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The diagnostic yield of cardiac screening in first-degree relatives of sudden arrhythmic death syndrome or unexplained cardiac arrest probands: A systematic review of the literature

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ABSTRACT

Background: First-degree relatives of Sudden Arrhythmic Death Syndrome (SADS) or Unexplained Cardiac Arrest (UCA) are recommended to undergo clinical evaluation for potential inherited cardiac conditions (ICC). However, data on the yield of family screening in these populations remains scarce.
Aim of review: This systematic review aimed to explore the diagnostic yield of clinical screening of first-degree relatives of SADS or UCA probands. A secondary aim was to compare the diagnostic yield of adult-aged and pediatric-aged relatives.
Key scientific concepts of review: Included studies described the clinical cardiac screening and yield of first-degree relatives of SADS and UCA probands. Quality of selected studies was assessed using a modified Joanna Briggs Institute checklist.
14 studies met inclusion criteria for this review, together including 1646 first-degree relatives of SADS probands and 656 first-degree relatives of UCA probands. Overall diagnostic yield described ranged from 0 to 32 %. The combined mean diagnostic yield of SADS relatives did not differ significantly from that of relatives of UCA probands. Three studies described outcomes of clinical screening in pediatric relatives, with an overall reported yield of 9.4 % ± 3.4 %, not significantly different from adult populations. Whilst there is a clear indication for clinical screening of first-degree relatives following SADS or an UCA, a lack of well-designed large population-based studies means that the evidence base is not robust. The yield in reported literature varies considerably, with no difference between SADS and UCA cohorts and a similar yield in pediatric and adult relatives. This supports screening for all first-degree relatives regardless of age.

1. Introduction

Sudden Arrhythmic Death Syndrome (SADS) is the most common cause of sudden cardiac death (SCD) in the young [1] and is defined as a sudden death of an individual which remains unexplained despite a thorough post-mortem and toxicology [2]. The prevalence of SADS is estimated to be 1.38/100,000 in England, equivalent to over 500 deaths per year [3]. Inherited cardiac conditions (ICCs), particularly inherited arrhythmia syndromes and cardiomyopathies, are thought to be the primary underlying etiology for SADS [4]. In the case of a sudden cardiac arrest (SCA) with successful resuscitation, the majority of events in patients over 35 years of age are attributed to ischaemic heart disease [5]. When the SCA remains unexplained following clinical assessment, the event is then termed an Unexplained Cardiac Arrest (UCA) or idiopathic ventricular fibrillation (IVF) [6]. It is thought that UCA could represent concealed forms of ion channelopathies or cardiomyopathies, and there is likely to be an overlap between UCA and SADS aetiologies [7] with ICCs, most commonly inherited as autosomal dominant traits,

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accounting for a proportion of these cases. Expert consensus documents have stated the need for first-degree relatives to undergo clinical cardiac screening [8] in order to identify ICCs, but this has not currently been adopted in international clinical practice guidelines [2]. These conditions share an increased risk of SCD, and therefore, timely and appropriate treatment and follow up can be lifesaving. In addition to clinical screening, referral to a specialist ICC center allows relatives to access expert advice and psychological support. However, despite this, reliable data on the yield and outcome of family screening in these populations remains scarce. The aim of this systematic review was to determine the diagnostic yield in first-degree relatives of SADS and UCA probands undergoing clinical cardiac screening and to compare the yield between relatives of SADS and UCA probands.

2. Methods

2.1. Literature search

The review protocol was created in line with PRISMA guidance [9] and was prospectively registered on PROSPERO (CRD:42023440658). The online databases Embase, Medline, and Web of Science were searched for original articles published in English from 1946 to June 2023 through Medical Subject Headings (MeSH) terms relating to Sudden Arrhythmic Death Syndrome, Sudden Infant Death Syndrome, Unexplained Cardiac Arrest, Relatives and Cardiac Evaluation (see Supplementary Data). A subsequent manual review of reference lists of included full text studies was also performed.

The titles and abstracts of all studies identified by the initial search were screened by two reviewers (IT & JT) for eligibility. All eligible texts were read in full by the same two reviewers and disagreements were resolved by consulting a third researcher (EF). The initial screening was conducted without language restriction, however only English language studies were considered for final full-text selection.

2.2. Eligibility criteria

Full inclusion and exclusion criteria were defined at the outset of the review process (Table 1). Quantitative studies describing the diagnostic yield of clinical cardiac screening in first-degree relatives of SADS and UCA probands were included. SADS was defined as the sudden death of an individual over one year old and <65 years old, which remains unexplained despite a thorough post-mortem and toxicology. Sudden Infant Death Syndrome (SIDS) was defined in the same way but relating to infants less than a year old. UCA was defined as the sudden and unexpected cardiac arrest of a previously healthy individual, successfully resuscitated with no diagnosis found despite cardiac evaluation. Minimum cardiac screening investigations for relatives were determined *a priori* to be a resting 12-lead electrocardiogram (ECG) and 2D echocardiogram. Studies were excluded if second-degree or more distant relatives were included in the data in a way in which it was not possible to extract data for first-degree relatives separately. Studies with probands who had cardiac diagnoses made at post-mortem, often termed more broadly as Sudden Cardiac Death (SCD), or probands who had no post-mortem performed were excluded. Studies were only included if the full published manuscript was available. As this review aimed to examine published evidence in relation to clinical cardiac investigations and their role in diagnosing relatives of SADS and UCA, studies which contained only diagnoses made on the basis of genetic testing or those where data was not extractable for diagnoses made by cardiac clinical investigation only, were excluded.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
First-degree relatives of SADS or UCA probands	Relatives of probands with either known diagnoses or positive, uncertain, or no autopsy
Quantitative studies with extractable data on diagnostic yield of first-degree relatives	Relatives of SCA survivors with confirmed diagnoses or without comprehensive clinical evaluations
	Second-degree or more distant relatives
	Genetic testing only with no clinical evaluation
	Qualitative data, systematic reviews, case reports or editorials

2.3. Study selection and data extraction

A data extraction sheet was developed, and the following data were extracted from all included studies where possible: study design, demographics of probands and first-degree relatives, circumstances of death of proband, length of follow up of relatives, investigations performed as part of clinical screening, overall diagnostic yield and the type and number of diagnoses made in first degree relatives. Supplementary material was also searched. Data extraction was performed independently by two reviewers (IT & JT), and a sample of their extracted data was cross-checked.

2.4. Quality of studies

A modified Joanna Briggs Institute (JBI) Checklist for Prevalence Studies was applied to assess the quality and bias of selected full texts. Existing tools for appraising diagnostic accuracy generally compared an index test with a reference standard, which is not applicable to this review. Articles were scored on nine items related to sample eligibility, sample selection, diagnostic protocol and criteria, and response rate to assess risk of bias. Quality and risk of bias of selected studies were assessed and cross-examined by two researchers independently, with discrepancies resolved through consensus. The summary of quality assessment is presented in Fig. 2.

2.5. Statistics and analysis

Data are presented using descriptive statistics (frequencies, numbers, percentages, means ± standard deviation (SD), and median and Interquartile Range (IQR) as appropriate). The Mann-Whitney *U* Test was used to determine statistical significance, with a *P*-value <0.05 considered significant. Statistical analyses were performed using IBM SPSS Statistics (Version 28.0). Meta-analysis was not conducted due to the heterogeneity of studies and large amount of missing data. Therefore, summary tables of selected studies are presented with descriptive statistics following Synthesis Without Metanalysis (SWiM) guidelines [10] and Cochrane guidance [11].

3. Results

The selection and screening process is depicted in the PRISMA Flow Diagram (Fig. 1). Briefly, the initial search identified 933 unique studies. By reading the titles and abstracts, 856 of these studies were excluded. The full text versions were evaluated for the remaining 77 articles. This excluded a further 67 articles. In total, 14 publications were included in the final review (Table 2) for data extraction and quality assessment. Overall, 1646 first-degree relatives of SADS probands and 656 first-degree relatives of UCA probands were in the included studies. Eleven studies were retrospective cohort studies, and cohort size varied from 56 to 398 (median 108, IQR 82–215). Included studies were published between 2003 and 2022. Nine out of fourteen studies defined the dates on which the data were collected, ranging from 1986 to 2020. Half ($n = 7$) of the included studies reported a population of patients from the

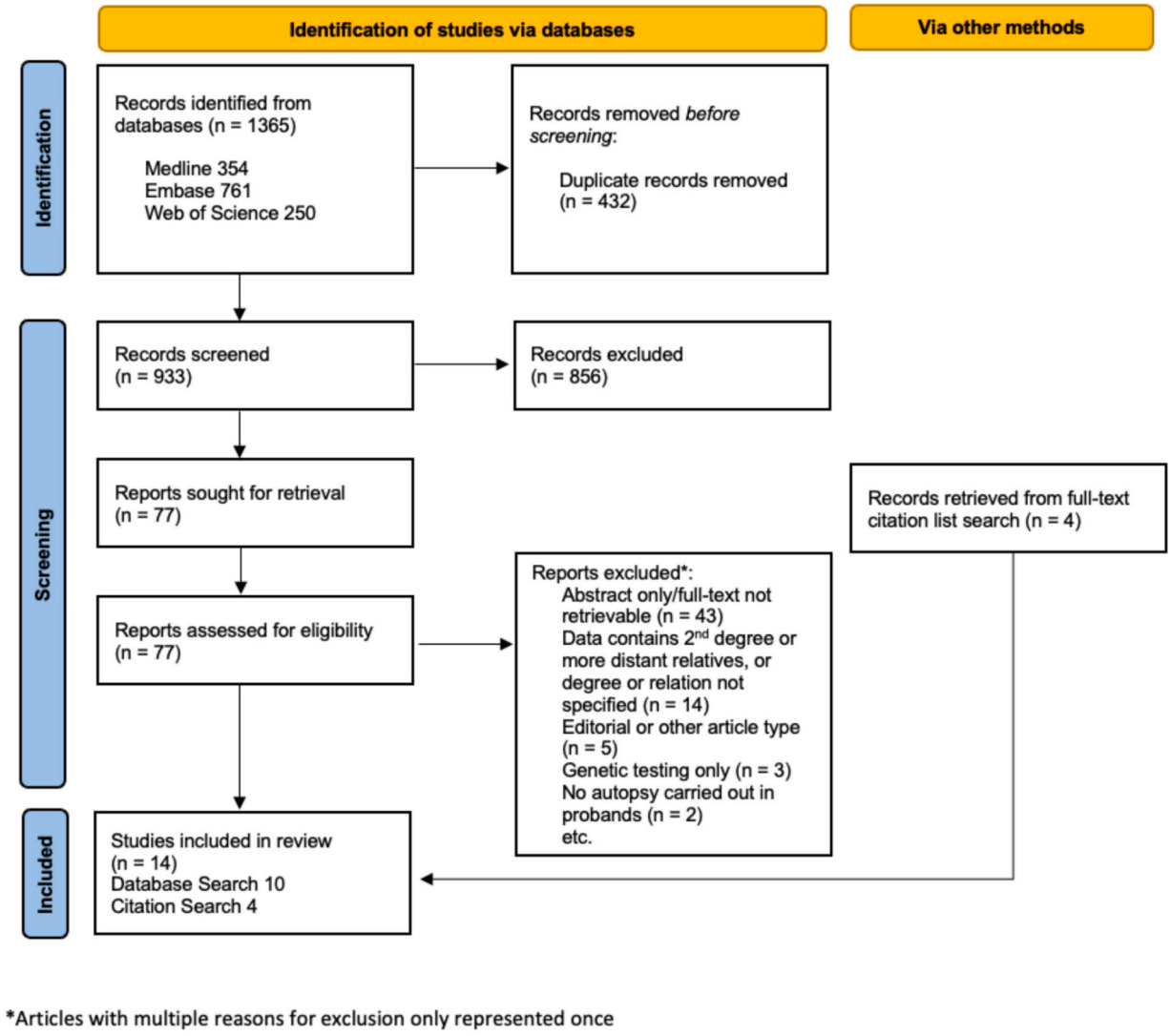

Fig. 1. PRISMA flow diagram.

United Kingdom, two reported a multicenter international population, and the remaining were from Denmark ($n = 2$), Spain ($n = 1$), Canada ($n = 1$) and Ireland ($n = 1$). One study [12] contained two datasets as it reported on screening from both a group of SADS relatives and a group of UCA relatives, resulting in 14 studies and 15 data sets.

3.1. Proband characteristics

Demographic information was not well described; extractable data for characteristics such as age, sex, and ethnicity of participants were not provided by all studies. Proband characteristics varied considerably, with an overall age range (reported by $n = 10$ studies) of 1–66 years. Probands were more likely to be male (combined mean 64 % from $n = 10$ studies).

3.2. Relative characteristics

Demographic information was not well described; extractable data for characteristics such as age range, sex, and ethnicity of participants were not provided by all studies (Table 2). Twelve studies reported gender ($n = 2114$), of which 41–56 % of participants were male. The same twelve studies also reported ages of participants, as displayed in Table 2. Ethnicity of first-degree relatives was reported in only four studies ($n = 930$) and demonstrated that relatives were mostly Caucasian ($n = 804$, 86 %).

3.3. Clinical screening strategy

Eleven studies described investigations performed on the relatives. Resting 12-lead ECG and echocardiogram were the most commonly performed investigations as reported. Resting 12-lead ECG was performed in 98–100 % of participants, and echocardiogram in 90–100 % of participants reported by $n = 10$ studies, with one study reporting only 79 % of participants. Five studies reported the proportion of relatives who had undergone specific additional cardiac investigations, including exercise testing (12.8–100 %), ambulatory ECG monitoring (34–100 %), Cardiac MRI (CMR) (6.3–27 %) and ajmaline provocation (5–27 %).

Only eight studies reported symptom status in the relatives; the most commonly reported symptoms were syncope (reported in 8.8 % ±3.3 of relatives) and palpitations (reported in 9.7 % ±5.3 of relatives). Of those studies that reported follow up length ($n = 8$), screening ranged from a one-off clinical evaluation ($n = 3$) to serial clinical screening (Table 2).

3.4. Diagnostic yield of clinical screening

The overall diagnostic yield for individual relatives ranged from 0 to 32 %. The pooled median diagnostic yield for all first-degree relatives was 13.2 % (IQR 6–23 %). The diagnostic yield for SADS relatives was

Table 2
Description of included studies ($n = 14$).

Reference	Study type	Study period (years)	*N* of first-degree relatives	Male (%)	Age of relatives		Follow-up length (years)		Diagnostic yield Proportion of individuals	Diagnostic yield proportion of families
					Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)		
SADS studies										
Dalgaard et al. 2022 [18]	Retrospective Cohort (single center)	13	276	46	33 ± 18	–	5.3 ± 3.2	–	31 (11 %)	19 (16 %)
Steinberg et al. 2016 [12]	Prospective Cohort (National Registry)	11	212	–	–	–	–	–	61 (29 %)	–
Giudici et al. 2014[a] [24]	Retrospective Cohort (single center)	10	90	56	–	7 (3–10)	–	–	7 (7.7 %)	7 (13.5 %)
Wong et al. 2014[a] [17]	Retrospective Cohort (two center)	3.5	85	48	–	8 (0.0.8–16)	–	2.1[b] (Range 0.2–8.2 years)	6 (7 %)	–
McGorrian et al. 2013 [16]	Prospective and Retrospective Cohort (single center)	4.5	220	44.3[b]	38.64 ± 15.59[b]	–	–	–	29 (13.2 %)	–
Caldwell et al. 2012 [25]	Observational Outcome (single center)	–	107	–	38 ± 17[b]	–	1.37[b] (Range 1 day – 61 months)	–	45 (23 %)	25 (30 %)
Nunn et al. 2011 [26]	Retrospective Cohort (single center)	5	363	43	35 ± 17	–	One-off assessment		51 (14 %)	49 (34 %)
Behr et al. 2008 [23]	Prospective Cohort (single center)	–	184	42	32.3	–	One-off assessment		46 (25 %)	30 (53 %)
Behr et al. 2003 [27]	Prospective (national)	1	109	41	31.9 ± 18.2	–	–	–	7 (6 %)	7 (22 %)
UCA studies										
Brunet-Garcia et al. 2022[a] [28]	Retrospective Cohort (single center)	12	60	50	6.5 ± 4.4	–	–	4.58 (2.25–7.25)	8 (13.3 %)	6 (18.8 %)
Mellor et al. 2021 [7]	Retrospective Cohort (National Registry)	–	201	57	39 ± 20	–	–	–	3 (1.5 %)	3 (3.1 %)
Jacobsen et al. 2020 [29]	Retrospective Cohort (single center)	13	56		–	–	–	–	1 (1.7 %)	1 (1.8 %)
Hornarbakhsh et al. 2017 [14]	Retrospective cohort (two center)	30	72	50	36 ± 13	–	One-off assessment		0 (0 %)	0 (0 %)
Steinberg et al. 2016 [12]	Prospective Cohort (National Registry)	11	186	–	–	–	–	2 (–)	59 (32 %)	–
Jiminez-Jaimez et al. 2015 [30]	Prospective Cohort (nine centers)	3	81	–	–	–	–	–	15 (18.5 %)	–

SADS = Sudden Arrhythmic Death Syndrome, IQR = Interquartile Range, UCA = Unexplained Cardiac Arrest.
[a] Pediatric study.
[b] Reported for first-degree and more distant relatives combined.

13.2 % (IQR 7.35–22 %) and UCA relatives 7.5 % (IQR 1.1–21.8 %), respectively. The difference in yield of diagnoses between SADS and UCA relatives was not statistically significant [$p = 0.15$]. The overall diagnostic yield, when calculated for families rather than individuals (available for $n = 9$ studies), was 16 % (IQR 2.45–26 %). The range of diagnostic yields for families of SADS ($n = 5$ studies) and UCA ($n = 4$ studies) relatives was 13.5–53 % and 0–18.8 %, respectively.

Nine of the included studies provided extractable data on diagnoses made in screening individuals (see Fig. 3). Three quarters ($n = 123$, 78.3 %) of all reported diagnoses were inherited arrhythmia syndromes, with long QT syndrome (LQTS) being the most common diagnosis ($n = 58$, 36.9 %) followed by Brugada syndrome ($n = 56$, 35.6 %) and catecholaminergic polymorphic ventricular tachycardia (CPVT) ($n = 9$, 5.7 %).

3.5. Pediatric relatives

Three studies described outcomes of clinical screening in 235 pediatric relatives, with an overall reported yield of 9.3 % ± 3.45 %. This is not significantly different from adult populations (14.57 % ± 11.05 %) [$p = 0.157$]. All studies reported which diagnoses were made in first-degree relatives. In the pediatric participants reported on by these two studies, Brugada Syndrome ($n = 10$) and LQTS ($n = 9$) were the most common diagnoses, followed by CPVT ($n = 1$) and dilated cardiomyopathy ($n = 1$).

3.6. Sudden infant death syndrome

No studies were identified which report the diagnostic yield of cardiac screening in relatives following a SIDS or Sudden Unexpected Death in Infancy (SUDI) death.

4. Discussion

This study is, to our knowledge, the first systematic review exploring the diagnostic yield of cardiac family screening following SADS or UCA and includes over 2000 first-degree relatives. There was considerable heterogeneity in screening strategy and quality of studies. The diagnostic yield in reported literature varies considerably, with no statistically significant difference between SADS and UCA cohorts and a similar yield in pediatric and adult relatives.

Fig. 2. Quality assessment of included studies. *See Appendix 2 for full description of each criterion.

4.1. Screening following SADS

Current international guidelines [2] recommend cardiac screening for first-degree relatives of SADS victims due to the autosomal dominant nature of inheritance of most ICCs. However, despite this recommendation it is currently unknown what the yield of clinical screening is in this group. These guidelines recommend first-degree relatives undergo baseline cardiac investigations to include resting 12-lead ECG, ECG in high parasternal lead positions, echocardiogram and exercise testing. Further follow-up for asymptomatic adults with normal investigation results is not recommended, as the guidelines assert that routine follow-up is unlikely to lead to new diagnoses, although this is only supported by a single study with follow-up data in <50 families [13]. Ambulatory ECG monitoring, drug provocation, and CMR are recommended only if baseline tests do not reveal a diagnosis. In contrast, North American guidelines [8] advise that regular (3–5 yearly) follow-up is offered to relatives until the age of 45 years old.

This review demonstrates a large range of reported yields. There was significant variability in the approach to clinical screening in this population, such as which investigations were performed and length of follow-up. However, included studies were published at different points over the last twenty years, and therefore practice may have become more standardized over time. The study reporting the smallest diagnostic yield [14] described no diagnoses from a cohort of $n = 72$ first-degree relatives. Although all relatives in this study underwent ECG and Echo, only half (48 %) had ETTs performed, and only 5 % underwent drug provocation. The lack of comprehensive investigation may account for the lower yield of diagnoses compared to other studies.

Only eight of the included studies defined which ICC diagnoses had been made in first-degree relatives; therefore, reporting frequency of individual diagnoses in this systematic review is incomplete. The majority of diagnoses from all studies were inherited arrhythmia syndromes, in line with the published literature on the yield of diagnoses from molecular autopsies [4]. Although these results show LQTS as the most common diagnosis, drug provocation with sodium channel blocker was only carried out by 5–29 % of participants in studies which reported this ($n = 5$), and therefore, it is possible that the number of Brugada Syndrome diagnoses may be under reported. Despite probands having no heart muscle phenotype on post-mortem or clinical evaluation, almost a quarter of relatives (from $n = 8$ studies) were diagnosed with inherited cardiomyopathies, most commonly Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). It is well reported that predisposition to malignant arrhythmia in ARVC can often precede structural changes [15], and this could account for the probands having normal post-mortem examinations, especially in cases where specialist cardiac post-mortem was not performed. Only one cardiomyopathy diagnosis was made in the pediatric population, potentially due to age-related variables and incomplete penetrance.

Despite the missing data in relation to investigations performed (Table 3), there does appear to be a correlation between the rates of detailed investigations carried out in relatives and the diagnostic yield. The study which reported the highest diagnostic yield [16] performed the highest proportion of CMRs and drug provocation testing and the second highest proportion of exercise tests in participants. Only two studies reported which investigations were diagnostic in participants, and no studies which followed-up participants, as opposed to one-off assessment, described whether diagnoses were made at baseline or at subsequent time points, meaning this review is unable to analyze evidence relating to optimum length of follow up for relatives. Future studies describing the yield of cardiac investigations in this population are needed.

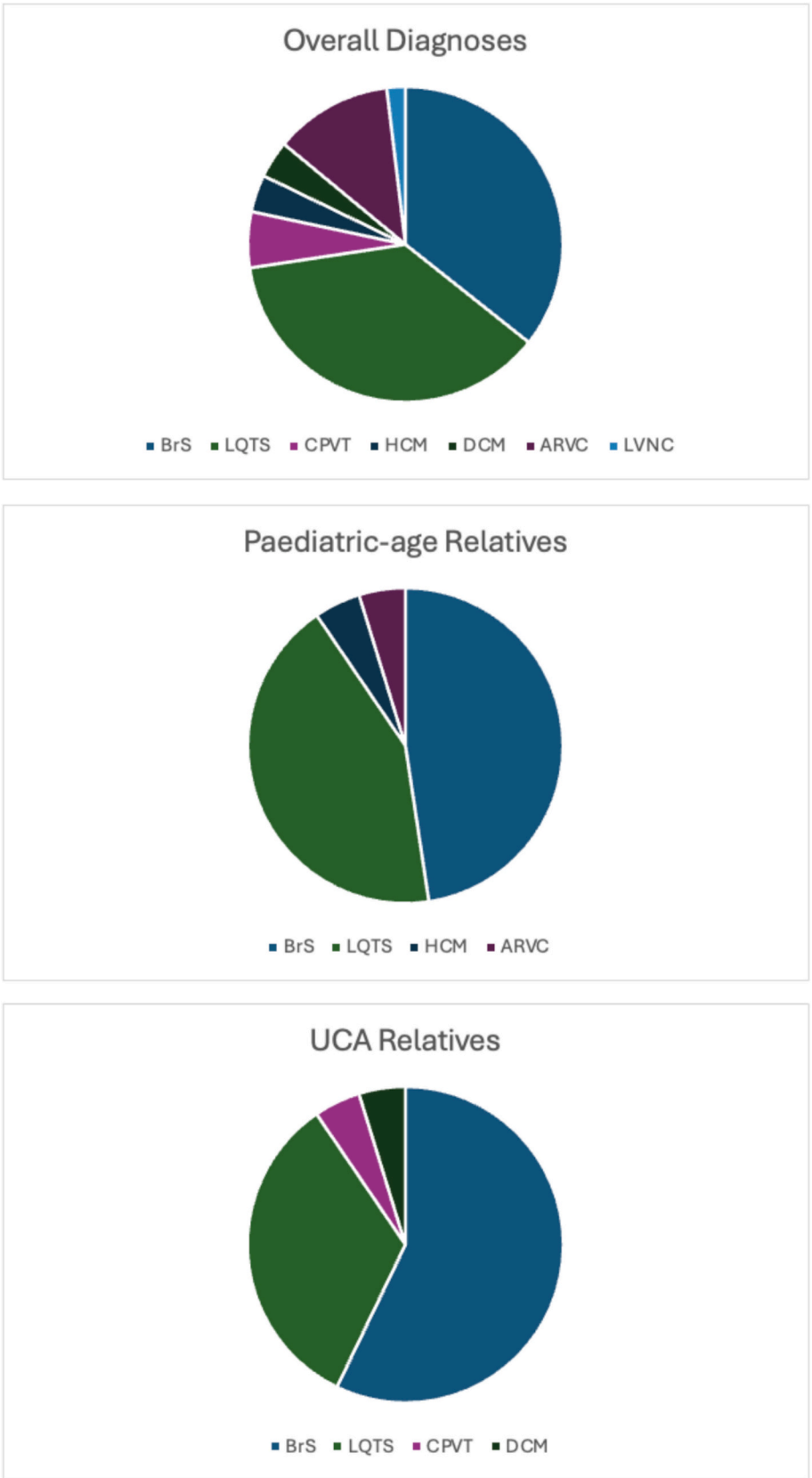

Fig. 3. Combined proportion of ICC diagnoses made in first-degree relatives (overall, SADS and UCA). BrS = Brugada Syndrome, LQTS = Long QT Syndrome, CPVT = Catecholaminergic Polymorphic Ventricular Tachycardia, HCM = Hypertrophic Cardiomyopathy, DCM = Dilated Cardiomyopathy, ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy, LVNC = Left Ventricular Non-Compaction.

Table 3
Investigations performed during cardiac screening of relatives.

Reference	*N* of first-degree relatives	Investigations performed	Diagnoses *n* (%)
SADS studies			
Dalgaard et al. 2022	276	ECG – 100 % Echo – 100 %	–
Steinberg et al. 2016	212	ECG – 100 % Echo – 91 % ETT – 84 % CMR – 49 % SCB – 29 % Adrenaline – 30 %	–
Giudici et al. 2014[a]	90	ECG – 100 % Echo – 100 %	BrS – 5 (71.4) LQTS – 1 (14.2) CPVT – 1 (14.2)
Wong et al. 2014[b]	85	ECG – 98 % Echo – 95 % Holter – 85 % CMR – 6.3 % SCB– 11.6 %	–
McGorrian et al. 2013[b]	220	ECG – 100 % Echo – 100 % Holter – 100 % ETT – 100 % CMR – 3.8 % SCB – 10.6 %	–
Caldwell et al. 2012	107	ECG – 100 % Echo – 100 %	–
Nunn et al. 2011	363	–	LQTS - 13 (25.4) BrS -26 (50.9) CPVT – 2 (3.9) CM – 10 (19.6)
Behr et al. 2008	184	ECG – 100 % Echo – 100 %	LQTS – 20 (43.4) BrS – 11 (23.9) CM – 15 (32.6)
Behr et al. 2003	109	ECG – 98 % Echo – 97 % Holter – 77 % ETT – 12.8 %	LQTS – 4 (66.6) MD – 1 (16.6) CM – 1 (16.6)
UCA studies			
Brunet-Garcia et al. 2022[a]	60	ECG – 100 % Echo – 100 %	LQTS – 4 (50) BrS – 3 (37.5) CM – 1 (12.5)
Mellor et al. 2021	201	ECG – 100 % Echo – 26 % HLECG – 79 % ETT – 62 % CMR – 11 % SCB – 10 % Adrenaline – 9 %	BrS – 3 (100 %)
Jacobsen et al. 2020	56	–	
Hornarbakhsh et al. 2017	72	ECG – 100 % Echo – 100 % SAECG – 100 % CMR – 8 % SCB – 5 %	–
Steinberg et al. 2016	186	ECG – 100 % Echo – 90 % ETT – 70 % CMR – 33 % SCB – 10 % Adrenaline – 17 %	–
Jiminez-Jaimez et al. 2015	81	–	–

ETT = Exercise Treadmill Test, SCB = Sodium Channel Blocker drug provocation, LQTS = Long QT Syndrome, BrS = Brugada Syndrome, CPVT = Catecholaminergic Polymorphic Ventricular Tachycardia, SQTS = Short QT Syndrome, CM = Cardiomyopathy, MD = Myotonic Dystrophy.

[a] Pediatric study.

[b] Reported for first-degree and more distant relatives combined.

4.2. Screening following an unexplained cardiac arrest

Screening first-degree relatives of UCA probands is included as a Class IIb recommendation in current international guidelines [8]. Studies on cardiac screening for relatives of UCA probands were more scarce compared to those on relatives of SADS probands; the overlap of etiology between SADS and UCA is a contentious issue.

Several studies (and editorials) have set out proposed definitions for SCA, UCA, and IVF. Terminology remains unstandardized [6], but the generally accepted definition for unexplained cardiac arrest (UCA) is a cardiac arrest in individuals in whom, after baseline investigations (echocardiogram, ECG, and coronary assessment), the cause remains unexplained. Once further systematic investigations such as cardiac magnetic resonance imaging (CMR) and drug provocation have been completed, if the cause for the event remains elusive, it is then termed idiopathic ventricular fibrillation (IVF) [7].

The variation in definition used affects the quality of the evidence and makes it difficult to synthesize the evidence gathered from the studies. In particular, the difference in the clinical investigations conducted in the proband makes it challenging to draw strong conclusions regarding whether these are all truly unexplained cardiac arrests or whether, if more stringent investigations had been conducted, a diagnosis might have been found. This highlights the importance of comprehensive clinical and genetic screening for individuals who have suffered an SCA in order to better direct screening for relatives. The small number of studies which met inclusion criteria for this review demonstrates diagnostic yields of ICCs in relatives ranging from 0 to 18.5 %. The difference in yield of diagnoses between SADS and UCA was not statistically significant. However, there is a trend towards a lower diagnostic yield in relatives of UCA probands.

4.3. Screening pediatric-age relatives of SADS or UCA victims

An additional aim of this review was to describe the clinical yield of ICCs in the pediatric population of first-degree relatives of SADS or UCA probands. Only three of the included studies reported exclusively on outcomes of pediatric-age relatives. Studies differed on their definition of child-age relatives, with one defining pediatric as $\leq$16 years old [17] and the remaining two studies defining this as $\leq$18 years old. Two of the three studies came from the same tertiary specialist pediatric center. Although at least one study [18] did include pediatric relatives in their cohort based on their demographic data, they did not provide extractable data on the child-age relatives alone.

There was no statistically significant difference between overall diagnostic yield in the pediatric age group compared to the overall yield. This may suggest a comparable prevalence of ICC in pediatric first-degree relatives, although the number of studies was small, and it is conceivable that potential differences in diagnostic yield between adult and pediatric relatives may not have been detected. Due to variable phenotypic expression and incomplete, age-related, penetrance, the most accepted strategy is to screen pediatric first-degree relatives regularly until adulthood; however, the optimum frequency and nature of follow-up are not well defined. The studies included in this review all described ongoing follow-up for pediatric-age relatives. The current guidelines are largely extrapolated from adult data and have not been validated in child-age relatives [8,19]. Importantly, European guidelines only specify the need for ongoing follow-up for children of decedents but make no comment on child-age siblings of probands who have the same risk profile (as both are first-degree relatives) [2].

It is recognized that some tests have age-related variations in positive and negative predictive value. For example, Ajmaline provocation

testing has been shown to be affected by age-related penetrance with the risk of a false negative test in pre-pubertal children [20]. Children may not be able to complete all necessary investigations due to body size or ability to comply with tests such as exercise testing or CMR. Although not specifically described in the guidelines, the challenges of screening in the pediatric population are best met in a specialist pediatric setting.

4.4. Studies on SIDS and SUDI

SIDS and Sudden Unexpected Death in Infancy (SUDI), like SADS, are diagnoses of exclusion in infants under one year old. Related search terms were included in the online search strategy; however, no papers which described the clinical yield of screening in these families were retrieved. It is unclear whether the scarcity of evidence is representative of a real-world clinical picture or whether relatives are undergoing clinical cardiac screening routinely. The sudden death of an infant is a deeply traumatic event for families, and it may be that this population is less inclined to undergo clinical evaluation in these circumstances. There have been many non-cardiac related theories suggested to account for SIDS deaths, such as the triple risk theory [21]. Clinical screening for first-degree relatives of SIDS, or SUDI, cases has been recommended in previous 2013 international guidelines [19]; however, this is based on evidence extrapolated from studies reporting on molecular autopsy results containing a proportion of ICC causative variants. Cardiac evaluation of first-degree relatives of SIDS or SUDI probands is not included as a recommendation in the most recently published guidelines [2,8]. Studies have shown that potentially >10 % of post-mortem genetic testing in the proband may reveal an ICC diagnosis in these cases [22], which is not dissimilar to the yield in SADS probands.

4.5. Quality of selected studies

Overall, the risk of bias in selected studies was high, particularly selection bias. There is a possibility of non-response bias, but, to our knowledge, no studies exist describing what proportion of families attend for screening following a SCD or SCA. Furthermore, as most of the studies were conducted in tertiary hospitals, where most patients were screened in specialist ICC clinics, referral filter bias is unavoidable. The majority of papers included in our review were of a retrospective cohort design, which carries an inherent bias. Except for two studies that drew from national registries [7,12], all others lacked sufficient sample size, which may lead to an underestimation of diagnostic yield. Measurement bias is low in most of the studies, clearly stating protocols for clinical evaluation of family members and diagnostic criteria in accordance with current guidelines. Evaluations were conducted in ICC clinics in tertiary hospitals by experienced specialists.

4.6. Limitations

Different understandings and definitions of the terms involved exist within the medical and scientific community, leading to inconsistency across the literature. SCA, UCA, IVF and others may be used interchangeably or be assigned specific definitions. For this review, all terms were included in the search strategy to capture all available literature. The difference in terminology causes heterogeneity in study design. The definition of a 'SADS' death varied across the studies; some employed a more stringent definition, whereas others exhibited a greater degree of flexibility in their criteria for inclusion. One included study used the term Sudden Unexpected Death (SUD) interchangeably with SADS [12]. The lower age range is almost universally agreed to be one year old (with any deaths below this age termed SIDS or SUDI). One study [23] set the lower age limit for inclusion at 4 years old. However, the reason for this was not given. The upper age limit also varies between definitions, with included studies defining this as between 35 and 64 years old.

By design, this study describes the diagnostic yield of clinical screening alone, as diagnoses made through genetic testing were not within the scope of this systematic review. In clinical practice, diagnosis in relatives of SADS or UCA probands occurs through a combination of clinical and genetic testing, and existing literature suggests that including genetic diagnoses would have likely increased the overall yield of ICC diagnoses [4].

All included studies were performed in Western countries; half of the included studies are from the UK, with the remaining coming from Denmark, Spain, Canada, and Ireland. This review focussed on the clinical cardiac investigation of relatives and did not include studies where diagnoses were made due to predictive genetic testing or yield of molecular autopsy. In practice, these are often performed concurrently, but this review aimed to describe the yield from clinical evaluation only. Additionally, missing data and heterogeneity of reporting in selected studies were a limitation as it precluded a meta-analysis being conducted.

5. Conclusion

The three conditions most frequently diagnosed in relatives were LQTS, Brugada syndrome, and CPVT, highlighting the need for relatives to be screened at a tertiary ICC center with the ability to perform ajmaline provocation and exercise testing in order that these conditions are not missed. Additionally, a quarter of all ICC diagnoses in relatives were cardiomyopathies despite reportedly normal autopsies in the probands, suggesting the need for expert cardiac pathology review in cases of sudden death. It may also act as a reasonable indication to continue to screen first-degree relatives beyond a one-off assessment, given the age-related penetrance of cardiomyopathies, particularly as it relates to pediatric-age patients.

Whilst there is a clear indication for clinical screening of first-degree relatives for ICCs following a SADS death or an UCA, a lack of well-designed population-based studies means that the evidence base supporting when or how relatives should be screened is not robust. The reported diagnostic yield varies considerably, with no significant difference between SADS and UCA cohorts, and a similar yield in pediatric and adult relatives. This supports systematic screening for all first-degree relatives regardless of age. No studies were found which described clinical screening in relatives of SIDS or SUDI cases.

CRediT authorship contribution statement

Jennifer Tollit: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **I-Ting Tu:** Writing – original draft, Formal analysis, Data curation. **Gabrielle Norrish:** Writing – review & editing, Formal analysis. **Ella Field:** Methodology. **Jo Wray:** Writing – review & editing. **Juan Pablo Kaski:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Editorial footnote

Given role as Associate Editor Juan Pablo Kaski had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Associate Editor, Jennifer Avira Silva.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jennifer Tollit reports financial support was provided by British Heart Foundation. Juan Pablo Kaski, corresponding author on the Journal's editorial board. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ppedcard.2025.101816.

References

[1] Westaby, J., et al., National sudden cardiac death autopsy database highlighting sudden arrhythmic death and cardiomyopathies, applying diagnostic criteria and expanding the concept of the molecular autopsy. Europace, 2023. 25(Supplement_1).
[2] Zeppenfeld K, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43(40):3997–4126.
[3] Behr ER, et al. Sudden arrhythmic death syndrome: a national survey of sudden unexplained cardiac death. Heart 2007;93(5):601–5.
[4] Lahrouchi N, et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. J Am Coll Cardiol 2017;69(17):2134–45.
[5] Victor Waldmann WB. Nicole Karam, Florence dumas, *characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: focus on idiopathic ventricular fibrilation*. Eur Heart J 2018;39:1981–7.
[6] Alqarawi W, et al. Defining idiopathic ventricular fibrillation: a systematic review of diagnostic testing yield in apparently unexplained cardiac arrest. Heart Rhythm 2021;18(7):1178–85.
[7] Mellor GJ, et al. Familial evaluation in idiopathic ventricular fibrillation: diagnostic yield and significance of J wave syndromes. Circ Arrhythm Electrophysiol 2021;14(3):E009089.
[8] Stiles MK, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm 2021;18(1):e1–50.
[9] Moher D, et al. Preferred reporting items for systematic reviews and Meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[10] Campbell M, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ 2020:l6890.
[11] McKenzie, J.E. and S.E. Brennan, *Synthesizing and presenting findings using other methods*, in *Cochrane handbook for systematic reviews of interventions*. 2024, Cochrane.
[12] Steinberg C, et al. Cardiac abnormalities in first-degree relatives of unexplained cardiac arrest victims. Circ Arrhythm Electrophysiol 2016;9(9).
[13] van der Werf C, et al. Low rate of cardiac events in first-degree relatives of diagnosis-negative young sudden unexplained death syndrome victims during follow-up. Heart Rhythm 2014;11(10):1728–32.
[14] Honarbakhsh S, et al. Medium-term outcomes of idiopathic ventricular fibrillation survivors and family screening: a multicentre experience. Europace 2017;19(11):1874–80.
[15] De Lazzari M, et al. Relationship between electrocardiographic findings and cardiac magnetic resonance phenotypes in Arrhythmogenic cardiomyopathy. J Am Heart Assoc 2018;7(22).
[16] McGorrian C, et al. Family-based cardiac screening in relatives of victims of sudden arrhythmic death syndrome. Europace 2013;15(7):1050–8.
[17] Wong LCH, et al. Cardiac evaluation of pediatric relatives in sudden arrhythmic death syndrome a 2-center experience. In: Circulation: Arrhythmia and electrophysiology. Lippincott Williams and Wilkins; 2014. p. 800–6.
[18] Dalgaard CV, et al. Sudden unexplained death versus nonautopsied possible sudden cardiac death: findings in relatives. J Cardiovasc Electrophysiol 2022;33(2):254–61.
[19] Priori SG, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and Management of Patients with inherited primary arrhythmia syndromes. Heart Rhythm 2013;10(12):1932–63.
[20] McMillan MR, et al. Feasibility and outcomes of ajmaline provocation testing for Brugada syndrome in children in a specialist paediatric inherited cardiovascular diseases Centre. Open Heart 2014;1(1):e000023.
[21] Spinelli J, et al. Evolution and significance of the triple risk model in sudden infant death syndrome. J Paediatr Child Health 2017;53(2):112–5.
[22] Tester DJ, et al. Cardiac genetic predisposition in sudden infant death syndrome. J Am Coll Cardiol 2018;71(11):1217–27.
[23] Behr ER, et al. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Heart J 2008;29(13):1670–80.
[24] Giudici V, et al. Sudden arrhythmic death syndrome: diagnostic yield of comprehensive clinical evaluation of pediatric first-degree relatives. PACE - Pacing and Clinical Electrophysiology 2014;37(12):1681–5.
[25] Caldwell J, et al. The clinical management of relatives of young sudden unexplained death victims; implantable defibrillators are rarely indicated. Heart 2012;98(8):631–6.
[26] Nunn LM, et al. Prevalence of J-point elevation in sudden arrhythmic death syndrome families. J Am Coll Cardiol 2011;58(3):286–90.
[27] Behr E, et al. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. Lancet 2003;362(9394):1457–9.
[28] Brunet-Garcia L, et al. Prevalence of inherited cardiac conditions in pediatric first-degree relatives of patients with idiopathic ventricular fibrillation. Pediatr Cardiol 2022;43(5):1114–21.
[29] Jacobsen EM, et al. Diagnostic yield and long-term outcome of nonischemic sudden cardiac arrest survivors and their relatives: results from a tertiary referral center. Heart Rhythm 2020;17(10):1679–86.
[30] Jiménez-Jáimez J, et al. Diagnostic approach to unexplained cardiac arrest (from the FIVI-gen study). American Journal of Cardiology 2015;116(6):894–9.