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# **Low rate of cardiac events in first-degree relatives of diagnosis-negative young sudden unexplained death syndrome victims during follow-up**

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20 **Conflicts of Interest** - None.

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## ABSTRACT

**Background:** Sudden unexplained death syndrome (SUDS) in young individuals often results from inherited cardiac disease. Accordingly, comprehensive examination in surviving first-degree relatives unmasks such disease in ~35% of families. It is unknown whether individuals from diagnosis-negative families are at risk of developing manifest disease or cardiac events during follow-up.

**Objectives:** To study the prognosis of first-degree relatives of young SUDS victims, in whom the initial cardiologic and genetic examination did not lead to a diagnosis.

**Methods:** We retrieved vital status of surviving first-degree relatives from 83 diagnosis-negative families who presented to our cardiogenetics department in 1996-2009 because of SUDS of  $\geq 1$  relative aged 1-50 years. Moreover, we contacted relatives who previously visited our center for detailed information.

**Results:** We obtained detailed information (median follow-up, 6.6 years; interquartile range, 4.7-9.6) in 340/417 first-degree relatives (81.5%) from 77 of 83 families (92.8%). Vital status, available in 405 relatives (97.1%), showed that 20 (4.9%) relatives died during follow-up, including one natural death under the age of 50. This girl belonged to a family with multiple cases of idiopathic ventricular fibrillation and SUDS, including another successfully resuscitated sibling during follow-up. 234 of 340 first-degree relatives (68.8%) underwent cardiologic examination. Of these, 76 (32.5%) were reevaluated. Inherited cardiac disease was diagnosed in 3 families (3.6%).

**Conclusion:** In first-degree relatives of young SUDS victims with no manifest abnormalities during initial examination, the risk of developing manifest inherited cardiac disease or cardiac events during follow-up is low. This does not apply to families with obvious familial SUDS.

## **ABBREVIATIONS**

ICD = implantable cardioverter-defibrillator

IVF = idiopathic ventricular fibrillation

SUDS = sudden unexplained death syndrome

## INTRODUCTION

Sudden death in apparently healthy young individuals is often caused by inherited cardiac diseases.<sup>1,2</sup>

Consequently, the risk of cardiovascular disease and ventricular arrhythmias is higher in relatives of young sudden cardiac death victims, in particular relatives under the age of 35, than in the general

5 population.<sup>3</sup> In approximately 18%<sup>1</sup> (range, 6%–35%)<sup>2,4-9</sup> of young sudden death cases, autopsy does not reveal the cause of death, and in many countries autopsy is not routinely performed in all of these fatalities. Sudden unexplained death syndrome (SUDS) is diagnosed in both cases.<sup>10</sup>

Comprehensive cardiologic and molecular-genetic evaluation of first-degree relatives of young SUDS victims is indicated.<sup>11,12</sup> This evaluation unmask an inherited cardiac disease, potentially  
10 explaining the fatal event, in approximately 35% of the families,<sup>13-16</sup> enabling timely prophylactic treatment.<sup>17</sup>

Relatives from SUDS victims in whom the initial comprehensive cardiologic and genetic examination does not lead to a familiar diagnosis are usually advised to undergo cardiologic reexamination on a regular basis, as inherited cardiac diseases may manifest during follow-up.<sup>10,18,19</sup>

15 Whether cardiologic examination during follow-up unmask previously undiagnosed inherited conditions and whether these relatives are at risk for SUDS has, to our knowledge, not been studied. Indeed, if relatives of an SUDS victim are carrier of an undiagnosed inherited cardiac disease, potentially fatal cardiac events could occur during follow-up.

To address these issues, we carried out an observational follow-up study among first-degree  
20 relatives of young SUDS victims, in whom the initial cardiologic and genetic examination did not lead to a diagnosis.

## **METHODS**

### **Setting**

5 Details on our multidisciplinary cardiogenetics outpatient clinic at the Academic Medical Center, Amsterdam, the Netherlands (teaching hospital),<sup>17</sup> and our SUDS registry comprising families who  
underwent cardiologic and genetic examination after the SUDS of a relative aged 1–50 years (the  
10 proband), have been described in detail.<sup>15</sup> SUDS was defined as out-of-hospital natural death in a  
previously healthy individual whose family had no known inherited cardiac disease, in whom death  
occurred within one hour after the start of complaints or within 24 hours of the victim being seen alive  
and well, and in whom autopsy was not performed or initially did not explain the death.<sup>15</sup> In our  
15 cardiogenetics clinic, relatives of SUDS victims are counseled by both a cardiologist and a clinical  
geneticist or genetic counselor, who collect detailed information on the SUDS proband (including  
circumstances of SUDS) and the family. This is followed by tailored cardiologic examination and  
targeted molecular genetic testing. When these investigations are completed, the relatives receive a letter  
that summarizes the complete evaluation that was performed in their family. When a diagnosis is made,  
20 appropriate follow-up is arranged. When no diagnosis is made (diagnosis-negative family), most relatives  
are advised to undergo repeated cardiologic evaluation, in particular when they develop possible cardiac  
symptoms. This advice is individualized and based on the level of suspicion of an inherited cardiac  
disease and age. For example, children are usually advised to undergo yearly cardiologic evaluation,  
whereas adults are advised to undergo evaluation every three to five years.

20

### **Study population**

This analysis comprised all surviving first-degree relatives (parent, sibling, or child) from diagnosis-  
negative families of a SUDS victim aged 1-50 years, of whom  $\geq 1$  first-degree relative presented to our  
cardiogenetics clinic between 1996 and mid 2009.<sup>15</sup>

25

## **Follow-up**

First, all first-degree relatives who had not visited our center recently were contacted by using a standardized questionnaire to obtain detailed information on themselves and their family. Second, we contacted at least one first-degree relative per family by phone for additional questioning, including on 5 non-first-degree relatives. Cardiologic reevaluation, newly diagnosed (inherited) cardiac disease and the occurrence of cardiac events (defined as aborted cardiac arrest or sudden death) as well as death due to other causes at any age in the family were questioned. In relatives who had visited our center and consented, additional information was obtained from the relative's general practitioner, cardiologist, or hospital records, when necessary. All the relatives who were examined within a year after the family 10 came to our attention were considered to be part of the initial examination. The yield of cardiologic evaluation during follow-up included the yield of cardiologic evaluation in all relatives who were evaluated for the first time  $\geq 1$  year after the family came to our attention and the yield of reevaluation in relatives who were part of the initial examination.

Information on vital status of first-degree relatives in whom no detailed information could be 15 collected was obtained from the Dutch national population registry and was verified until January 1, 2013. This national population registry does not contain information on the cause of death.

Follow-up durations were counted from the date when the first relative of that family presented to our center to the date when information on a relative was obtained or the relative's death.

## **20 Statistical analysis**

Continuous data are presented as median (interquartile range) and categorical variables as number (percentage). Descriptive statistics were used for analysis.



## RESULTS

### Study population

Ten of the 93 SUDS families who were classified diagnosis-negative SUDS after the first cardiologic examination<sup>15</sup> were excluded from the present analysis: five families because only second-degree relatives were examined, three who were double-counted because it was found after initial analysis that they were related to each other, and two because no follow-up information, including vital status, was available in any relative. Hence, we included the first-degree relatives of 83 SUDS victims. Nineteen probands (22.9%) were aged 1 to 21 years, and autopsy was performed in 40 (48.2%) (Table 1).

At time of their death, the 83 SUDS victims had 417 living first-degree relatives. Complete detailed follow-up information was available in 63 families (75.9%), comprising 308 first-degree relatives. In 20 families (24.1%) follow-up was incomplete, with detailed follow-up information in 34 relatives, vital status only in 61, and no follow-up information in 12. The median follow-up period was 6.6 years (interquartile range, 4.7-9.6).

### Mortality

Overall, vital status was retrieved in 405 of 417 relatives (97.1%; median of 4 per family [range, 1-13]) from all 83 families. Their median age was 41.5 years (interquartile range, 26-55) when their family first came to our attention, 267 relatives were below the age of 50, and 177 (44.1%) were male. During follow-up, 20 (4.9%) relatives died, including two under the age of 50 (0.7% of this age-group). One girl died suddenly at the age of ten while watching television (II:5 in Figure 1; see text below), although the cardiologic evaluation that was performed three months earlier was unremarkable. A female relative from another family committed suicide at the age of 44. Of the 18 deceased individuals over the age of 50, eight died from a definite non-cardiac cause, while the cause of death was unknown in 10 relatives (of whom at least five were above the age of 75 years). Thus, 11 relatives (2.7%) died of cardiac or unknown causes.

In addition, four sudden death events among non-first-degree related relatives were reported in four families: one 48-year old uncle of a SUDS proband died suddenly from an unknown cause while gardening; one 41-year old aunt of a SUDS proband died presumably from a ruptured abdominal aortic aneurysm; and a second cousin of a SUDS proband died suddenly and unexpectedly in his early forties.

5 Finally, the aunt of a SUDS proband died suddenly at the age of 44 while vacuum cleaning. Autopsy revealed arrhythmogenic cardiomyopathy. Molecular-genetic testing of all genes linked to arrhythmogenic cardiomyopathy (*PKP2*, *DSP*, *DSC2*, *DSG2*, *JUP*, *TMEM43*, and *PLN*) was negative.

### **Nonfatal cardiac events**

10 Detailed follow-up information was available in 340 relatives (81.5%; median of 4 per family [range, 0-13]) from 77 of 83 families (92.8%). These relatives had a median age of 41 years (interquartile range, 27-54) when their family first came to our attention, including 230 below the age of 50, and 157 (46.2%) were male. During follow-up, one more definite cardiac event occurred: a younger sister (II:6 in Figure 1) of the 10-year old girl that died suddenly, was successfully resuscitated and received an appropriate  
15 implantable cardioverter-defibrillator (ICD) shock after an episode of ventricular fibrillation one year later. The girls originated from a Moroccan family with an extremely malignant family history in one generation including multiple cases of idiopathic ventricular fibrillation (IVF) and SUDS (Figure 1). This family came to our attention in 2001 after the aborted cardiac arrest of a 16-year old boy (II:3). His family history included SUDS of his sister at the age of 9 (II:4). Consanguinity was denied. Comprehensive  
20 cardiologic examination in the 16-year old boy, the parents and the other children did not reveal any abnormalities. Very recently, the causal genetic substrate, a mutation in the gene encoding calmodulin (*CALM1*), was identified in all affected individuals.<sup>20</sup>

### **Cardiologic reevaluation and inherited cardiac disease**

25 Of the 340 relatives with detailed follow-up information, 223 were evaluated once following the SUDS event in their family. In addition, the information of 11 relatives who underwent cardiologic examination

for other reasons could also be used. Thus, 234 of 340 first-degree relatives (68.8%) were part of the initial evaluation. Of these, 76 (32.5%) were reevaluated as recommended after the negative initial examination (N=66) or for another reason (N=10). The reevaluation was performed at our center or the referring center, so no uniform approach was applied.

5            In three families (3.6%) an inherited cardiac disease was identified during follow-up. In the first family, a brother of the 39-year-old male SUDS victim was diagnosed with Brugada syndrome. No autopsy had been performed in the proband. Only the daughter of the SUDS victim had previously been examined, and results of all tests, including ajmaline challenge, were unremarkable. The individual in whom Brugada syndrome was diagnosed, was cardiologically evaluated for the first time during follow-  
10 up.

              The second family underwent evaluation because of the SUDS of 42-year-old man in whom no autopsy was performed. Initial cardiologic examination revealed a slightly dilated aorta in the proband's brother. During follow-up, minimal aorta dilatation was identified in two other brothers. In all three brothers and their mother a missense mutation in the *TGFBR1* gene was identified. Because none of the  
15 relatives showed signs of Marfan syndrome or Loeys-Dietz syndrome, the final diagnosis was familial thoracic aortic aneurysms/dissections.

              In a third family, three first-degree relatives who were aged 37 to 53 years experienced myocardial infarction during 10.5 years of follow-up. In addition, one relative underwent coronary artery bypass graft surgery. All affected relatives were diabetic and had hyperhomocysteinemia, possibly related to folate  
20 deficiency. Two of these relatives were part of the initial evaluation in their family. At that time, premature atherosclerosis was already suspected based on the family history, but an inherited dyslipidemia or definite coronary artery disease could not be identified in the evaluated relatives.

              Finally, one first-degree relatives got an ICD implanted in his fifties, but information on the indication was not available.

25

## DISCUSSION

This study demonstrates that first-degree relatives from young SUDS victims in whom the initial cardiologic and genetic evaluation did not lead to a diagnosis, have a favorable prognosis. In this large cohort of diagnosis-negative SUDS families the cardiac event rate during follow-up was low. Importantly, all events that were definitely related to the SUDS of the proband occurred in one family with an extremely malignant history of IVF and SUDS. During follow-up, inherited cardiac disease manifested in three families (3.6%). In these families, the first relative in whom the diagnosis was made showed discrete, non-diagnostic abnormalities at the initial evaluation, or had not been examined before.

### 10 **Follow-up of patients and families with IVF or SUDS**

IVF or SUDS may ultimately be explained through a manifested phenotype during long-term follow-up. However, follow-up data of relatives of young victims of IVF or SUDS are scarce. In a study on the role of provocative testing with procainamide and epinephrine in IVF, Krahn and co-workers included 47 unaffected first- and second-degree relatives of IVF and SUDS victims.<sup>21</sup> Second-degree were only included when evidence suggested that more than one relative was affected. During 4.8±3.8 years of follow-up no events occurred, suggesting a favorable prognosis.

Indeed, in the present large cohort of first-degree relatives from diagnosis-negative SUDS families, outcomes after a median period of over six years were favorable. Clearly the presence of undiagnosed inherited cardiac disease in SUDS families, including conditions that remain to be discovered, can never completely be excluded. However, based on the present data relatives may be reassured that the odds of such a scenario are low. Importantly, cardiac events or detection of previously undiagnosed inherited cardiac disease during follow-up were not observed in relatives who did not show any abnormalities when first evaluated.

25

## **Clinical implications**

Cardiac events or newly diagnosed inherited cardiac disease were only observed in siblings from a family with multiple cases of IVF and SUDS, relatives with subtle abnormalities at the initial cardiologic examination, or relatives who did not undergo cardiologic examination when members from their family first presented to our cardiogenetics department. Thus, following relatives with a malignant family history or the presence of subtle abnormalities at the initial examination as well as stressing the importance of (at least) a single evaluation for all first-degree relatives of a young SUDS victim, especially in the presence of possible cardiac symptoms, seems pertinent.

Based on the favorable outcomes of the large population of adults from diagnosis-negative SUDS families in this study, it is conceivable that in these relatives a completely unremarkable first evaluation is sufficient to exclude the presence of an inherited cardiac disease. Thus, intensity of repeated cardiologic examination during follow-up may be diminished. However, in children from diagnosis-negative SUDS families manifestations of a particular inherited cardiac disease may develop with increasing age, so we still consider repeated cardiologic follow-up safe and indicated in these children.

These recommendations are further supported by recent observations in a nationwide study from Denmark in which the incidence of cardiovascular disease in relatives of young sudden cardiac death victims was compared with that in the general population.<sup>3</sup> The risks of both cardiovascular disease and ventricular arrhythmia among first- and second-degree of young autopsy-negative SUDS victims was increased among those younger than 35 years, but similar to the general population in relatives of all ages.

## **Study limitations**

First, detailed follow-up information could not be collected in all relatives. To compensate for this lack of data, we obtained information on vital status in almost all of these relatives, so only the risk of non-fatal cardiac events or developing inherited cardiac disease may be underestimated.

Second, only a minority of relatives underwent cardiologic reevaluation, most probably because they or their cardiologists felt reassured after the unremarkable results of their first evaluation. Thus,

inherited cardiac disease may have remained undiagnosed in families that were only evaluated once. Yet, the relatives that underwent reevaluation may well be those in whom cardiologic reevaluation was strongly recommended because of the family history and/or discrete abnormalities at the initial examination, making the odds of diagnosing inherited cardiac disease during follow-up higher in these reevaluated relatives than in other individuals.

Third, first-degree relatives of the proband who died suddenly before the proband did, were not included in this study because of the previously outlined objectives of this study. These inclusion criteria introduce survival bias.

Finally, the median follow-up duration of 6.6 years was relatively short.

10

### **Conclusion**

In first-degree relatives of young SUDS victims with no manifest abnormalities during initial cardiologic examination, the risk of developing manifest inherited cardiac disease or potentially fatal cardiac events during follow-up is low. In adult relatives with a completely unremarkable first evaluation, repeated cardiologic examination during follow-up may not be necessary. This does not apply to children, adults with subtle abnormalities at the first examination, and families with a clear idiopathic inherited arrhythmia syndrome leading to multiple cases of IVF and SUDS.

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**TABLE****Table 1. Characteristics of sudden unexplained death syndrome probands.**

<b>Variable</b>	<b>SUDS probands</b>
	<b>N = 83</b>
Age, years	34 34 (6-49)
Children (<21 years of age)	22.9 (19/83)
Male sex	72.3 (60/83)
Circumstances of event known	88.0 (73/83)
At rest	63.0 (46/73)
During exertion	32.9 (24/73)
Other trigger	4.1 (3/73)
Autopsy performed	48.2 (40/83)

Values are median (range), or percentage (number/total number).

**FIGURE LEGEND**

**Figure 1. Family tree of a family with multiple cases of SUDS and IVF.**

SUDS indicates sudden unexplained death syndrome; IVF, idiopathic ventricular fibrillation.