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Febrile seizures prior to sudden cardiac death: a Danish nationwide study

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Aims Febrile seizure (FS) is a common disorder affecting 2–5% of children up to 5 years of age. The aim of this study was to determine whether FS in early childhood are over-represented in young adults dying from sudden cardiac death (SCD).

Methods and results We included all deaths ($n = 4595$) nationwide and through review of all death certificates, we identified 245 SCD in Danes aged 1–30 years in 2000–09. Through the usage of nationwide registries, we identified all persons admitted with first FS among SCD cases (14/245; 5.7%) and in the corresponding living Danish population (71 027/2 369 785; 3.0%) and also in victims of transport accidents (26/917; 2.8%). The frequency of FS among SCD cases was significantly increased by an odds ratio of 1.96 [95% confidence interval (CI) 1.14–3.36; $P = 0.021$] compared with the living Danish population and with an odds ratio of 2.08 (95% CI 1.07–4.04; $P = 0.046$) compared with transport accident victims. SCD cases did not differ statistically in birth year ($P = 0.272$), age at SCD ($P = 0.667$) or prior medical conditions, except for epilepsy ($P < 0.001$), when comparing SCD with and without prior FS. The most common cause of death in autopsied SCD cases with FS was sudden arrhythmic death syndrome (5/8; 62.5%).

Conclusion In conclusion, this study demonstrates a significantly two-fold increase in the frequency of FS prior to death in young SCD cases compared with the two control groups, suggesting that FS could potentially contribute in a risk stratification model for SCD and warrant further studies.

Keywords Febrile seizures • Sudden cardiac death • Sudden arrhythmic death syndrome • Sudden death

Introduction

Febrile seizure (FS) is a common disorder affecting 2–5% of children up to 5 years of age.[1,2] Although FS can be a terrifying experience for the parents, FS is generally not considered to increase long-term mortality.[3,4] However, a study based on referred cases ($n = 123$) of sudden unexplained death in childhood (1–18 years) have shown that FS was present in 39 (32%) patients prior to death.[5] A Danish nationwide study identified sudden unexpected death through registries and found an association with FS, in which the risk of sudden unexpected death was significantly increased five-fold with prior FS.[3] Since sudden cardiac death (SCD) constitute more than 75% of all sudden unexpected death among the young and adults in Denmark, this could imply an increased risk of SCD with prior FS.[6–8]

There is an inadequate understanding of the clinical implication of FS prior to SCD, and the possible pathophysiological relation between SCD and FS is unclear. A potential and partial explanation is fever-induced tachycardia,[9] which may trigger a concealed underlying arrhythmic disorder that subsequently could cause transient cerebral hypoperfusion and induce seizure-like attacks.[10] Fever by itself is a potent arrhythmogenic factor in Brugada syndrome (BrS) patients.[11] Furthermore, a transient arrhythmic episode could be mistaken as FS, as shown in a case report on BrS masquerading FS.[12] Similarly, fever-induced QTc prolongation among long QT syndrome (LQTS) type 2

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What's new?

- The frequency of febrile seizures (FS) prior to death was increased two-fold among young sudden cardiac death (SCD) cases compared to both a living and a dead control group.
- The most common cause of death in autopsied SCD with FS cases was sudden arrhythmic death syndrome.

patients has been suggested.[13] FS may have an additive value to the known risk factors for SCD.

To our knowledge, an association between SCD among the young and FS have not been previously investigated in an unselected population. The aim of this study was to determine whether FS in early childhood (0.25–5 years) are over-represented in young adults (1–30 years) dying from SCD compared with both the living background population and people who died in transport accidents.

Methods

Study design

This study used data from two previously conducted retrospective nationwide studies that identified all SCD cases aged 1–30 years in Denmark between 2000 and 2009.[6,7] In brief, these two studies identified SCD cases using death certificates, the registration of all inpatient and outpatient activities in Danish hospitals and emergency departments (EDs), and access to all medical records and autopsy reports. All death certificates were read independently by two physicians; in case of disagreementm the two investigators re-evaluated the death certificate together to reach a consensus. This study was approved by Danish Data Protection Agency (RH-2016-362, I-Suite ID: 05119). A control cohort was analysed in an anonymous register-based retrospective setting with encrypted identification numbers and hence did not require an ethical approval in Denmark.

Danish registries and death certificates

All Danish residents are assigned a permanent unique personal Civil Registration Number (CRN) using the Danish Civil Registration System (CRS), which contains individual-level demographical information of all persons in Denmark. The CRN is linked to all Danish national health and administrative registries, allowing us to retrieve information from the National Patient Registry (NPR). Since 1977, NPR has functioned as a governmental enterprise and obtained information on all admissions at Danish hospitals and EDs. Outpatient visits were included from 1995. Diagnoses for each visit are coded according to the 8th revision of the International Classification of Diseases (ICD-8) until 1993 and the 10th revision (ICD-10) from 1994. Danish death certificates are highly suitable for the identification of sudden unexpected deaths and SCD, due to the supplemental information field (see supplementary material online of Winkel *et al.*'s[6] study). The supplemental field specifies previous medical conditions, the circumstances leading to death, and interviews with witnesses and family members. We used the information from the comprehensive Danish national registries, death certificates, autopsy reports, and medical records from hospitals to describe medical conditions and co-morbidities prior to SCD.

A validation study on FS registration in NPR has been performed with parental questionnaires, telephone interviews, and review of medical records. The study concluded that FS registration in NPR is of good quality with a completeness of 71.5% [95% confidence interval (CI) 66.3–76.4%], regardless of the child outcome.[14] Among the NPR-registered FS cases, the predictive value of a positive registration was 92.8% (95% CI 88.8–95.7%).[14]

Study population

The SCD with prior FS (SCD-FS) case group was limited by the establishment of NPR in 1977, thereby excluding all prior births and confining our population to 1–30-year-old Danes in the period 2000–09. For comparison, our control group was obtained from the national CRS registry as a subset of the entire Danish population. To mimic the SCD group, we identified all singletons born between 1977 and 2008, alive at the end of 2009 and aged 1–30 years. Furthermore, we used a second control group of individuals who died in transport accidents (ICD-10 code: V00-V99) in the same age and study period. The case and control groups were subject to the same method of first FS identification through the NPR.

Definitions

There are two operational definitions of FS as defined by the American Academy of Paediatrics and International League Against Epilepsy. Through the NPR we identified all persons with FS (ICD-10 code: R56.0; ICD-8 code: 780.21) and from the suggested diagnostic criteria, we defined FS as: (i) onset between the age of 3 months and 5 years with (ii) no prior or concurrent (within 1 month) history of epilepsy (ICD-10 code: G40-G41; ICD-8 code: 345) and (iii) no prior or concurrent (within 1 month) intracranial infection (ICD-10 code: G00-G09; ICD-8 code: 320-324).

As in previous studies, we defined SCD in autopsied cases as the 'sudden, natural unexpected death of unknown, or cardiac cause; in unwitnessed cases as a person last seen alive and functioning normally, <24 h before being found dead and in witnessed cases as an acute change in cardiovascular status with the time to death being <1 h'.[6,15] SCD verified by autopsy was subdivided into two groups: (i) explained SCD, in which a known cause of death was established and (ii) sudden arrhythmic death syndrome (SADS) if the cause of death remained unknown after autopsy. If no autopsy was performed, the same criteria were used in cases presumed to be of cardiac origin based on all the available information and circumstances leading to death. In the explained SCD group, we excluded deaths caused by ischaemic heart disease or myocarditis as these—in this setting—were considered as acquired heart diseases.

Statistical analysis

Calculations and data analysis were performed in R version 3.3.1 (R development Core Team). Categorized nominal data were compared using the χ^2 test or the Fisher's exact test where appropriate. Medians among more than two samples were compared using the Kruskal–Wallis test. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Study population

During the study period, Denmark had a mean population of 5.4 million people, of whom 2.4 million were in the age group 1–30 years and born after 1977. A total of 4595 Danish residents died within the defined age and study period of which 384 (8.4%) died sudden and unexpected. After exclusion of definite acquired heart diseases, we found 245 SCD cases (5.3% of all deaths) of which 14 had FS (5.7%) prior to death (*Figure 1*).

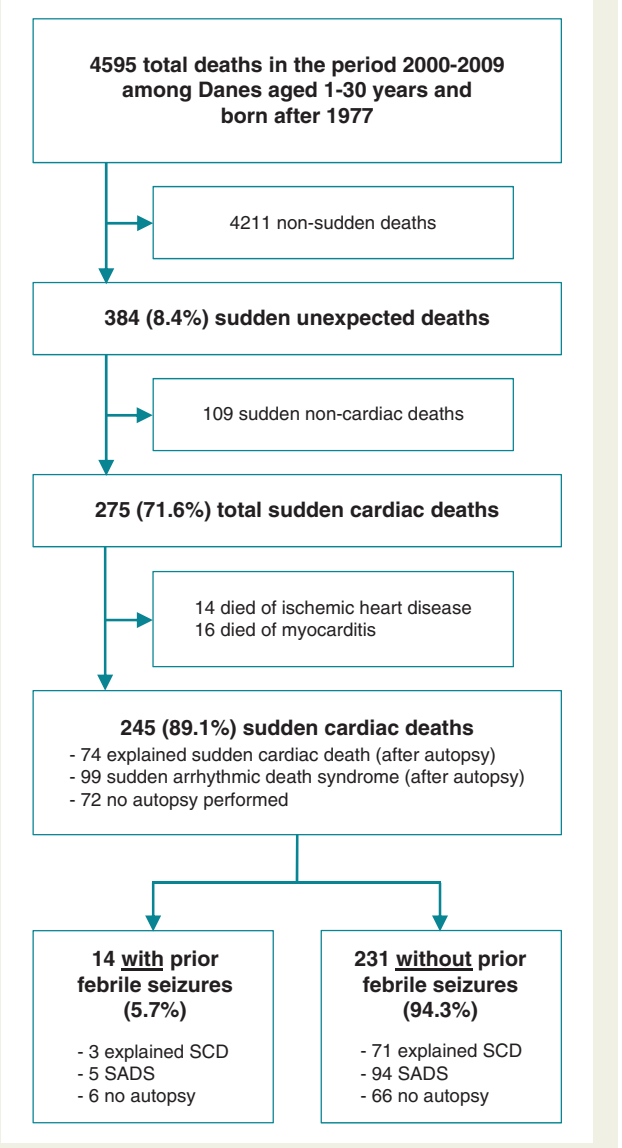

Figure 1 Flow chart of the process used to identify sudden cardiac death with prior febrile seizures.

Clinical characteristics of sudden cardiac death with and without febrile seizure prior to death

Two-thirds of SCD-FS ($n = 10$) cases were men (*Table 1*). Both SCD-FS and SCD without FS patients had few previous medical conditions. No differences in birth year were found in SCD-FS compared with SCD without FS ($P = 0.272$). The SCD with prior FS cases died at the median age of 18.9 [interquartile range (IQR) 14.4–22.7] years and SCD patients without FS died at the median age of 20.6 (IQR 14.4–25.4) years ($P = 0.273$). Subsequent diagnosis of epilepsy was seen in 7 (50%) of SCD-FS patients (of these 5 had no autopsy performed), which were significantly higher than in 25 (10.8%) of SCD patients without prior FS ($P < 0.001$). Epilepsy in SCD-FS was diagnosed after a median of 9.9 (IQR 0.3–10.1) years subsequent to FS.

We stratified SCD-FS cases according to the aetiology of SCD (*Table 2*). The median onset age of FS in SCD was 1.2 (IQR 0.8–1.6) years and occurred at a median of 16.8 (IQR 13.1–19.8) years prior to SCD. The most common cause of death (in SCD) was SADS ($n = 99$, 40.4%), of which 5 (5.1%) persons had prior FS. Of the explained SCD ($n = 74$, 30.2%), 3 (4.1%) had prior FS and among SCD cases without autopsy ($n = 72$, 29.4%), FS was seen in 6 (8.3%) cases.

We pooled SCD-FS with explained causes and SCD-FS without autopsy (non-SADS-FS, $n = 9$) and compared this group to SADS with prior FS (SADS-FS, $n = 5$). We found that SADS-FS had a median of 0.9 (IQR 0.9–17.2) years from FS till death compared with non-SADS-FS with a median of 17.2 (IQR 16.1–22.8) years from FS till death ($P = 0.109$). Similarly, SADS-FS cases died at a median age of 2.2 (IQR 1.8–20.8) years and compared with non-SADS-FS cases with a median age of 22.5 (IQR: 16.4–24.4) years at death ($P = 0.053$).

Comparison with the control groups

During the 10-year study period, 2 369 785 Danes comprised the living control group. Through the NPR, we identified that 3.0% ($n = 71027$) of the living control group had been admitted with FS. In comparison, the incidence of FS was significantly increased by an odds ratio of 1.96 (95% CI 1.14–3.36; $P = 0.021$) among the SCD cases (*Table 3*). A total of 4414 (6.2%) people in the living control group with FS were subsequently diagnosed with epilepsy after a median of 3.9 (IQR 1.3–8.7) years from the FS diagnosis.

In the study period, 917 (20.0%) of the 4595 deceased died in transport accidents, of which 26 (2.8%) had FS prior to death. Similar to the living control group, the FS incidence among the SCD cases was higher than in those who died in transport accidents with an odds ratio of 2.08 (95% CI 1.07–4.04; $P = 0.046$). FS was diagnosed with a median of 15.9 (IQR 13.4–20.1) years prior to lethal transport accidents. Only 17 (1.9%) people who died in a transport accident had an epilepsy diagnosis of which only 1 had prior FS.

Similarly, we compared the smaller SADS subset ($n = 99$) to the living control group resulting in an odds ratio of 1.72 (95% CI 0.55–4.16; $P = 0.226$). Comparing the SADS subset with the control group of transport accident victims resulted in an odds ratio of 1.82 (95% CI 0.53–4.98; $P = 0.216$).

Discussion

In this nationwide study, we found a two-fold increase in the frequency of FS among SCD cases compared with both the living general population and the deceased transport accident victims. The prevalence of FS in the Danish population (2000–09, born after 1977, 1–30 years) was 3.0%, which is consistent with the previously reported prevalence among the Western countries.[1,2]

The FS prevalence was 5.7% among the SCD cases in general and 5.1% in the SADS cases. This differ greatly from other similar studies,[5,16] in which 24–32% had FS prior to sudden unexplained death in childhood (1–6 years and 1–18 years, respectively), which is a four- to five-fold increase compared with our two-fold increase. This could be explained due to multiple reasons: (i) the earlier studies were based on selected cases and may not be representative for the

Table 1 Baseline table and co-morbidities among the SCD cases divided in with or without FS

	SCD with FS ($n = 14$)	SCD without FS ($n = 231$)	Total SCD ($n = 245$)	*P*-value
Male gender, *n* (%)	10 (71.4)	153 (66.2)	163 (66.5)	0.914
Year of birth, *n* (%)				0.272
1977–1986	6 (42.9)	139 (60.2)	145 (59.2)	
1987–1996	5 (35.7)	61 (26.4)	66 (26.9)	
1997–2006	2 (14.3)	28 (12.1)	30 (12.2)	
2007–2009	1 (7.1)	3 (1.3)	4 (1.6)	
Age at death (years), *n* (%)				0.667
1–10	3 (21.4)	39 (16.9)	42 (17.1)	
11–20	6 (42.9)	81 (35.1)	87 (35.5)	
21–30	5 (35.7)	111 (48.1)	116 (47.3)	
SCD subcategory, *n* (%)				0.503
Explained after autopsy	3 (21.4)	71 (30.7)	74 (30.2)	
Sudden arrhythmic death syndrome	5 (35.7)	94 (40.7)	99 (40.4)	
No autopsy performed	6 (42.9)	66 (28.6)	72 (29.4)	
Epilepsy diagnosis†, *n* (%)	7 (50.0)	25 (10.8)	32 (13.1)	<0.001*
IC infection†, *n* (%)	1 (7.1)	2 (0.9)	3 (1.2)	0.411
Co-morbidities, *n* (%)				
Cerebral palsy	0 (0.0)	8 (3.5)	8 (3.3)	NA
Asthmatic	0 (0.0)	23 (10.0)	23 (9.4)	0.442
Chronic obstructive lung disease	0 (0.0)	0 (0.0)	0 (0.0)	NA
Hypertension	0 (0.0)	3 (1.3)	3 (1.2)	NA
Diabetes	1 (7.1)	5 (2.2)	6 (2.4)	0.780
Hypercholesterolaemia	0 (0.0)	1 (0.4)	1 (0.4)	NA
Ischaemic heart disease	0 (0.0)	3 (1.3)	3 (1.2)	NA
Psychiatric disorder	1 (7.1)	41 (17.7)	42 (17.1)	0.511
Substance abuse	0 (0.0)	23 (10.0)	23 (9.4)	0.442
Other heart disease	1 (7.1)	38 (16.5)	39 (15.9)	0.584
Congenital heart disease	1 (7.1)	39 (16.9)	40 (16.3)	0.558
Obesity	0 (0.0)	8 (3.5)	8 (3.3)	NA
Metabolic disorder	0 (0.0)	4 (1.7)	4 (1.6)	NA
Kidney insufficiency	0 (0.0)	0 (0.0)	0 (0.0)	NA

*$P < 0.05$, statistically significant. *P*-values are calculated comparing SCD with or without FS.
†In SCD with FS cases the diagnosis is made >1 month subsequent to the first FS diagnosis.

Table 2 All SCDs with prior FS ($n = 14$) stratified on SCD subgroups

	Explained cause of SCD ($n = 3$)	SADS ($n = 5$)	No autopsy performed ($n = 6$)	Total SCD ($n = 14$)	*P*-value
Male gender, *n* (%)	3 (100)	3 (60.0)	4 (66.7)	10 (71.4)	0.452
Age at first FS (years), median (IQR)	1.6 (1.3–3.5)	1.2 (0.8–1.2)	1.1 (0.6–1.6)	1.2 (0.8–1.6)	0.499
Age at death (years), median (IQR)	22.8 (18.4–23.6)	2.2 (1.8–20.8)	19.8 (16.6–23.9)	18.9 (14.4–22.7)	0.153
Years from FS till death, median (IQR)	17.2 (15.0–20.0)	0.9 (0.9–17.2)	17.2 (16.2–22.1)	16.8 (13.1–19.8)	0.261
Subsequent epilepsy diagnosis, *n* (%)	0 (0.0)	2 (40.0)	5 (83.3)	7 (50.0)	0.053
Subsequent IC infection, *n* (%)	0 (0.0)	1 (20.0)	0 (0.0)	1 (7.1)	0.379

P-values are calculated comparing the three SCD subgroups.

Table 3 Comparison of SCD cases with the control groups

	With FS, *n* (%)	Without FS, *n* (%)	OR (95% CI)	*P*-value
Corresponding Danish population	71 027 (3.0)	2 298 758 (97.0)	Reference	NA
Sudden cardiac death	14 (5.7)	231 (94.3)	1.96 (1.14–3.36)	0.021*
Victims of transport accidents	26 (2.8)	891 (97.2)	Reference	NA
Sudden cardiac death	14 (5.7)	231 (94.3)	2.08 (1.07–4.04)	0.046*

P-values are calculated comparing the SCD with the two control groups.
*$P < 0.05$: statistically significant.

general population; (ii) the studies were dependent on either an interview or a written survey that might cause reporting bias of FS, resulting in a high reported FS prevalence; and (iii) the risk of death could be greater among younger patients, or the cohorts could be incomparable due to variation in SCD in the young and sudden unexplained death in childhood. Compared with the prevalence of FS in the general population, SCD-FS cases are rare occurrences, hence a low absolute risk of SCD after FS.

The included 245 SCD cases did not differ in birth year, age at SCD, or prior medical conditions, except for epilepsy, when comparing SCD with or without prior FS. Subsequent diagnosis of epilepsy among all SCD-FS patients was high, and there are several possible explanations to this finding. (i) Seizure-like attacks of presumed epileptic origin could be attributed to transient cerebral hypoperfusion secondary to cardiac arrhythmias or other cardiovascular diseases[10,17] and could explain misdiagnosis of epilepsy in cardiac patients. Furthermore, diagnosis of epilepsy only require two afebrile seizures occurring >24 h apart. Since FS reoccur in 25% of patients,[18] the risk of an epilepsy misdiagnosis is increased. In a clinical setting, fever might be the only symptom that separate FS from a cardiovascular-induced seizure-like attack or epilepsy. (ii) In addition, previous studies have found that children with FS have a 6–6.9% cumulative long-term incidence of developing epilepsy, which was a 10-fold increase compared with the general population.[19,20] A 26-fold increased risk of epilepsy was found in the first 3 months after FS, decreasing to a three-fold increase after 8 years, although remaining significantly elevated.[19] This might indicate that SCD-FS have common attributes with sudden unexpected death among epilepsy (SUDEP) as previously suggested.[5] A potential explanation might be a shared predisposing underlying condition at the cellular level, such as the possibility of a cardiocerebral channelopathy.[21]

Sudden cardiac death cases without autopsy (SCD no-autopsy rate 72/245, 29.4%) had the highest frequency of prior FS (6/72, 8.3%) that could be indicative of a similar pathology leading to SCD. The circumstances in all these deaths are indicative of SCD, though 5 (83.3%) had an epilepsy diagnosis that might negatively affect the likelihood of an autopsy.

If FS potentially triggers or mimics a concealed underlying arrhythmic disorder, we would expect SADS-FS ($n = 5$) to be a high-risk group. We found similar prevalence of FS among SADS patients (5.1%) compared with SCD patients in general (5.7%); this was likely due to the small SADS population size. Supporting the theory, SADS-FS cases died at a median age of 2.2 (IQR 1.8–20.8) years and non-SADS-FS cases died at a median age of 22.5 (IQR 16.4–24.4) years at death ($P = 0.053$). The same tendency applied in years from FS till death, where SADS-FS cases again was notably lower than non-SADS-FS and died after a median period of 0.9 (IQR 0.9–17.2) years from FS ($P = 0.109$), see *Table 2* for non-pooled comparison. It is speculated that SADS-FS cases might have died from primary arrhythmic disorders such as BrS, LQTS, short QT syndrome, or catecholaminergic polymorphic ventricular tachycardia. Further supporting this, fever is a well-known trigger of arrhythmia among BrS patients,[11,12] and possibly also some LQTS patients,[13] suggesting these disorders as a potential underlying cause of death. Without an established pathophysiological relation between FS and SCD, we can only speculate on the cause of time delay between FS and SCD. One explanation could be that the random onset of arrhythmic diseases leading to SCD might have had an earlier onset than first anticipated masquerading as FS. A thorough history should be obtained in children with FS and particularly for those with known high-risk features for sudden death, such as family history of sudden death according to the current guidelines.[15]

Strengths and limitations

This is a nationwide study where we used an unselected nationwide cohort consisting of all deaths in Denmark in 1–30-year olds in a 10-year study period. The combination of unique person identification (access to all death certificates, autopsy reports, and medical records) and Danish registries (with registration of all hospital, ED, and outpatient activity), provides ideal conditions for long-term retrospective collection of information in both the case and the control groups. Danish health care is financed by taxes and equally available to all Danish residents, and therefore, this study is predominantly independent of socio-economic status.

Due to the small sample size of SCD-FS, we could only perform a univariate analysis, though we did not find any statistical difference with regard to prior medical history (except epilepsy) between SCD cases with or without FS prior to death. Additionally, not all SCD-FS cases were autopsied, which might affect the reliability of SADS as the commonest cause of death in SCD-FS cases. The use of all transport accident victims as a control group is potentially confounding, because not all accidents can be considered as traumatic deaths without an underlying cause. Even though it might be a negligible problem, we also used the background population as control group to minimize the risk of false conclusions. Subsequent diagnosis or misdiagnosis of epilepsy conceivably confounds our higher reported prevalence of FS among SCD patients. Registration of FS in the Danish NPR does not differ between whether the FS was simple or complex. Sudden

cardiac death cases with potential complex FS might have a higher general mortality rate,[3] which could overestimate our results among SCD patients with prior simple FS. Furthermore, we were currently not able to identify the known risk factors of FS through the registries or to access medication status at the time of FS and death.

Conclusion

This nationwide study demonstrates a significantly two-fold increase in the frequency of FS prior to death in young SCD cases (1–30 years), when compared with both the living background population in Denmark and to the deceased transport accident victim controls. The most common cause of death in autopsied SCD-FS cases was SADS. These results could indicate that FS triggers or mimics a primary arrhythmic disorder in SADS patients. Febrile seizure could potentially contribute in a risk stratification model for SCD and warrant further studies with more statistical power to support these findings.

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