prescriptions of proarrhythmic pharmacotherapy prior to death, which highlights that an increased focus on identification of individuals at high risk of SCD among patients receiving proarrhythmic drugs is warranted.

Limitations

We have previously discussed limitations of defining DM status from the registration of all usage of antidiabetic pharmacotherapy in the Danish Register of Medicinal Product Statistics.[1] In brief, although using the Danish Register of Medicinal Product Statistics represents a conservative way of identifying DM patients, this approach has been shown to capture at least 85% of patients with DM in Denmark and it has a positive predictive value of 98%.[27,28]

Non-autopsied cases of sudden unexpected death were included if death was presumed to be of cardiac origin after thorough review of all available information. It cannot be excluded that some of these cases died from non-cardiac causes such as pulmonary embolism or hypoglycaemia. Non-autopsied sudden death cases with clinical signs of a non-cardiac cause of death, however, were not classified as SCD.

We were not able to obtain information on life style factors (e.g. smoking status, body mass index, lipid levels, and diet) and other important clinical information such as blood glucose values and hemoglobin A1C (HbA1c).

Conclusion

In this large nationwide study on SCD-DM, persons with DM had increased SCD rates compared to person without DM with an IR ratio of ≈9 in persons aged 1–35 years. Only one-third of the SCD-DM cases had an autopsy conducted and almost half of these were autopsy-negative and potentially caused by inherited heart disease or cardiac arrhythmias induced by diabetes-related complications such as hypoglycaemia or CAN.

Our study highlights the need for early cardiovascular risk monitoring and assessment in young persons with DM. Furthermore, the findings support use of autopsy in all cases of sudden and unexpected death aged 1–49 years, including persons with DM.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This work was supported by the Novo Nordisk Foundation, Copenhagen, Denmark [NNFOC140011573]. JS, reciewed salary from the Department of Forensic Medicine, Univiserty of Copenhagen.

Conflict of interest: G.G. reports grants from Bayer, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim and have personal shares in Novo Nordisk. U.P.-B. reports grants and personal fees from Novo Nordisk, SanofiAventis, AstraZeneca and Zealand Pharma. The study complies with the Declaration of Helsinki and was approved by the local ethics committee (H-KF-272484).

References

1. Svane J, Lynge TH, Pedersen-Bjergaard U, Jespersen T, Gislason GH, Risgaard B, Winkel BG, Tfelt-Hansen J. Cause-specific mortality in children and young adults with diabetes mellitus: a Danish Nationwide Cohort Study. *Eur J Prev Cardiol* 2019; doi:10.1177/2047487319836555.
2. Aune D, Schlesinger S, Norat T, Riboli E. Diabetes mellitus and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis* 2018;**28**:543–556.
3. Collaboration TERF. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;**364**:829–841.
4. Amiel SA, Aschner P, Childs B, Cryer PE, de Galan BE, Frier BM, Gonder-Frederick L, Heller SR, Jones T, Khunti K, Leiter LA, Luo Y, McCrimmon RJ, Pedersen-Bjergaard U, Seaquist ER, Zoungas S. Hypoglycaemia, cardiovascular disease, and mortality in diabetes. *Lancet Diabetes Endocrinol* 2019;**7**:385–396.
5. Bergner DW, Goldberger JJ. Diabetes mellitus and sudden cardiac death. *Cardiol J* 2010;**17**:117–129.
6. Zaccardi F, Khan H, Laukkanen JA. Diabetes mellitus and risk of sudden cardiac death. *Int J Cardiol* 2014;**177**:535–537.
7. Jouven X, Lemaître RN, Rea TD, Sotoodehnia N, Empana J-P, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. *Eur Heart J* 2005;**26**:2142–2147.
8. Jayaraman R, Reinier K, Nair S, Aro AL, Uy-Evanado A, Rusinaru C, Stecker EC, Gunson K, Jui J, Chugh SS. Risk factors of sudden cardiac death in the young. *Circulation* 2018;**137**:1561–1570.
9. Junttila MJ, Kiviniemi AM, Lepojärvi ES, Tulppo M, Piira O-P, Kenttä T, Perkiömäki JS, Ukkola OH, Myerburg RJ, Huikuri HV. Type 2 diabetes and coronary artery disease. *Heart Rhythm* 2018;**15**:1450–1456.
10. Winkel BG, Holst AG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, Bundgaard H, Svendsen JH, Haunso S, Tfelt-Hansen J. Nationwide study of sudden cardiac death in persons aged 1-35 years. *Eur Heart J* 2011;**32**:983–990.
11. Risgaard B, Winkel BG, Jabbari R, Behr ER, Ingemann-Hansen O, Thomsen JL, Ottesen GL, Gislason GH, Bundgaard H, Haunsø S, Holst AG, Tfelt-Hansen J. Burden of sudden cardiac death in persons aged 1 to 49 years. *Circ Arrhythm Electrophysiol* 2014;**7**:205–211.
12. Wallach Kildemoes H, Toft Sorensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;**39**(7 Suppl):38–41.
13. Bjune T, Risgaard B, Kruckow L, Glinge C, Ingemann-Hansen O, Leth PM, Linnet K, Banner J, Winkel BG, Tfelt-Hansen J. Post-mortem toxicology in young sudden cardiac death victims: a Nationwide Cohort Study. *Europace* 2018;**20**:614–621.
14. Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A, Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk. *Circulation* 2008;**117**:1945–1954.
15. Weeke PE, Kellemann JS, Jespersen CB, Theilade J, Kanters JK, Hansen MS, Christiansen M, Marstrand P, Gislason GH, Torp-Pedersen C, Bundgaard H, Jensen HK, Tfelt-Hansen J. Long-term proarrhythmic pharmacotherapy among patients with congenital long QT syndrome and risk of arrhythmia and mortality. *Eur Heart J* 2019;**40**:3110–3117.
16. Semsarian C, Ingles J, Wilde A. Sudden cardiac death in the young. *Eur Heart J* 2015;**36**:1290–1296.
17. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck K-H, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2015;**36**:2793–2867.
18. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, Davis AM, Thompson T, Connell V, Wallace J, Naylor C, Crawford J, Love DR, Hallam L, White J, Lawrence C, Lynch M, Morgan N, James P, Du Sart D, Puranik R, Langlois N, Vohra J, Winship I, Atherton J, McGaughran J, Skinner JR, Semsarian C. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 2016;**374**:2441–2452.
19. Lahrouchi N, Raju H, Lodder EM, Papatheodorou E, Ware JS, Papadakis M, Tadros R, Cole D, Skinner JR, Crawford J, Love DR, Pua CJ, Soh BY, Bhalshankar JD, Govind R, Tfelt-Hansen J, Winkel BG, van der Werf C, Wijeyeratne YD, Mellor G, Till J, Cohen MC, Tome-Esteban M, Sharma S, Wilde A, Cook SA, Bezzina CR, Sheppard MN, Behr ER. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. *J Am Coll Cardiol* 2017;**69**:2134–2145.
20. Tester DJ, Ackerman MJ. Postmortem long QT syndrome genetic testing for sudden unexplained death in the young. *J Am Coll Cardiol* 2007;**49**:240–246.
21. Chugh SS, Senashova O, Watts A, Tran PT, Zhou Z, Gong Q, Titus JL, Hayflick SJ. Postmortem molecular screening in unexplained sudden death. *J Am Coll Cardiol* 2004;**43**:1625–1629.
22. Skinner JR, Crawford J, Smith W, Aitken A, Heaven D, Evans C-A, Hayes I, Neas KR, Stables S, Koelmeyer T, Denmark L, Vuletic J, Maxwell F, White K, Yang T, Roden DM, Leren TP, Shelling A, Love DR. Prospective, population-based long QT molecular autopsy study of postmortem negative sudden death in 1 to 40 year olds. *Heart Rhythm* 2011;**8**:412–419.
23. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT, Rowland E, Jeffery S, McKenna WJ. Sudden arrhythmic death syndrome. *Eur Heart J* 2008;**29**:1670–1680.
24. McGorrian C, Constant O, Harper N, O'Donnell C, Codd M, Keelan E, Green A, O'Neill J, Galvin J, Mahon NG. Family-based cardiac screening in relatives of victims of sudden arrhythmic death syndrome. *Europace* 2013;**15**:1050–1058.
25. van der Werf C, Hofman N, Tan HL, van Dessel PF, Alders M, van der Wal AC, van Langen IM, Wilde A. Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young. *Heart Rhythm* 2010;**7**:1383–1389.
26. Kumar S, Peters S, Thompson T, Morgan N, Maccicoca I, Trainer A, Zentner D, Kalman JM, Winship I, Vohra JK. Familial cardiological and targeted genetic evaluation. *Heart Rhythm* 2013;**10**:1653–1660.
27. Jørgensen CH, Gislason GH, Ahlehoff O, Andersson C, Torp-Pedersen C, Hansen PR. Use of secondary prevention pharmacotherapy after first myocardial infarction in patients with diabetes mellitus. *BMC Cardiovasc Disord* 2014;**14**:4.
28. Drivsholm TB, Frederiksen K, de Fine Olivarius N, Ødegaard B, Kristensen JK. [The prevalence of diabetes in Denmark. Development of a method for a registry-based assessment]. *Ugeskr Laeger* 2003;**165**:2887–2891.
29. Baena-Díez JM, Peñafiel J, Subirana I, Ramos R, Elosua R, Marín-Ibañez A, Guembe MJ, Rigo F, Tormo-Díaz MJ, Moreno-Iribas C, Cabré JJ, Segura A, García-Lareo M, Gómez de la Cámara A, Lapetra J, Quesada M, Marrugat J, Medrano MJ, Berjón J, Frontera G, Gavrila D, Barricarte A, Basora J, García JM, Pavone NC, Lora-Pablos D, Mayoral E, Franch J, Mata M, Castell C, Frances A, Grau M. Risk of cause-specific death in individuals with diabetes: a competing risks analysis. *Diabetes Care* 2016;**39**:1987–1995.
30. Tancredi M, Rosengren A, Svensson A-M, Kosiborod M, Pivodic A, Gudbjörnsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess mortality among persons with type 2 diabetes. *N Engl J Med* 2015;**373**:1720–1732.
31. Hsieh A, Twigg SM. The enigma of the dead-in-bed syndrome: challenges in predicting and preventing this devastating complication of type 1 diabetes. *J Diabetes Complications* 2014;**28**:585–587.
32. Tanenberg R, Newton C, Drake A. Confirmation of hypoglycemia in the 'Dead-in-Bed' syndrome, as captured by a retrospective continuous glucose monitoring system. *Endocr Pract* 2010;**16**:244–248.
33. Eranti A, Kerola T, Aro AL, Tikkanen JT, Rissanen HA, Anttonen O, Junttila MJ, Knekt P, Huikuri HV. Diabetes, glucose tolerance, and the risk of sudden cardiac death. *BMC Cardiovasc Disord*. 2016;**16**:51. http://www.biomedcentral.com/1471-2261/16/51