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Harmonization of the Definition of Sudden Cardiac Death in Longitudinal Cohorts of the ESCAPE-NET Consortium

Longitudinal cohorts in the European Sudden Cardiac Arrest network – towards Prevention, Education, and New Effective Treatments (ESCAPE-NET)

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Abstract

Background

The burden of sudden cardiac death (SCD) in the general population is substantial and SCD frequently occurs among people with few or no known risk factors for cardiac disease. Reported incidences of SCD vary due to differences in definitions and methodology between cohorts. This study aimed to develop a method for adjudicating SCD cases in research settings and to describe uniform case definitions of SCD in an international consortium harmonizing multiple longitudinal study cohorts.

Methods

The harmonized SCD definitions include both case definitions using data from multiple sources (e.g. autopsy reports, medical history, eyewitnesses) as well as a method using only information from registers (e.g. cause of death registers, ICD-10 codes). Validation of the register-based method was done within the consortium using the multiple sources definition as gold standard and presenting sensitivity, specificity, accuracy and positive predictive value (PPV).

Results

Consensus definitions of 'definite', 'possible' and 'probable' SCD for longitudinal study cohorts were reached. The definitions are based on a stratified approach to reflect the level of certainty of

diagnosis and degree of information. The definitions can be applied to both multisource and register-based methods. Validation of the method using register-information in a cohort comprising 1335 cases yielded a sensitivity of 74%, specificity of 88%, accuracy of 86%, and PPV of 54%.

Conclusions

This study demonstrated that a harmonization of SCD classification across different methodological approaches is feasible. The developed classification can be used to study SCD in longitudinal cohorts and to merge cohorts with different levels of information.

Keywords

Sudden cardiac death, case definition, longitudinal cohort, epidemiology

Highlights

- We propose categorizing SCD into definite, probable, and possible depending on the level of information and certainty of diagnosis
- The method allows a transparent harmonization of longitudinal study cohorts with different sources of information
- It is possible to adjudicate SCD using ICD-codes with reasonable specificity and sensitivity

Introduction

In general, sudden cardiac arrest (SCA) has two distinct outcomes: Sudden cardiac death (SCD) or aborted SCD (i.e. sudden cardiac arrest survivors). Studies of cardiac arrest report a wide range of incidences depending on whether SCA, SCD, or both are counted. Half of these fatal events in the general population occur in apparently healthy individuals with no or few known risk factors of SCD(1–5). According to the most recent estimations, SCD is responsible for between 5% and 20% of all deaths in the adult general population(3,4) and has an incidence in the range of 50-150 per 100,000 person-years(1,4,6).

Approaches to SCD ascertainment range from diagnosis code algorithms (International Classification of Diseases, ICD-coding) to prospective collection of cases, and with varying definitions of SCD(3–5,7,8). This difference in methodology leads to diverging estimates of the SCD burden in similar populations(3). Moreover, this lack of harmonization hinders collaborative analyses of studies to advance the knowledge on risk factors of SCD and strengthen the evidence base for prevention of SCD. Therefore, valid identification of cases in the general population is imperative to achieve a clear SCD phenotype that is possible to harmonize and examine across nations, contexts, and studies(9–11). So far, this has been hampered by a lack of a comprehensive definition as well as large-scale collaborative efforts.

The “European Sudden Cardiac Arrest network: towards Prevention, Education, and New Effective Treatments (ESCAPE-NET)” consortium is an international research collaboration with the main aims of improving the knowledge on SCA and increasing the survival after SCA(12,13). One of ESCAPE-NET’s main projects concerns the study of longitudinal cohorts with an outcome of SCA or SCD to improve the preventative strategies and investigate possible SCD predictors.

The aims of this study were; i) to give an overview of generally used definitions of SCD, ii) to develop a stratified definition based on accepted criteria while accounting for variations in availability of data across cohorts, iii) to apply this definition to a longitudinal cohort using multiple sources of information, iv) to validate a method using only cause of death diagnoses, and finally v) to present the longitudinal study cohorts in the ESCAPE-NET.

Methods

Harmonization of the longitudinal cohorts in ESCAPE-NET revealed a need for a shared definition of SCD. We examined definitions recognized by authoritative professional associations and definitions used in selected published studies on SCD. We then outlined potential uncertainties in these definitions, which can give rise to different estimates between cohorts with different methodologies. These previous definitions serve as the basis for the proposed method in this paper. The first draft was circulated in the consortium in late 2019 and was afterwards discussed among representatives of the longitudinal cohort partners. In autumn 2020 a final definition was agreed upon by relevant partners in the consortium.

Data sources

ESCAPE-NET comprises four longitudinal cohort studies initiated between 1977 and 2015 from three EU countries: 1) Denmark, Copenhagen City Heart Study (CCHS), Capital Region of Denmark(14), 2) France, Paris Prospective Study 3 (PPS3), Université de Paris(15), and 3) the Netherlands, The Hoorn Studies (HS)(16), 4) Hoorn Diabetes Care System (DCS)(17), Amsterdam UMC. CCHS, PPS3, and HS examine cardiovascular disease in the general population, while the DCS examines cardiovascular disease in a population of people with type 2 diabetes (T2DM). These cohorts differ from each other regarding sample sizes, follow-up durations, gathered data, and data storage. For several decades, participants have been examined with both clinical measurements and questionnaires and subsequently followed for, among other outcomes, SCD. Sources of information used for follow-up in the cohorts differed, but national registers (e.g. cause of death, prescription, hospital admissions), medical records, and information collected for study

purposes were available to different extent. Further information about each study is available in the supplementary material (detailed description and overview in two tables).

The proposed method of adjudicating SCD was applied to the Danish cohort CCHS, which uses all available written information, including data from Danish high-quality death certificates(18,19), prior diagnoses, and discharge summaries. To validate the SCD adjudication method, it was also applied to a subset of the Dutch ARREST registry (AmsteRdam REsuscitation STudies), which prospectively records out-of-hospital resuscitation attempts and studies determinants of outcome and risk factors of sudden cardiac arrest(20). The ARREST registry excludes arrests from the most obvious non-medical causes (e.g. trauma or drowning). To make the ARREST registry comparable to an SCD-register, we restricted the cohort to persons with a registered death date from one day before (to take errors in registration into account) to two days after the cardiac arrest date. Cause of death diagnoses were obtained through linkage with Statistics Netherlands. We also measured the sensitivity while excluding persons with a non-cardiac cause of death-diagnosis for better comparison with SCD-cohorts.

Statistics

Counts are presented as n (%). Incidence rates were calculated by dividing the number of SCDs by total person-time at risk. Incidence rates are reported along with exact Poisson confidence intervals. Using multiple source method as the gold standard, the register-based method was validated using standard calculations for sensitivity, specificity, accuracy, and positive predictive value. Participants with incomplete death certificates were excluded. Statistics were done using SAS Enterprise Guide 7.15.

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Results

Overview of the generally used definitions

At present, a generally accepted definition of SCD, recognized by most authoritative professional associations across the world is “a sudden, unexpected, and natural death due to a cardiac cause”(21–23). While this definition outlines the circumstances of death, it lacks the elaboration of timing and cause. So while the definition of SCD ought to be uniform across study populations as a clinically relevant endpoint, varying methods of ascertaining SCD cases have previously been used due to different interpretations(4,24,25).

Different time spans have been used to describe the term “sudden”. For the past decades, "sudden" has been used when a witnessed case dies within 1 hour from a change in cardiovascular status, or when an unwitnessed case is found dead within 24 hours from being last seen alive and functioning normally(3,5,22,26,27).

An "unexpected" death implies that an individual had no diseases that were expected to lead to a non-sudden death, generally including terminal illness and severe disease(4,5,28). For instance, malignancy does not by itself exclude a person from being an SCD case, but it must not be part of the chain of events leading to SCD, and the underlying or immediate cause of death. If national registries are available, a registered terminal illness may be observed in morbidity registries, and if not, studies have used information from death certificates, available hospital records, or family members(4,5,18,28,29).

"Natural death" is a non-violent death with no evidence of self-inflicted cause, trauma, or toxic drug overdose. Especially drug overdose can be difficult to assess if no obvious signs are seen

(empty pill bottles or medical intravenous needles) or without statements from relatives, and underestimations of these cases have been described(5).

A "cardiac cause of death" should ultimately rely on autopsy findings as the gold standard. However, the autopsy rate has been steadily decreasing from 25.2% (range 4.6%-43.1%) in 1989 to 13.6% (range 1.8%-74.1%) in 2015 for all deaths in the European Union(30). For instance, in the three countries where the longitudinal cohorts of ESCAPE-NET derive from, the latest registered forensic autopsy rate for all deaths in Denmark was 3.9% in 2012 and in the Netherlands it was 1.9% in 2017, while no national autopsy rate is available for France(30). Combining the low autopsy rate in Europe with around 50% out-of-hospital cardiac arrests and SCD being unwitnessed(31,32), the cause of death becomes more indefinite. If no autopsy is performed, the cause of death is based on the circumstances up until the time of death and the prior medical history, which makes it more difficult to distinguish, e.g., a myocardial infarction from a stroke in an unwitnessed case with no apparent medical history or symptoms preceding death.

SCD researchers are in the dilemma of either having well-phenotyped and small cohorts or larger but less specific cohorts when it comes to SCD. This balancing act of either being precise but restrictive or accommodative but less precise promotes either an under- or overestimation of the true incidence, resulting in differing incidence rates between studies.

Sources of information

In general, different types of information have been obtained in observational studies of SCD:

1) A multisource method using all available information where prospectively collected cases have been adjudicated by pre-specified criteria for autopsy, contact to eyewitnesses or next of kin, as well as an examination of medical records and death certificates. This demands a large setup and is often only feasible in limited geographic areas and relatively small study populations.

2) A retrospective multisource method would use all available written information, such as death certificates, autopsy reports, medical records, and administrative claims data (data for billing, insurance, or quality control purposes), however is affected by autopsy rate and quality of death certificates. If a multisource method is not possible, register-based studies using data from administrative claims databases and studies using only ICD-codes from the cause of death registers or morbidity registers could be performed. These type of register-based studies have been done with different methods and results(33–35) and previous studies have found that by using only death registry-information, the burden of SCD is overestimated. The lack of confirmed suddenness of death contributes, at least partly, to the inclusion of too many cases(3,36). Studies limiting the SCD cases to only emergency medical services (EMS) attended deaths underestimate the true incidence of SCD. This is due to the exclusion of all in-hospital cardiac arrests and most of unwitnessed deaths, where resuscitation is rarely initiated, and unwitnessed deaths have been shown to account for up to 40-50% of SCD cases(4,28).

Development of the proposed method

Considerations of the authors

The general consensus was that the definition of SCD should deal with the timing as well as the observed or presumed cause of death. The timing of SCD should be consistent with previous definitions, but it should at least consider the inclusion of unwitnessed cases. Regarding the cause of death, the underlying pathophysiology of SCD in the adult population is heterogeneous, as it is a combination of structural, functional, and electrophysiologic factors. In addition, SCD affects both people with known cardiac disease and presumably healthy persons, as over half of the SCD cases

in the general population are without any previously diagnosed cardiac disease. The definitions should not only include the persons with an autopsy or EMS care, as only a small fraction of all SCD cases are autopsied, and EMS attendance varies across cohorts. Terminal or severe disease (except for severe heart failure) should exclude a person if it cannot be ruled out that the disease itself was part of the underlying or immediate cause of death. This includes terminal illnesses such as cancer, dialysis-dependent end-stage renal disease, or end-stage chronic obstructive pulmonary disease.

Furthermore, the definition should consider that SCD-cases typically are a heterogeneous group, where witnessed cases with an identified dysrhythmia are merged in the same category as unwitnessed presumed cases. Subcategorization of SCD that differentiates cases based on available information gives more depth and transparency in the provided data. Finally, the ideal method for harmonizing SCD across cohorts has a practice that considers what information is available in each cohort. Thus, definitions should allow for both multisource and register-based adjudication of SCD.

We limit the definitions to non-survivors, though some previous studies(3) have included SCA survivors (aborted SCD). This should be taken into consideration when interpreting the results in studies derived from the ESCAPE-NET SCD cohorts.

The proposed method of defining sudden cardiac death

The definition of sudden cardiac death is based on varying degrees of available information in cohorts in the ESCAPE-NET consortium (see descriptions in the supplementary material table 1 and

2). To accommodate these variations, we subcategorized SCD into three categories: 'definite', 'probable', and 'possible SCD' (Table 1):

1) 'Definite SCD' is a sudden death in a person with either an autopsy confirming the cardiac cause, an autopsy with unknown cause of death after extensive investigation, or a death with confirmed ventricular arrhythmia preceding death.
2) 'Probable SCD' is a sudden death in a person in usual health with presumed cardiac origin after review of all available information where no autopsy has been performed. Furthermore, there is an established time frame (see below) from change in cardiovascular status to death.
3) 'Possible SCD' is a sudden death in a person in usual health with presumed cardiac origin after review of all available information where no autopsy has been performed. For these cases the time frame from change in cardiovascular status to death is not fully established.

This definition is applied to the cohorts using a multisource method. When a time frame is available, the applied time frame for witnessed cases is an acute change in cardiovascular status leading to death within 1 hour, and for unwitnessed cases, the deceased was seen alive and functioning normally within 24 hours before being found dead. All persons included as 'possible SCD' were free of any severe and/or chronic diseases expected to result in an impending non-sudden death. Accordingly, patients with a severe or terminal illness can be classified as 'definite' or 'probable SCD' if an autopsy or established time frame is available. All deaths occurring in-hospital are categorized as non-SCD, unless an autopsy or a death certificate concludes that the death clearly was sudden and unexpected in a person hospitalized for a non-severe disease. Therefore, for multisource method cohorts, all cases in the 'possible SCD'-category died out-of-

hospital. These categories are weighting the probability of SCD considering the amount of available information.

Cohorts using a register-based approach (i.e. primarily information on ICD-codes of prior diagnoses and cause of death) are missing the time frame of multisource cohorts, and almost all SCD cases from these cohorts will be categorized in the 'possible SCD'-category; an autopsy or other information about the death can recategorize a case (however, this information is rarely available in registers). SCD adjudication is performed using a comprehensive list of ICD-codes. These comprised inclusion and exclusion codes for SCD (listed in Table 2). An SCD case is a case with an inclusion ICD-code and with no exclusion code. Thus, cases with ICD-codes indicating a terminal disease or acute non-cardiac disease as the underlying or immediate cause of death were excluded. These ICD-codes were selected by experience and subject matter knowledge of the authors and by weighing the probability of SCD versus non-SCD for different ICD-codes while keeping methods from other studies in mind(3,33,34,37).

Application of the proposed method

SCD subcategories in the ESCAPE-NET consortium

The CCHS included 14,562 Danish adults between the years 1993 to 2016. By applying the proposed method to the individual cohorts, we found in the CCHS, where a multisource method for ascertaining SCD cases was used, a total of 8,555 deaths (flowchart, supplementary figure 1). Of those, 161 cases were excluded due to missing or incomplete information. The remaining 8,394 cases were reviewed and 1335 of these were classified as SCD (16% of total mortality). Subcategorization gave the following SCD subgroups: 105 (8%) definite SCDs, 438 (33%) probable

SCDs, and 792 (59%) possible SCDs. The incidence among persons aged 40-90 years during 2012-2016 was 399 SCDs per 100,000 person-years (95% confidence interval = 330-478).

Validation of the register-based method

The register-based method using inclusion and exclusion ICD-codes was validated in the CCHS cohort using only deaths registered with ICD-10 codes (years 1994-2016). This yielded a sensitivity of 76%, specificity of 86%, accuracy of 85%, and positive predictive value (PPV) of 51% in the entire period (Table 3). Restricting the period to the most recent five years of observation, the sensitivity was 83%, specificity 90%, accuracy 89%, and PPV 55%.

In the ARREST registry (n = 3869 (flowchart, supplementary figure 2)), the ICD-code method classified 2,389 persons as SCD resulting in a sensitivity of 61.7%. However, even though obvious non-cardiac causes have been excluded, resuscitation attempts may be performed in patients who were later judged to have a non-cardiac cause of death. If we presume that patients with a cause of death ICD-code of chronic obstructive pulmonary disease/emphysema (n = 101), pneumonia (n = 24), cancer (n = 112), diabetes (n = 166), sepsis (n = 12), and gastrointestinal bleeding (n = 28) were true non-SCD and exclude these cases (cohort size now 3,426), the sensitivity of the method improves to 69.7%.

Discussion

The development of a standardized method for harmonizing SCD cases, both in multisource cohorts and in register-based research cohorts, was the focus of this paper. We have defined a method for merging SCD cases from different study designs without losing essential information in the process. The accuracy of the SCD phenotype is key when combining the different study designs with different data sources. Therefore, an SCD subcategorization was implemented to make the underlying data more transparent. Furthermore, we implemented a method for register-based SCD cohorts, which showed reasonable sensitivity and specificity when validating the method internally in the ESCAPE-NET consortium.

Without an autopsy, SCD ascertainment will in most cases be subjective and our method accounts for the level of certainty in assessing cases. Depending on the scientific question, researchers might want to analyze only definite SCD-cases with the highest probability of being a true SCD, or researchers might want to also include probable or possible SCD-cases thereby capturing a higher proportion of SCD-cases.

As described above, definitions have been published before. However, our method is not in disagreement with prior methods but elaborates on the previous methods. For instance, Fishman et. al in a report from National Heart, Lung, and Blood Institute from 2010(38) proposed subcategorizing into “established SCD” and “probable SCD” accounting for level of certainty. We have made small adjustments of definitions and added “possible SCD” allowing for cases without certain timeframes. The major addition we have made is the subcategorization, which is the improvement needed to allow transparent reporting and harmonization across different cohorts.

Estimating sudden cardiac death incidence

Register-based methods might overestimate the incidence of SCD. In our definitions, we have accommodated this by excluding people with diseases that most likely are not associated with SCD. We excluded terminal and chronic illnesses, but we acknowledge that the definitions might still overestimate the true burden. Still, when validating the register-based method in a multisource SCD cohort within the consortium, we found a relatively high specificity.

The cause of sudden death is cardiac in most cases with coronary artery disease being the cause in 75% of all SCD in the adult population(6). But as seen in previous autopsy studies, non-cardiac sudden death accounts for up to 40% of all sudden deaths(5,18,28). As there is no evidence of an increase in the autopsy rates in most European countries, the gold standard is unachievable in most cases. With low autopsy rates, the cause of death is deduced from medical records, circumstances and treatment surrounding the death, resulting in a best-qualified guess. From our perspective, the SCD subcategorization increases the transparency of the underlying data thereby clarifying potential limits to the research. As seen in the results, the subcategorization was feasible in the CCHS. Studies only including register-based SCD cases will only be able to add *possible SCD* cases, but not *probable SCD*, to the merged database due to the proposed SCD definitions where the time frame is of importance.

Perspectives

As phenotypically well-defined cases are grouped, it is possible to do preliminary research on the individuals with high certainty with a subsequent analysis, to confirm the possible findings in the pooled cohort. We showed that a stratified definition can be successfully applied to harmonize complex outcomes across different studies and contexts. With the resulting immense amount of

longitudinally harmonized data, we can broaden the knowledge regarding SCD pathophysiology with available data on symptoms, medical health, psychosocial aspects, socioeconomic status, clinical tests, and genetic data. Furthermore, since the cohorts have been conducted in different countries beginning at various points in time, we are able to investigate the burden of SCD over many decades.

Moreover, preventative measures in the general population are warranted, as most SCD occur in this setting(6). Especially the discriminative ability and predictive validity of risk prediction models are of interest(11), as many risk factors for SCD overlap with the risk factors for non-sudden cardiac death(39). Further addition of other longitudinal SCD cohorts in the ESCAPE-NET consortium is planned in near future.

Limitations

Although we believe our method and the harmonization of cohorts poses many advantages, there are still limitations. Our collaboration originates in European countries and the methods is created with knowledge about European registers and health-care systems. In other geographical areas or systems, the method might not be directly applicable. However, we believe the categorization allows for flexible and transparent adjudication in most cases. For example, in some countries there might be substantial delay in reporting, which needs to be considered.

The register-based method has its limitations primarily in the lack of timeframe and circumstances of death. If one needs SCD cases with high certainty, using only ICD-codes is not possible. The method is applicable in cases where there is no further information and, in that case, have acceptable performance. Another subset of ICD-codes could be chosen and, perhaps, show higher specificity with lower sensitivity. However, this would require further studies.

The long-lasting time period of investigations makes it possible to investigate temporal trends of SCD and changes in risk factors' effect on the incidence. However, researchers must be cautious to examine the temporal trends, as the diagnostic criteria for diseases have changed over time as well as risk factors' influence, and these differences may vary between nations. Improvements in treatment and modifiable risk factors during the study periods have changed the prevalence of causes and incidences of SCD (e.g., reduction in the incidence of coronary heart disease(40)). For instance, as the CCHS was initiated in 1976, the investigated population is not directly comparable to studies started in e.g. 2009 with regards to risk factors, both in their prevalence as well as methods of measuring. We will take this change into consideration in future statistical analyses.

The cohorts described above include only SCD, so a temporal or geographical difference in survival after cardiac arrest will influence incidences. A combination of SCA and SCD cohorts could potentially alleviate these differences and could be used to answer different scientific questions. Studies in the USA have investigated the different approaches for examining SCD cases and found the retrospective approach using USA death certificates to overestimate the SCD incidence(3,5). Initiatives should be done to improve the cause of death reporting and increase autopsy rates and alternative measures such as post-mortem imaging(41).

Lastly, in the register-based cohorts, we included a few SCD cases whereby it was uncertain if the SCD occurred outside the hospital. However, this concerns a limited number of cases and will therefore only have a small influence on the reliability of the data.

Conclusions

Harmonization of international SCD cohorts is possible and provides great research potential. A new SCD definition with subcategorization allows us to compare different cohorts with transparent reporting and without loss of information.

author contributions

Peder Emil Warming: Writing - Original Draft, Writing - Review & Editing, Formal analysis

Frederik Nybye Ågesen: Writing - Original Draft, Writing - Review & Editing, Conceptualization, Formal analysis

Thomas Hadberg Lynge: Writing - Review & Editing

Reza Jabbari: Writing - Review & Editing

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Jean-Philippe Empana: Writing - Review & Editing

Jacob Tfelt-Hansen: Writing - Review & Editing, Conceptualization, Supervision

Disclosures

The authors are solely responsible for the conduct of this study, all analyses, drafting and editing of paper and final contents.

The authors declare that they have no conflicts of interest relevant to the content of this paper.

References

1. Myerburg RJ, Junttila MJ. Sudden Cardiac Death Caused by Coronary Heart Disease. Circulation. 2012 Feb 28;125(8):1043–52.

2. Myerburg RJ. Sudden Cardiac Death: Exploring the Limits of Our Knowledge. J Cardiovasc Electrophysiol. 2001 Mar;12(3):369–81.

3. Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, et al. Current burden of sudden cardiac death: Multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol. 2004 Sep;44(6):1268–75.

4. de Vreede-Swagemakers JJM, Gorgels APM, Dubois-Arbouw WI, van Ree JW, Daemen MJAP, Houben LGE, et al. Out-of-Hospital Cardiac Arrest in the 1990s: A Population-Based Study in the Maastricht Area on Incidence, Characteristics and Survival. J Am Coll Cardiol. 1997 Nov;30(6):1500–5.

5. Tseng ZH, Olgin JE, Vittinghoff E, Ursell PC, Kim AS, Sporer K, et al. Prospective Countywide Surveillance and Autopsy Characterization of Sudden Cardiac Death: POST SCD Study. Circulation. 2018 Jun 19;137(25):2689–700.

6. Deo R, Albert CM. Epidemiology and Genetics of Sudden Cardiac Death. Circulation. 2012 Jan 31;125(4):620–37.

7. Kong MH, Fonarow GC, Peterson ED, Curtis AB, Hernandez AF, Sanders GD, et al. Systematic Review of the Incidence of Sudden Cardiac Death in the United States. J Am Coll Cardiol. 2011 Feb;57(7):794–801.

8. Hayashi M, Shimizu W, Albert CM. The Spectrum of Epidemiology Underlying Sudden Cardiac Death. Circ Res. 2015 Jun 5;116(12):1887–906.

9. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, et al. Epidemiology of Sudden Cardiac Death: Clinical and Research Implications. Prog Cardiovasc Dis. 2008 Nov;51(3):213–28.

10. Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, et al. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch Int J Pathol. 2017 Dec;471(6):691–705.

11. Wellens HJJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, et al. Risk stratification for sudden cardiac death: current status and challenges for the future. Eur Heart J. 2014 Jul 1;35(25):1642–51.

12. Empana J-P, Blom MT, Böttiger BW, Dagres N, Dekker JM, Gislason G, et al. Determinants of occurrence and survival after sudden cardiac arrest–A European perspective: The ESCAPE-NET project. Resuscitation. 2018 Mar;124:7–13.

13. Tan HL, Dagres N, Böttiger BW, Schwartz PJ, ESCAPE-NET Investigators. European Sudden Cardiac Arrest network: towards Prevention, Education and New Effective Treatments (ESCAPE-NET). Eur Heart J. 2018 Jan 7;39(2):86–8.

14. Schnohr P, Jensen G, Nyboe J, Eybjaerg Hansen A. [The Copenhagen City Heart Study. A prospective cardiovascular population study of 20,000 men and women]. Ugeskr Laeger. 1977 Aug 8;139(32):1921–3.

15. Empana J-P, Bean K, Guibout C, Thomas F, Bingham A, Pannier B, et al. Paris Prospective Study III: a study of novel heart rate parameters, baroreflex sensitivity and risk of sudden death. Eur J Epidemiol. 2011 Nov;26(11):887–92.

16. Rutters F, Nijpels G, Elders P, Stehouwer CDA, van der Heijden AA, Groeneveld L, et al. Cohort Profile: The Hoorn Studies. Int J Epidemiol. 2018 Apr 1;47(2):396–396j.

17. van der Heijden AA, Rauh SP, Dekker JM, Beulens JW, Elders P, 't Hart LM, et al. The Hoorn Diabetes Care System (DCS) cohort. A prospective cohort of persons with type 2 diabetes treated in primary care in the Netherlands. BMJ Open. 2017 Jun 6;7(5):e015599.

18. Winkel BG, Holst AG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, et al. Nationwide study of sudden cardiac death in persons aged 1–35 years. Eur Heart J. 2011 Apr;32(8):983–90.

19. Lynge TH, Risgaard B, Banner J, Nielsen JL, Jespersen T, Stampe NK, et al. Nationwide burden of sudden cardiac death: A study of 54,028 deaths in Denmark. Heart Rhythm. 2021 May;S1547527121004227.

20. Blom MT, van Hoeijen DA, Bardai A, Berdowski J, Souverein PC, De Bruin ML, et al. Genetic, clinical and pharmacological determinants of out-of-hospital cardiac arrest: rationale and outline of the AmsteRdam Resuscitation Studies (ARREST) registry. Open Heart. 2014 Aug;1(1):e000112.

21. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, Camm AJ, Borggrefe M, Buxton AE, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006 Sep 5;48(5):e247-346.

22. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015 Nov 1;36(41):2793–867.

23. Sudden cardiac death. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1985;726:5–25.

24. Risgaard B, Lynge TH, Wissenberg M, Jabbari R, Glinge C, Gislason GH, et al. Risk factors and causes of sudden noncardiac death: A nationwide cohort study in Denmark. Heart Rhythm. 2015 May;12(5):968–74.

25. Norrish G, Cantarutti N, Pissaridou E, Ridout DA, Limongelli G, Elliott PM, et al. Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: A systematic review and meta-analysis. Eur J Prev Cardiol. 2017 Jul;24(11):1220–30.

26. Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Breithardt G, Brugada P, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J. 2001 Aug;22(16):1374–450.

27. Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. Circulation. 2000 Aug 8;102(6):649–54.

28. Risgaard B, Winkel BG, Jabbari R, Behr ER, Ingemann-Hansen O, Thomsen JL, et al. Burden of Sudden Cardiac Death in Persons Aged 1 to 49 Years: Nationwide Study in Denmark. Circ Arrhythm Electrophysiol. 2014 Apr;7(2):205–11.

29. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, et al. Population-Based Analysis of Sudden Cardiac Death With and Without Left Ventricular Systolic Dysfunction. J Am Coll Cardiol. 2006 Mar;47(6):1161–6.

30. WHO European health information at your fingertips. [Internet]. [cited 2021 Nov 4]. Available from: https://gateway.euro.who.int/en/indicators/hfa_545-6410-autopsy-rate-for-all-deaths/

31. Svane J, Lynge TH, Hansen CJ, Risgaard B, Winkel BG, Tfelt-Hansen J. Witnessed and unwitnessed sudden cardiac death: a nationwide study of persons aged 1–35 years. EP Eur. 2021 Feb 17;euab017.

32. Wissenberg M, Hansen CM, Folke F, Lippert FK, Weeke P, Karlsson L, et al. Survival after out-of-hospital cardiac arrest in relation to sex: A nationwide registry-based study. Resuscitation. 2014 Sep;85(9):1212–8.

33. Chung CP, Murray KT, Stein CM, Hall K, Ray WA. A computer case definition for sudden cardiac death. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):563–72.

34. Ye Y, Larrat EP, Caffrey AR. Algorithms used to identify ventricular arrhythmias and sudden cardiac death in retrospective studies: a systematic literature review. Ther Adv Cardiovasc Dis. 2018 Feb;12(2):39–51.

35. Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and Long-Term Cause of Death in Patients Treated With Primary PCI for STEMI. J Am Coll Cardiol. 2014 Nov;64(20):2101–8.

36. Fox CS, Evans JC, Larson MG, Lloyd-Jones DM, O'Donnell CJ, Sorlie PD, et al. A comparison of death certificate out-of-hospital coronary heart disease death with physician-adjudicated sudden cardiac death. Am J Cardiol. 2005 Apr;95(7):856–9.

37. Zheng Z-J, Croft JB, Giles WH, Mensah GA. Sudden Cardiac Death in the United States, 1989 to 1998. Circulation. 2001 Oct 30;104(18):2158–63.

38. Fishman GI, Chugh SS, DiMarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden Cardiac Death Prediction and Prevention: Report From a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010 Nov 30;122(22):2335–48.

39. Chen LY, Sotoodehnia N, Bůžková P, Lopez FL, Yee LM, Heckbert SR, et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. JAMA Intern Med. 2013 Jan 14;173(1):29–35.

40. Wijeysundera HC, Machado M, Farahati F, Wang X, Witteman W, van der Velde G, et al. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. JAMA. 2010 May 12;303(18):1841–7.

41. Roberts ISD, Benamore RE, Benbow EW, Lee SH, Harris JN, Jackson A, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. Lancet Lond Engl. 2012 Jan 14;379(9811):136–42.

Tables and Figures

Table 1. Proposed method of defining sudden cardiac death.

SCD subcategory	Timeframe	Criteria for cause of death
Definite SCD	Sudden death	Autopsy confirming cardiac cause or unknown cause after extensive investigation OR Confirmed ventricular arrhythmia preceding death.
Probable SCD	Sudden death Witnessed: < 1 hour from symptoms Unwitnessed: < 24 hours from seen functioning normally	Presumed cardiac origin, in a person in usual health, after review of all available information
Possible SCD	Presumed sudden death Timeframe not fully established	Presumed cardiac origin, in a person in usual health, after review of all available information

Note: As the register-based method do not take timeframes into account, this method can only adjudicate 'possible SCD'. A multisource method can adjudicate all three categories.

Table 2. International Classification of Diseases (ICD-codes version -9 and -10) used for defining possible sudden cardiac death.

Inclusion criteria:

	ICD-9	ICD-10
Angina pectoris	413	I20
Atherosclerosis	440	I70
Atrial fibrillation	427.3	I48
AV block and conduction disorders	426	I44-I45
Cardiac arrest and sudden cardiac death	427.5	I46.0, I46.1, I46.9
Cardiac dysrhythmia	427.6-427.9	I49
Cardiomyopathy	425	I42-I43
Cardiovascular disease	429	I51
Chronic ischemic heart disease	414	I25
Heart failure, acute, 'acute on chronic', and 'not otherwise specified'	428.0, 428.20, 428.1, 428.23, 428.31, 428.33, 428.41, 428.43 428.9	I50.1, I50.21, I50.23, I50.31, I50.33, I50.41, I50.43, I50.9
Heart valve disease	394-397, 424	I34-I39
Hypertensive disease	401-402	I10-I11
Myocardial infarction	410	I21, I22, I23
Other acute/subacute ischemic heart disease	411	I24
Sudden death and found dead	798	R96, R98, R99
Thoracic aortic dissection	441.01	I71.0, I71.1
Ventricular fibrillation or flutter	427.41-427.42	I49.0
Ventricular tachycardia	427.0-427.2	I47

Exclusion criteria:

	ICD-9	ICD-10
Abdominal aortic dissection	441.02, 441.03	I71.3, I71.5
Accidents and trauma	E00.0-E99.9	V01-Y99
Acute respiratory disease	460-466, 480-488	J1-J2
Alzheimer's, Parkinson's, and other neurodegenerative and motor neuron diseases	330-349	G1-G3
Anemia and blood disease	279-289	D5, D6, D7, D8
Other aneurysms	442	I72
Cachexia	799.4	R649
Cancer	140-239	C00-C99, D38.1
Chronic liver disease	570.0, 571	K70, K72, K73, K74
Chronic Obstructive Pulmonary Disease	491-493	J42-J44

Dehydration	276.5	E86
Dementia	290	F00-F03
Gastrointestinal bleeding	538, 557, 569.8, 578	K55, K92
Kidney disease, chronic	585-586	N189, N199
Myopathies	359	G71
Peri- and endocarditis	420, 421	I30-I33
Pulmonary embolism	415.1	I26
Pulmonary edema	514, 518.4	J81
Senility and fatigue	780.7	R53-R54
Sepsis	003.1, 020.2, 022.3, 027.0- 027.1, 038, 039, 112, 670	A021, A207, A227, A267, A327, A40-A41, A427, B377, O85
Stroke	430-438	I6

Table 3. Adjudication of sudden cardiac death (SCD) according to method.

Register-based	Multisource		Total
	Non-SCD	SCD	
Non-SCD	5,845	301	6,146
SCD	924	960	1,884
Total	6,769	1,261	8,030