Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Does the Age of Sudden Cardiac Death in Family Members Matter in Brugada Syndrome?

Pattara Rattanawong, MD; Jakrin Kewcharoen, MD; Chanavuth Kanitsoraphan, MD; Timothy Barry, MD; Anusha Shanbhag, MD; Nway L. Ko Ko, MD; Wasawat Vutthikraivit, MD; Madhurima Home, MD; Pradyumna Agasthi, MD; Hasan Ashraf, MD; Wataru Shimizu, MD, PhD; Win-Kuang Shen, MD

BACKGROUND: Brugada syndrome is an inherited cardiac channelopathy associated with major arrhythmic events (MAEs). The presence of a positive family history of sudden cardiac death (SCD) as a risk predictor of MAE remains controversial. We aimed to examine the association between family history of SCD and MAEs stratified by age of SCD with a systematic review and meta-analysis.

METHODS AND RESULTS: We searched the databases of MEDLINE and EMBASE from January 1992 to January 2020. Data from each study were combined using the random-effects model. Fitted metaregression was performed to evaluate the association between the age of SCD in families and the risk of MAE. Twenty-two studies from 2004 to 2019 were included in this meta-analysis involving 3386 patients with Brugada syndrome. The overall family history of SCD was not associated with increased risk of MAE in Brugada syndrome (pooled odds ratio [OR], 1.11; 95% CI, 0.82–1.51; P=0.489, I^2=45.0%). However, a history of SCD in family members of age younger than 40 years of age did increase the risk of MAE by ≈2-fold (pooled OR, 2.03; 95% CI, 1.11–3.73; P=0.022, I^2=0.0%). When stratified by the age of cut point at 50, 45, 40, and 35 years old, a history of SCD in younger family member was significantly associated with a higher risk of MAE (pooled OR, 0.49, 1.30, 1.51, and 2.97, respectively; P=0.046).

CONCLUSIONS: A history of SCD among family members of age younger than 40 years was associated with a higher risk of MAE.

Key Words: Brugada syndrome ■ family history ■ sudden cardiac death

Brugada syndrome (BrS) is a heterogeneous genetic ion channel disorder that is associated with an increased risk of major arrhythmic events (MAE) and sudden cardiac death (SCD).[1] Brugada syndrome is characterized by coved-type (Type-1) ST elevation appearances in the right precordial leads.[1,2] The prevalence of patients with a Brugada ECG Type-1 pattern varies among different populations, ranging from 0% to 0.4%.[1,3] The most common mutation responsible for BrS is the *SCN5A* mutation, which is present in 20% to 30% of patients and has an autosomal dominant inheritance pattern.[4] Several studies have demonstrated the importance of a family history of SCD in characterizing the disease and prognosis.[2] However, data from other studies report conflicting results and suggest that a family history of SCD is not useful as a risk stratification tool.[5-8] Risk stratification for ventricular arrhythmias and increased risk of SCD remains challenging in asymptomatic patients with Brugada syndrome. In this study, we aimed to assess whether a family history of

Correspondence to: Win-Kuang Shen, MD, Department of Cardiovascular Medicine, Mayo Clinic, 5777, E. Mayo Blvd., Phoenix, AZ, 85054. E-mail: wshen@mayo.edu

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.019788

This manuscript was sent to John Jefferies, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- A history of sudden cardiac death among family members of age younger than 40 years was associated with a higher risk of major arrhythmic event.
- A mere presence of a family history of sudden cardiac death without a clear age definition is not a risk predictor in Brugada syndrome.

What Are the Clinical Implications?

- We propose that a family history of sudden cardiac death in the young could be a prognostic factor to predict major arrhythmic event in patients with Brugada syndrome.

Nonstandard Abbreviations and Acronyms

BrS	Brugada syndrome
MAE	major arrhythmic event
SCA	sudden cardiac arrest
SCD	sudden cardiac death

SCD is associated with an increased risk of MAE in patients with BrS by performing a systematic review and meta-analysis.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Search Strategy

Two investigators (C.K. and W.V.) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to January 2020 using a search strategy as described in Data S1. Only full articles in English were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

Inclusion Criteria

The eligibility criteria included the following:

1. Cohort, case-control, or cross-sectional studies reporting end points of MAE in patients with BrS with and without a family history of SCD or MAE.
2. The calculation by the studies of odds ratios (OR) or hazard ratios with 95% CI, or the presence of sufficient raw data for manual calculation. Patients without a family history of SCD were used as controls. The risk ratio and hazard ratio were converted to OR by previously reported principal equations.[9]

Study eligibility was independently determined by 2 investigators (A.S. and N.K.), and differences were resolved by mutual consensus. In case of an overlap or duplication between populations among studies, the study with largest sample size and clear age of cut point definition from each representative population was selected, whereas the rest of the overlap or duplicated populations were excluded. If the identity of the declared participating institutions was unclear, the corresponding author of each study was contacted. The Newcastle-Ottawa quality assessment scale was used to assess each study's quality.[10] This study complies with the Meta-analysis of Observational Studies in Epidemiology reporting guideline[11] (Table S1).

Data Extraction

A standardized data collection form was used to obtain the information. Two investigators (J.K. and C.K.) independently performed this data extraction process to ensure accurate data extraction. Any data discrepancy was resolved by referring back to the original articles.

Definition

Family History

Positive family history was defined as at least 1 first- or second-degree relative who had sudden unexplained death, sudden cardiac death (SCD), or sudden cardiac arrest or as defined in each study (Table).[12–31]

Brugada Syndrome

BrS was diagnosed according to recently published guidelines.[1] Only studies evaluating a type-1 Brugada pattern were included in this meta-analysis.

End Point: Major Arrhythmic Event

Major arrhythmic events were defined by either of SCD, sudden cardiac arrest, ventricular fibrillation, sustained ventricular tachycardia, or appropriate implantable cardioverter defibrillator discharge. Nonsustained ventricular tachycardia and inappropriate implantable cardioverter defibrillator discharge were not considered as end points of interest.

Statistical Analysis

Meta-Analysis

We performed a meta-analysis of the included studies using a random-effects model using the

Table. Summary Characteristics of Individual Included in Studies of Patients With BrS

Study/Year	Study Design	N	Major Arrhythmic Events	Country	Centers (N)	Men (%)	Mean Age±SD (y)	Symptomatic BrS (%)	Follow-Up (mo)	Analysis Model	Positive Family History (%)	Positive *SCN5A* (% [N])	Definition of Family History	Outcomes
Daoulah et al, 2012[12]	Retrospective cohort	25	6	Kingdom of Saudi Arabia, United Arab Emirates, Oman, Bahrain, and Kuwait	6	100%	28±7	80%	41.2±17.6	Univariate	32%	NA	SCD in a family member older than 45 y old	Appropriate ICD discharge, SCA
Deliniere et al, 2019[13]	Retrospective cohort	80	28	France, Switzerland, Romania	13	91%	45.1±12.8	36%	12	Univariate	18%	9% [57]	SCD in a family member younger than 50 y old in the first or second degree relatives	VF, SCA
Garcia-Iglesias et al, 2019[14]	Prospective cohort	155	14	Spain, Mexico, India	6	70%	41.0±14.7	40%	55.8±39.4	Multivariate	47%	NA	SCD in a family member younger than 45 y old	VF, appropriate ICD discharge, SCA
Gray et al, 2017[15]	Prospective cohort	54	18	Australia	4	81%	44±13	26%	27.6±30	Univariate	20%	20% [54]	SCD or SCA in a family member younger than 45 y old	Sustained VT, SCA
Huang et al, 2009[16]	Prospective cohort	43	7	China	7	56%	45.2±10.8	55.8%	32.2±8.6	Multivariate	NA	12% [43]	SCD in a family member younger than 45 y old	Sustained VT, VF, SCD
Juang et al, 2015[17]	Case-control	14	5	Taiwan	2	100%	40±13	100%	NA	Univariate	10%	100%	SCD in a family member younger than 45 y old	Sustained VT, VF, SCD
Kharazi et al, 2007[18]	Prospective Cohort	11	2	Iran	1	92%	46.5±11.8	83%	27.83±11.25	Univariate	16%	NA	Family history of SCD	Sustained VT, VF, appropriate ICD discharge
Leong et al, 2019[19]	Prospective cohort	133	10	United Kingdom	2	61%	45±15	53%	42±25	Univariate	33%	NA	SCD in a family member younger than 40 y old	Sustained VT, VF, appropriate ICD discharge, SCA
Letsas et al, 2019[20]	Prospective cohort	111	7	Greece and United States	9	77%	45.3±13.3	33%	54±42	Univariate	6.3%	NA	SCD in a family member younger than 45 y old	Sustained VT, VF, appropriate ICD discharge
Makarawate et al, 2017[21]	Prospective cohort	40	14	Thailand	2	96%	43.5±12.7	100%	28.3±11.3	Multivariate	35%	23% [40]	SCD or SCA in a family member younger than 45 y old	Appropriate ICD discharge

(*Continued*)

Table. Continued

Study/Year	Study Design	N	Major Arrhythmic Events	Country	Centers (N)	Men (%)	Mean Age±SD (y)	Symptomatic BrS (%)	Follow-Up (mo)	Analysis Model	Positive Family History (%)	Positive *SCN5A* (% [N])	Definition of Family History	Outcomes
Migliore et al, 2019[22]	Prospective cohort	272	17	Italy	2	82%	43±12	30%	85±55	Univariate	27%	NA	SCD in a family member younger than 40 y old in male and 50 y old in female*	Sustained VT, VF, appropriate ICD discharge
Mok et al, 2004[23]	Retrospective cohort	50	26	China	7	94%	41±12	40%	25.8±10.5	Univariate	14%	14% [36]	Family history of SCD	SCD
Nagase et al, 2018[24]	Retrospective cohort	209	8	Japan	1	96%	45±14	38%	56±48	Univariate	17%	18% [93]	SCD in a family member younger than 45 y	VF
Oaili et al, 2011[25]	Prospective cohort	24	1	Tunisia	4	92%	40.8±13.7	21%	26±21	Univariate	46%	NA	Family history of SCD	Sustained VT, VF, appropriate ICD discharge, SCD
Ohkubo et al, 2007[26]	Prospective cohort	34	1	Japan	1	97%	52±13	32%	47.1±33.7	Univariate	9%	NA	Family history of SCD	SCD
Pappone et al, 2018[27]	Case-control	191	88	Italy	1	78%	40.3±11.2	45%	NA	Univariate	24%	18% [191]	Family history of SCD	Sustained VT
Probst et al, 2010[2]	Prospective cohort	1017	43	France, Italy, Netherlands	13	72%	45±5.7	36%	33.3±12.0	Univariate	26%	28% [850]	SCD in a family member younger than 45 y	Appropriate ICD discharge, SCD
Rivard et al, 2016[28]	Retrospective cohort	105	16	Canada	3	79%	46.2±13.3	44.7%	59.6±16.4	Univariate	26.7%	20.6% [63]	Family history of SCD	Appropriate ICD discharge, SCD
Sieira et al, 2017[29]	Prospective cohort	400	20	Belgium	1	58%	41.1±17.8	32%	80.7±57.2	Univariate	46%	26% [53]	SCD in a family member younger than 35 y	Sustained VT, VF, appropriate ICD discharge, SCD
Son et al, 2014[30]	Prospective cohort	69	38	Korea	5	98%	46.2±13.5	80%	59±46	Multivariate	19%	NA	Family history of SCD	Appropriate ICD discharge
Subramanian et al, 2019[31]	Prospective cohort	103	13	India	2	86%	47.8±7.2	12%	85.3	Univariate	32%	NA	Family history of SCD	Sustained VT, VF, appropriate ICD discharge
Tokioka et al, 2014[8]	Retrospective cohort	246	24	Japan	1	96%	47.6±13.6	21.6%	47.6±13.6	Univariate	28%	14% [123]	SCD in a family member younger than 45 y	VF, SCD

BrS indicates Brugada syndrome; ICD, implantable cardioverter defibrillator;NA, not applicable; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.
*Migliore et al, 2019 was included in age-stratified analysis as <40-years-old group because of male predominance in BrS.

generic inverse-variance method of Der Simonian and Laird.[32] The event rate was pooled using variance-stabilizing arcsine transformation method of Freeman-Tukey.[33] The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic (I^2<25%, low; I^2=25–50%, moderate; and I^2>50%, substantial).[34] Subgroup analyses and metaregression were performed if the heterogeneity was moderate or substantial to explore the source of heterogeneity.[34,35] Publication bias was assessed using a funnel plot and the Egger's regression test.[36] A *P* value of <0.05 was considered significant. All data analyses were performed using the STATA SE version 14.2.

Sensitivity Analysis

A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting 1 study at a time, as described by Patsopoulos et al, to examine whether overall estimates were influenced by the substantial heterogeneity observed.[37]

Subgroup Analysis

The subgroup analysis was performed in a family history of younger than 40 and 45 years old SCD, family history of SCD in spontaneous Type-1 population, analysis type (univariate versus multivariate), and ethnicity. The subgroup analysis was also performed to explore the source of heterogeneity (moderate or substantial) in analysis type (univariate versus multivariate) and ethnicity (White and Asian) in overall analysis as well as studies with a family history of younger than 45 years old SCD.

Metaregression

Fitted random-effects model with truncated Knapp–Hartung method metaregression was performed to evaluate the association between the age of cut point of SCD in family members in each study and the risk of MAE (OR of each study). The metaregression was also performed to explore the source of heterogeneity.

RESULTS

Search Results

Our search strategy yielded 821 potentially relevant articles (223 articles from EMBASE and 598 articles from MEDLINE). After the exclusion of duplicate articles, 693 articles underwent title and abstract review. Following the review, 580 articles were excluded as they were not cohort, case-control, or randomized controlled trials, were not conducted in patients with BrS, or had irrelevant titles and abstracts. 113 articles remained for a full-length review. An additional 47 studies were further excluded as they did not report data regarding family history of SCD. Additionally, they did not provide sufficient data to calculate hazard ratio (HR), risk ratio, or odds ratio (OR). Forty-four studies were excluded because of a duplicated population. Therefore, a total of 22 studies were included in this meta-analysis. Figure 1

outlines the search and literature review process.

Description of Included Studies

A total of 22 (20 cohorts and 2 case-control) studies from 27 countries (95 studied centers) involving 3386 patients with BrS during the study period of 2004–2019 were included in our meta-analysis.[2,8,12–31] The ages of cut point of SCD among family members in different studies were >45 years old,[12] <50 years old,[13] <45 years old,[8,14-17,20,21,24,29] <40 years old,[19,22] and <35 years old.[29] a Nine studies did not report age of cut point of SCD among family members. The mean age was 43.9±12.2 years. Patients were predominantly men (77.3%), White (86.0%), and asymptomatic (63.5%). The mean follow-up was 50.88±39.6 months. *SCN5A* was reported in 12 studies. A family history of SCD and *SCN5A* was positive in 23.6% and 21.0%, respectively.

Twelve studies were included in subgroup analysis of a history of younger than 45 years old SCD in the family involving 2694 patients with BrS.[2,8,14–17,19–22,29] The mean age was 44.0±12.2 years. Patients were predominantly men (80.0%), White (86.7%), and asymptomatic (62.2%). The mean follow-up was 51.3±40.6 months. A family history of SCD and *SCN5A* was positive in 21.6% and 21.9%, respectively. A summary of study characteristics is shown in Table.

Three studies were included in subgroup analysis in cohorts with history of SCD among family members of age younger than 40 years involving 805 patients BrS.[19,22,29] The mean age was 42.4±15.6 years. Patients were predominantly men (66.6%), White (100%), and asymptomatic (65.2%). The mean follow-up was 75.8±54.5 months. Family history of SCD and *SCN5A* were positive in 37.4% and 26.0%, respectively. A summary of study characteristics is shown in Table.

Quality Assessment of Included Studies

The Newcastle-Ottawa quality assessment scale scores of included studies are described in Table S2. The scale uses a star system (0–9) to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent a higher study quality (8–9: high, 6–7: moderate, and 0–5: low). Two studies were categorized as moderate quality,[17,18]

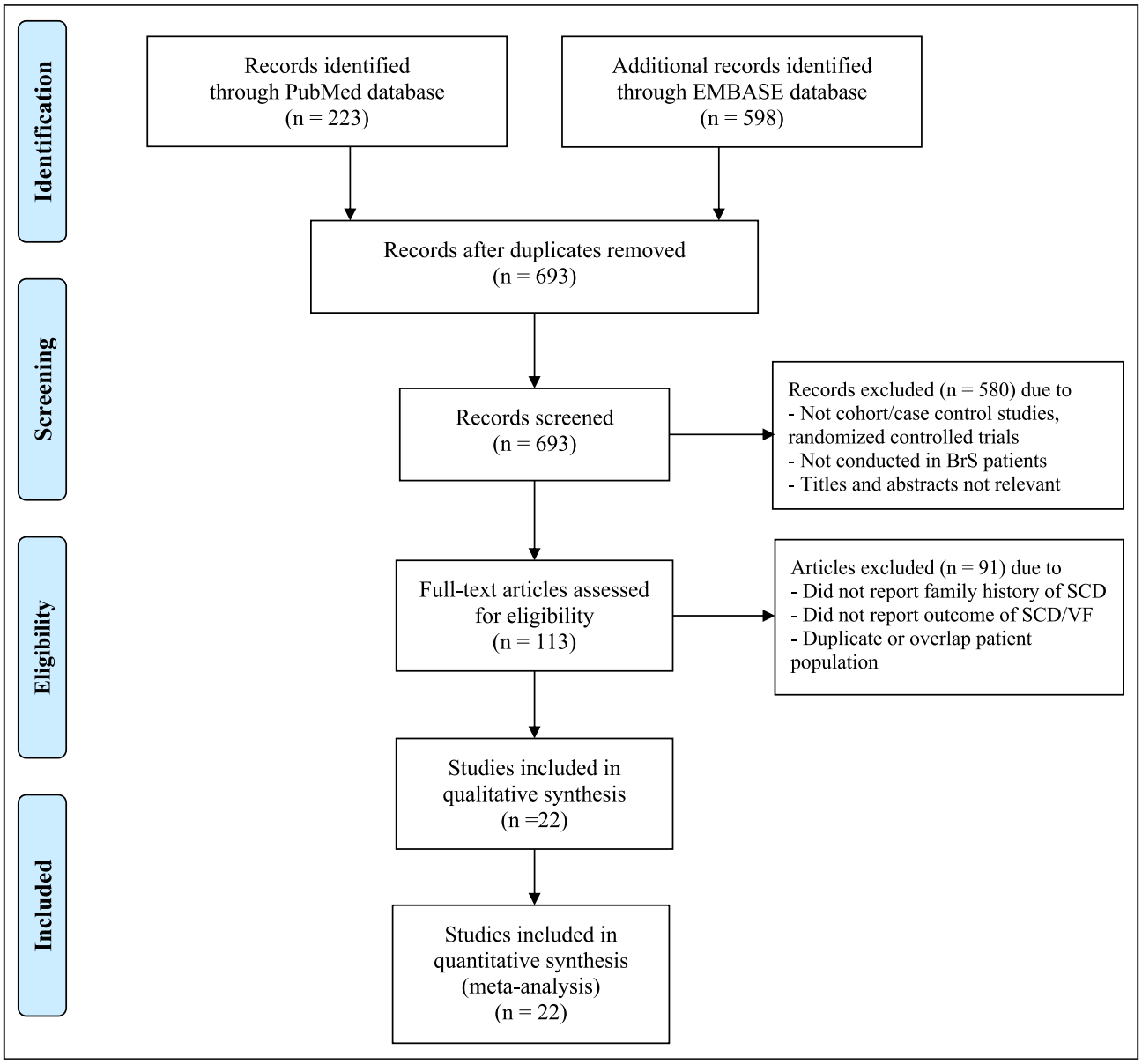


Figure 1. Search methodology and selection process.
BrS indicates Brugada syndrome; SCD, sudden cardiac death; and VF, ventricular fibrillation.

whereas the remainder of the studies were categorized as high quality.

Meta-Analysis Results

Family History of Sudden Cardiac Death on Major Arrhythmic Event

In the overall analysis, a family history of SCD was not significantly associated with increased risk of MAE in patients with BrS (pooled OR, 1.11; 95% CI, 0.82–1.51; *P*=0.489). The statistical heterogeneity was moderate, with an I^2 of 46.1%. Eleven studies reported OR <1.0 (decreased risk of MAE) and the majority (7 of 11) did not report age of cut point or used age of cut point more than 45 years old. A forest plot of this meta-analysis is shown in Figure 2. The subgroup analysis of a family history of SCD in spontaneous Type-1 population was performed from 5 studies with 280 patients with BrS[13,17,24–26]; this subgroup analysis increased the overall pooled OR by 9% (pooled OR, 1.20; 95% CI, 0.45–3.18; I^2=30.7%, *P*=0.716). The pooled event rate in patients with BrS with and without a family history of SCD were 16% (95% CI, 9–23%) and 15% (95% CI, 9–22%) respectively (Figures S1 and S2).

Among the 12 studies that defined a family history of SCD <45 years of age (9 studies used 45 years old,[2,8,14-17,20,21,24] 2 studies used 40 years old,[19,22]

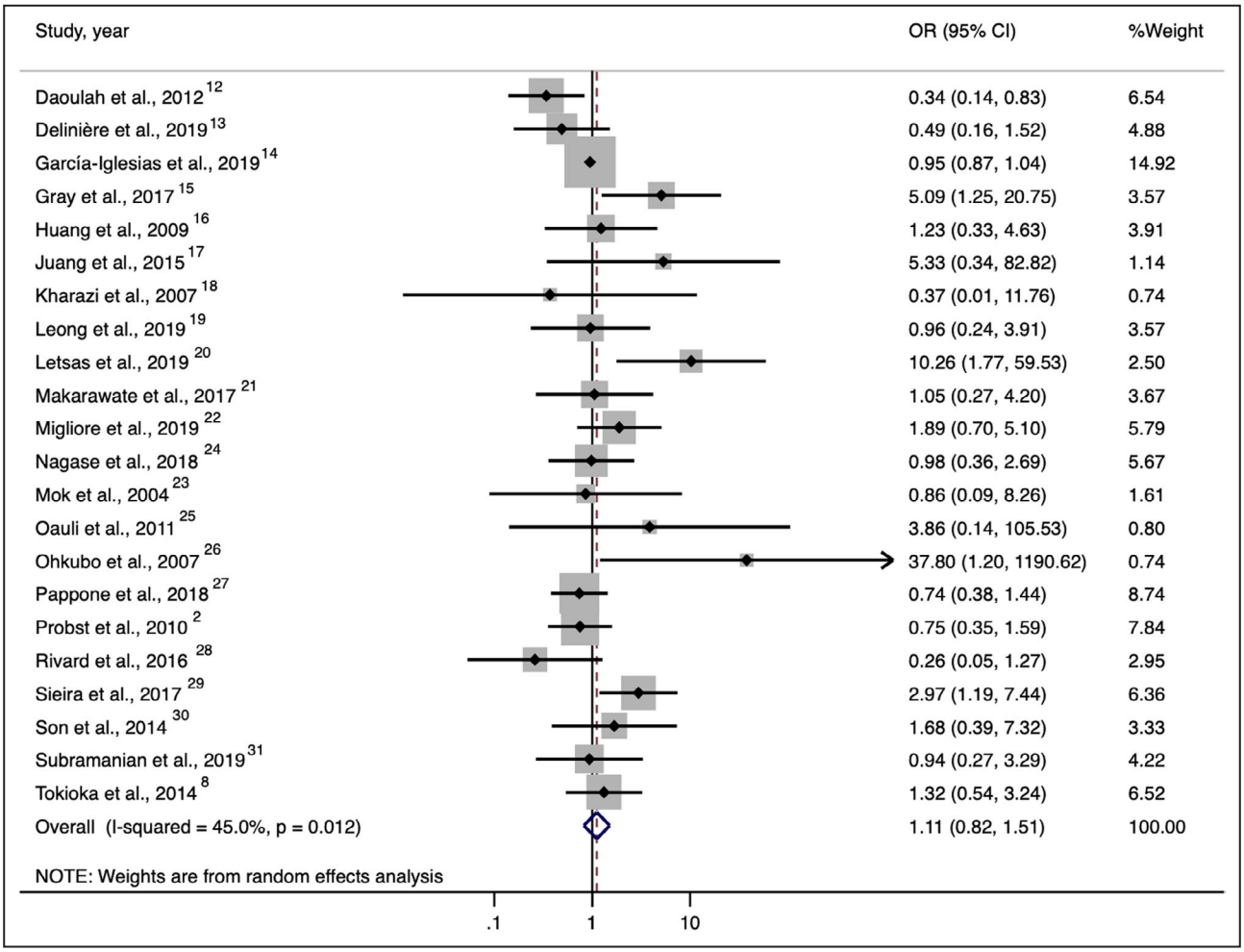


Figure 2. Forest plot demonstrating the association of family history of sudden cardiac death and major arrhythmic event in patients with Brugada syndrome.
OR indicates odds ratio.

and 1 study used 35 years old[29] as ages of cut point), the majority (8 of 12) showed an increased risk of MAE (OR, >1.0)[8,15–17,20–22,29] (Figure 3); of the 8 studies, 3 studies[15,20,29] showed the associations were statistically significant.

For the age-specific analysis, a family history of younger than 45 years old SCD, from 12 studies with 2694 patients with BrS,[2,8,14–17,19–22,29] showed an increased risk of MAE by ≈45%, and although not statistically significant (pooled OR, 1.45; 95% CI, 0.98–2.13; P=0.060), there was substantial heterogeneity (I^2=50.8). A family history of younger than 40 years old with SCD, from 3 studies with 807 patients with BrS,[19,22,29] was associated with an increased risk of MAE by ≈2-fold (pooled OR, 2.03; 95% CI, 1.11–3.73; P=0.022) without heterogeneity (I^2=0.0%). The forest plot of this meta-analysis is shown in Figure 3.

The pooled event rate in patients with BrS with and without a family history of SCD younger than 45 years old was 15% (95% CI, 8–24%) and 9% (95% CI, 6–13%) respectively; whereas, SCD younger than 40 years old was 9% (95% CI, 5–15%) and 5% (95% CI, 3–7%) respectively (Figures S3 and S4).

When stratified by age of cut point, at 50, 45, 40, and 35 years old, the risk of MAE increased in association with decremented age of cut point of SCD in the family (pooled OR, 0.49; CI, 0.16–1.52; OR, 1.30; CI, 0.85–1.99; OR, 1.51; CI, 0.67–3.39; and OR, 2.97; CI, 1.19–7.44, respectively) (Figure 4). Metaregression of age cut point showed that a history of SCD in younger family members was significantly associated with a higher risk of MAE (P=0.046) (Figure 5). The bubble plot and fitted metaregression line are shown in Figure 5.

To examine the source of heterogeneity, subgroup analysis of analysis type (Figures S5 and S6) and ethnicity (Figures S7 and S8) were performed. There was substantial heterogeneity in univariate analysis and White population but no heterogeneity (I^2=0) in

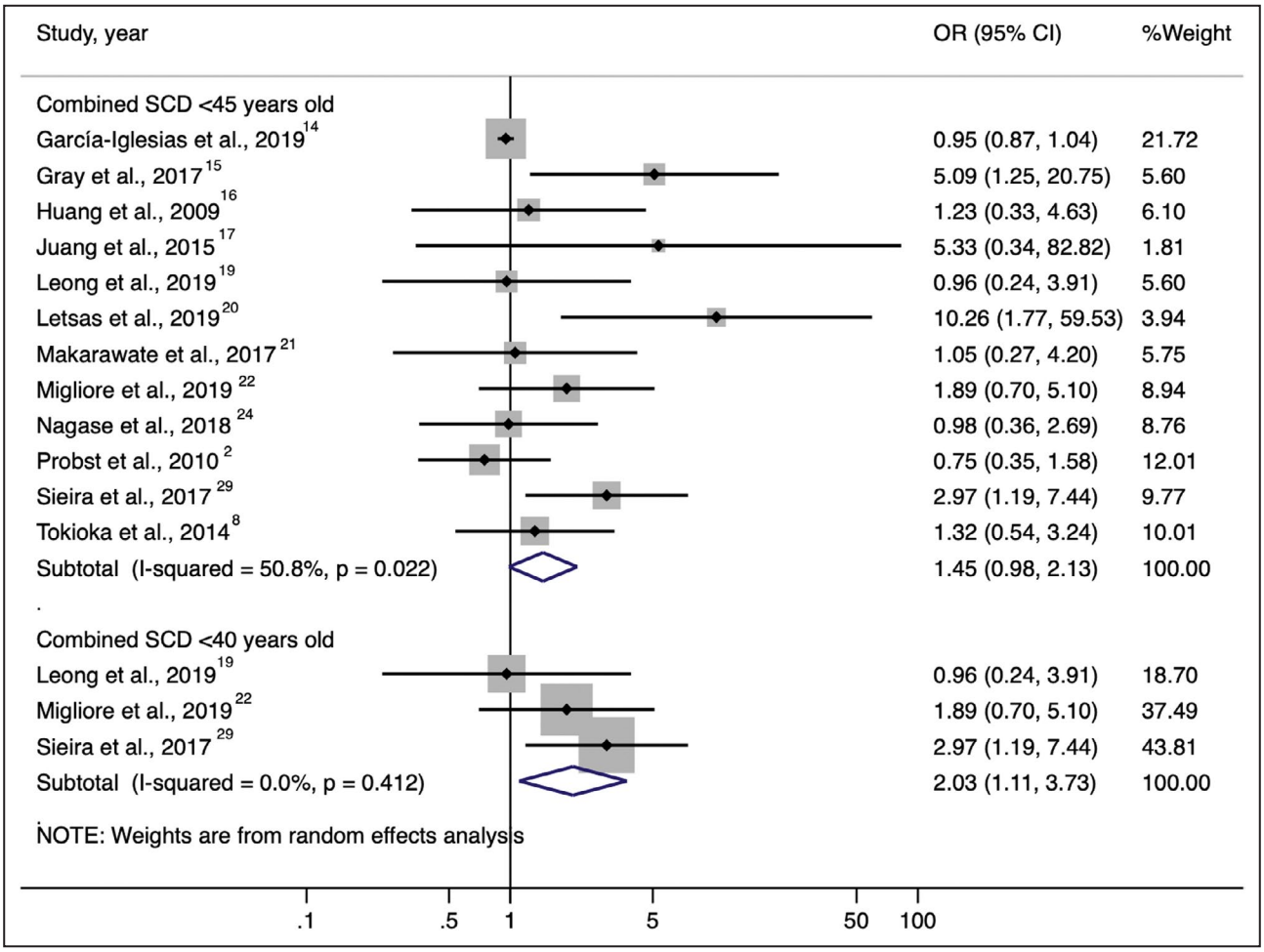


Figure 3. Forest plot demonstrating the association of family history of sudden cardiac death at age <45 and <40 years old and major arrhythmic event in patients with Brugada syndrome.
OR indicates odds ratio; and SCD, sudden cardiac death.

multivariate analysis and Asian population; therefore, univariate analysis and White ethnicity were likely the sources of heterogeneity. Metaregression of the percentage of SCD at presentation, male sex, symptomatic patients, family history of SCD, positive *SCN5A*, ethnicity, mean age, and follow-up duration showed no significant effect on the pooled results in both overall (Table S3) and younger than 45 years old (Table S4) analysis. However, mean age had significant effects of heterogeneity in the younger than 45 years old analysis (P=0.022).

Sensitivity Analysis

To assess the stability of the results of the meta-analysis, we conducted a sensitivity analysis by excluding 1 study at a time. None of the results was significantly altered in the overall analysis (Figure S9). However, sensitivity analysis of younger than 45 years old showed that the results would become significant if Probst et al, García-Iglesias et al, or Nagase et al[2,14,24] were omitted (Figure S10A). Sensitivity analysis of younger than 40 years old also showed that the results would become nonsignificant if Migliore et al or Siera et al[22,29] were omitted (Figure S10B). This is because of a lack of power of the analysis.

Publication Bias

To investigate potential publication bias, we examined the contour-enhanced funnel plot of the included studies in assessing change in log OR of MAE and Egger's test.[38,39] No publication bias was observed on the funnel plots or Egger's test in overall analysis (P=0.190) and family history younger than 40 years old analysis (P=0.208). However, there was a significant small study effect in the family history of younger than 45 years old SCD (P=0.017). An asymmetric funnel plot was observed in a family history of younger than 45 years old SCD (Figures S11 through S13).

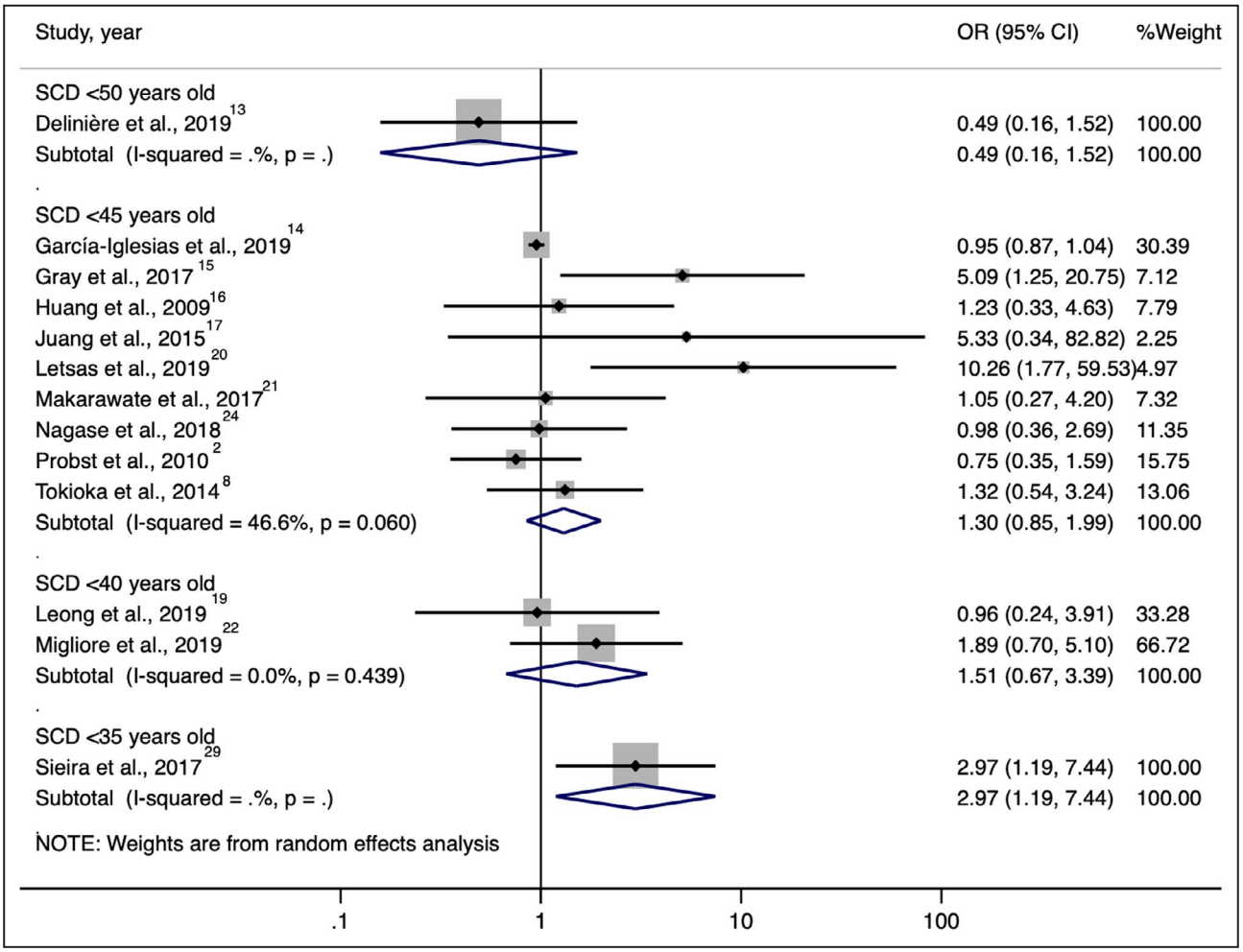


Figure 4. Forest plot demonstrating an increase in the major arrhythmic event odds ratio with decrementing age definition of sudden cardiac death in the family of Brugada syndrome patient.
OR indicates odds ratio; and SCD, sudden cardiac death.

DISCUSSION

The main finding from this meta-analysis is that a history of SCD in family members younger than 40 years of age increased the risk of MAE by ≈2-fold in patients with BrS. When stratified by age decrement, the history of SCD in younger family members showed a statistically significant difference with a higher risk of MAE in younger patients with BrS. However, a pooled analysis of the mere presence of family history of SCD without an age specificity in BrS was not associated with MAE.

Identifying prognostic factors of MAE in patients with BrS is essential in order to prevent undesirable outcomes. Few risk factors have been identified as predictors of MAE among patients with BrS. A family history of SCD is common among patients with BrS (27.5% from our pooled analysis). The prognostic significance of a family history of SCD has been reported in previous studies but remains inconclusive.[2,6,15,18,29] Kamakura and colleagues reported that a family history of SCD increased the risk of MAE up to 5-fold in a Japanese cohort.[6] Siera and colleagues also reported similar findings with increased risk of MAE 3-fold in Belgian patients.[29] However, a family history of SCD was not a significant prognostic factor in the FINGER (France, Italy, Netherlands, Germany) registry.[2]

Our meta-analysis shows that pooled analysis of the mere presence of family history of SCD in BrS was not associated with MAE. However, we illustrated that a family history of SCD in members younger than 40 years was associated with MAE in BrS with statistical significance in the meta-analysis (P=0.022) and a metaregression analysis showed that the history of SCD in younger family member was significantly associated with a higher risk of MAE (P=0.046). In the general population, the most common cause of SCD in adult >35 years old is coronary artery disease, especially in men.[40] It is plausible that the cause of SCD in age-undifferentiated family cohorts is less BrS specific,

that is, higher prevalence of ischemic or structural heart disease-mediated SCD in older family members.

Eleven studies reported an OR <1.0 (family history of SCD decreased risk of MAE in BrS)[1] and the majority (7 of 11) did not report an age of cut point or used age of cut point more than 45 years old.[12,13,18,23,27,28,31] Similar to a large registry from Belgium, without a specific age of cut point, the HR was <1.0 (HR, 0.6; 95% CI, 0.3–1.3; *P*=0.20). On the contrary, in the same population, with a definition of a family history of SCD <35 years old, the presence of a family history of SCD was associated with a significant increase in the risk of MAE by 3-fold in BrS (HR, 2.9; 95% CI, 1.2–7.0; *P*=0.02). Moreover, our study highlighted that a history of SCD in younger family members was significantly associated with a higher risk of MAE by a fitted linear metaregression model (Figure 5). These findings support our hypothesis that confounders such as ischemic or structural heart disease-mediated SCD in older patients may have been introduced in studies without a clear delineation of age.

Siera et al [29] used the lowest age of cut point of SCD in family member among the included studies (<35 years old). Interestingly, the mean age of the population included in this study was relatively low and the proportion of positive family history (46%) as well as proportion of positive *SCN5A* (26%) were relatively high when compared with other studies. These findings may suggest that *SCN5A* gene mutation may explain earlier and more severe manifestation of BrS similar to previous reports. However, the correlation between *SCN5A* positivity and the younger SCD in family member is not yet to be determined.

Earlier meta-analyses by Wu and colleagues included 7 studies,[41] and Gehi and colleagues included only 2 studies,[42] compared with 22 studies in the current meta-analysis. Both of the earlier studies did not stratify the family history by age, and metaregression was not performed. Sample size, power of meta-analysis, and statistic methodology were significant limitations of the previous studies. Our study included more studies, pooled the risk of MAE according to the SCD age definition, and confirmed the association of stratified age of SCD in the family and MAE with fitted linear metaregression model. The larger sample size, regression validation methodology, and a more contemporary data set render our results with higher certainty. Furthermore, the majority of the included studies with a family history of SCD <45 years old (8 of 12)[8,15–17,20–22,29] and <40 years old[22,29] (2 of 3) reported increased risk of MAE (OR>1), which supported our findings.

The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guideline on SCD prevention and 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus stated that positive family history of SCD is not a significant predicting factor of SCD in BrS.[1,43] Additionally, the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus stated that defibrillator implantation in asymptomatic BrS is not indicated with a family history of SCD alone.[1] However, both guidelines did not specify an age cutoff because there was a lack of consistent data regarding the specific age of SCD in the family. Moreover, early sudden cardiac death in the family member was also included the composite score model to predict MAE in BrS. Our meta-analysis is the first study to provide compelling evidence demonstrating a significant association between a family history of SCD in the young and MAE in BrS. We propose that a family history of SCD in the young in BrS could be considered as a prognostic factor to predict MAE in patients with BrS. Larger prospective cohort studies are needed to support our proposal.

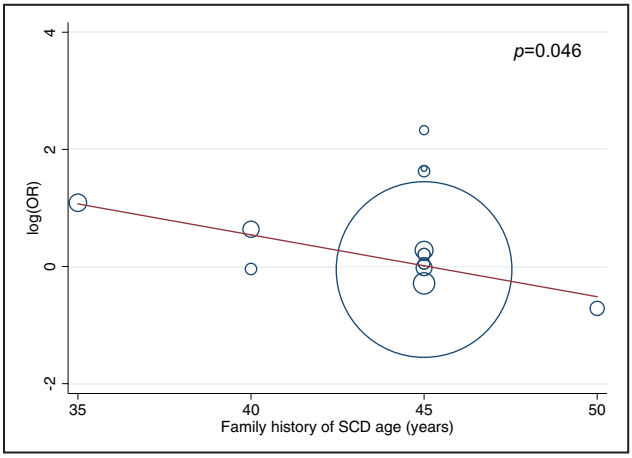


Figure 5. The bubble plot and fitted metaregression line demonstrating a strong trend of the association between the increasing of major arrhythmic event odds ratio and decrementing of age definition of sudden cardiac death in the family of a patient with Brugada syndrome.
OR indicates odd ratio; and SCD, sudden cardiac death.

Limitations

There are some inevitable discrepancies of end points definition among studies. There are substantial heterogeneities observed in this analysis owing to analysis types and ethnicity. The percentage of patients with a family history of SCD in our analysis is lower than previously reported in European registries. This is likely from lower SCD rates reported from the Asian studies included in the study. SCD is a largely heterogeneous condition, which is attributable to multiple etiologies, including coronary artery diseases, especially when SCD occurs in patients at older age. A large number studies were excluded because of insufficient data for analysis,

*References 2, 12–14, 18, 19, 23, 24, 27, 28, 31.

which may have introduced publication and selection bias. Available data were not sufficient to perform subgroup analysis in asymptomatic patients and those who presented with SCD. Moreover, only 3 studies were included in the analysis in patients <40 years old and 1 in patients <35 years of age. Additional cohort studies are needed to explore the association between MAE and family history of SCD in the young in BrS.

CONCLUSIONS

Our study demonstrated that a history of SCD among family members of age younger than 40 years was associated with a higher risk of MAE. A mere presence of a family history of SCD without a clear age definition is not a risk predictor in BrS. We propose that a family history of SCD in the young could be a prognostic factor to predict MAE in patients with BrS. Larger prospective cohort studies are needed to valid our observation.

ARTICLE INFORMATION

Received October 14, 2020; accepted March 9, 2021.

Affiliations

Department of Cardiovascular Medicine, Mayo Clinic, Phoenix, AZ (P.R., T.B., A.S., N.L.K.K., P.A., H.A., W.S.); Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (P.R.); University of Hawaii Internal Medicine Residency Program, Honolulu, HI (J.K., C.K.); Division of Cardiovascular Medicine, Department of Internal Medicine, University of Iowa, IA (W.V.); Saint Vincent Hospital, Worcester, MA (M.H.); and Department of Cardiovascular Medicine, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan (W.S.).

Sources of Funding

This publication was supported and funded by Mayo Clinic Arizona Cardiovascular Clinical Research Center. We are thankful for their generous support. Contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the Mayo Clinic Arizona Cardiovascular Clinical Research Center.

Disclosures

None.

Supplementary Material

Data S1
Tables S1–S4
Figures S1–S13

REFERENCES

1. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang C-E, Huikuri H, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10:1932–1963. DOI: 10.1016/j.hrthm.2013.05.014.
2. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635–643. DOI: 10.1161/CIRCULATIONAHA.109.887026.
3. Vutthikraivit W, Rattanawong P, Putthapiban P, Sukhumthammarat W, Vathesatogkit P, Ngarmukos T, Thakkinstian A. Worldwide prevalence of Brugada syndrome: a systematic review and meta-analysis. *Acta Cardiol Sin*. 2018;34:267–277. DOI: 10.6515/ACS.201805_34(3).20180302B.
4. Wilde AAM, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RNW, Kass RS, Nademanee K, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation*. 2002;106:2514–2519. DOI: 10.1161/01.CIR.0000034169.45752.4A.
5. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59:37–45. DOI: 10.1016/j.jacc.2011.08.064.
6. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, et al. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1–V3. *Circ Arrhythm Electrophysiol*. 2009;2:495–503. DOI: 10.1161/CIRCEP.108.816892.
7. Maury P, Rollin A, Sacher F, Gourraud J-B, Raczka F, Pasquié J-L, Duparc A, Mondoly P, Cardin C, Delay M, et al. Prevalence and prognostic role of various conduction disturbances in patients with the Brugada syndrome. *Am J Cardiol*. 2013;112:1384–1389. DOI: 10.1016/j.amjcard.2013.06.033.
8. Tokioka K, Kusano KF, Morita H, Miura D, Nishii N, Nagase S, Nakamura K, Kohno K, Ito H, Ohe T. Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. *J Am Coll Cardiol*. 2014;63:2131–2138. DOI: 10.1016/j.jacc.2014.01.072.
9. Shor E, Roelfs D, Vang ZM. The "Hispanic mortality paradox" revisited: meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality. *Soc Sci Med*. 2017;186:20–33. DOI: 10.1016/j.socscimed.2017.05.049.
10. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605. DOI: 10.1007/s10654-010-9491-z.
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012. DOI: 10.1001/jama.283.15.2008.
12. Daoulah A, Alsheikh-Ali AA, Ocheltree AH, Ocheltree S, Al-Kaabi S, Malik M, Al-Habib A-K, Hamed A, Al-Rawahi N, Al-Sayegh A, et al. Outcome after implantable cardioverter-defibrillator in patients with Brugada syndrome: the Gulf Brugada syndrome registry. *J Electrocardiol*. 2012;45:327–332. DOI: 10.1016/j.jelectrocard.2011.10.002.
13. Delinière A, Baranchuk A, Giai J, Bessiere F, Maucort-Boulch D, Defaye P, Marijon E, Le Vavasseur O, Dobreanu D, Scridon A, et al. Prediction of ventricular arrhythmias in patients with a spontaneous Brugada type 1 pattern: the key is in the electrocardiogram. *Europace*. 2019;21:1400–1409. DOI: 10.1093/europace/euz156.
14. García-Iglesias D, de Cos FJ, Romero FJ, Polana S, Rubín JM, Pérez D, Reguero J, de la Hera JM, Avanzas P, Gómez J, et al. Spectral analysis of the QT interval increases the prediction accuracy of clinical variables in Brugada syndrome. *J Clin Med*. 2019;8:1629. DOI: 10.3390/jcm8101629.
15. Gray B, Kirby A, Kabunga P, Freedman SB, Yeates L, Kanthan A, Medi C, Keech A, Semsarian C, Sy RW. Twelve-lead ambulatory electrocardiographic monitoring in Brugada syndrome: potential diagnostic and prognostic implications. *Heart Rhythm*. 2017;14:866–874. DOI: 10.1016/j.hrthm.2017.02.026.
16. Huang Z, Patel C, Li W, Xie Q, Wu R, Zhang L, Tang R, Wan X, Ma Y, Zhen W, et al. Role of signal-averaged electrocardiograms in arrhythmic risk stratification of patients with Brugada syndrome: a prospective study. *Heart Rhythm*. 2009;6:1156–1162. DOI: 10.1016/j.hrthm.2009.05.007.
17. Juang J-M, Tsai C-T, Lin L-Y, Liu Y-B, Yu C-C, Hwang J-J, Chen J-J, Chiu F-C, Chen W-J, Tseng C-D, et al. Unique clinical characteristics and SCN5A mutations in patients with Brugada syndrome in Taiwan. *J Formos Med Assoc*. 2015;114:620–626. DOI: 10.1016/j.jfma.2013.02.002.
18. Kharazi A, Emkanjoo Z, Alizadeh A, Nikoo MH, Jorat MV, Sadr-Ameli MA. Mid-term follow-up of patients with Brugada syndrome following a cardioverter defibrillator implantation: a single center experience. *Indian Pacing Electrophysiol J*. 2007;7:33–39.

19. Leong KMW, Ng FS, Jones S, Chow J-J, Qureshi N, Koa-Wing M, Linton NWF, Whinnett ZI, Lefroy DC, Davies DW, et al. Prevalence of spontaneous type I ECG pattern, syncope, and other risk markers in sudden cardiac arrest survivors with Brugada syndrome. *Pacing Clin Electrophysiol*. 2019;42:257–264. DOI: 10.1111/pace.13587.
20. Letsas KP, Bazoukis G, Efremidis M, Georgopoulos S, Korantzopoulos P, Fragakis N, Asvestas D, Vlachos K, Saplaouras A, Sakellaropoulou A, et al. Clinical characteristics and long-term clinical course of patients with Brugada syndrome without previous cardiac arrest: a multiparametric risk stratification approach. *Europace*. 2019;21:1911–1918. DOI: 10.1093/europace/euz288.
21. Makarawate P, Chaosuwannakit N, Vannaprasaht S, Sahasthas D, Koo SH, Lee EJD, Tassaneeyakul W, Barajas-Martinez H, Hu D, Sawanyawisuth K. SCN5A genetic polymorphisms associated with increased defibrillator shocks in Brugada syndrome. *J Am Heart Assoc*. 2017;6:e005009. DOI: 10.1161/JAHA.116.005009.
22. Migliore F, Testolina M, Zorzi A, Bertaglia E, Silvano M, Leoni L, Bellin A, Basso C, Thiene G, Allocca G, et al. First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome: a long-term follow-up study from the Veneto region of Northeastern Italy. *Europace*. 2019;21:322–331. DOI: 10.1093/europace/euy144.
23. Mok NS, Priori SG, Napolitano C, Chan KK, Bloise R, Chan HW, Fung WH, Chan YS, Chan WK, Lam C, et al. Clinical profile and genetic basis of Brugada syndrome in the Chinese population. *Hong Kong Med J*. 2004;10:32–37.
24. Nagase S, Kamakura T, Kataoka N, Wada M, Yamagata K, Ishibashi K, Inoue YY, Miyamoto K, Noda T, Aiba T, et al. Low-voltage type 1 ECG is associated with fatal ventricular tachyarrhythmia in Brugada syndrome. *J Am Heart Assoc*. 2018;7:e009713. DOI: 10.1161/JAHA.118.009713.
25. Ouali S, Boughzela E, Haggui A, Haouala H, Battikh K, Ben Ameur Y, Kraiem S, Krichen S, Hentati M, Kammoun S. Clinical and electrophysiological profile of Brugada syndrome in the Tunisian population. *Pacing Clin Electrophysiol*. 2011;34:47–53. DOI: 10.1111/j.1540-8159.2010.02890.x.
26. Ohkubo K, Watanabe I, Takagi Y, Okumura Y, Ashino S, Kofune M, Kawauchi K, Yamada T, Kofune T, Hashimoto K, et al. Electrocardiographic and electrophysiologic characteristics in patients with Brugada type electrocardiogram and inducible ventricular fibrillation: single center experience. *Circ J*. 2007;71:1437–1441. DOI: 10.1253/circj.71.1437.
27. Pappone C, Ciconte G, Manguso F, Vicedomini G, Mecarocci V, Conti M, Giannelli L, Pozzi P, Borrelli V, Menicanti L, et al. Assessing the malignant ventricular arrhythmic substrate in patients with Brugada syndrome. *J Am Coll Cardiol*. 2018;71:1631–1646. DOI: 10.1016/j.jacc.2018.02.022.
28. Rivard L, Roux A, Nault I, Champagne J, Roux JF, Tadros R, Talajic M, Cadrin-Tourigny J, Shohoudi A, Mondesert B, et al. Predictors of ventricular arrhythmias and sudden death in a Quebec cohort with Brugada syndrome. *Can J Cardiol*. 2016;32:1355.e1–1355.e7. DOI: 10.1016/j.cjca.2016.03.012.
29. Sieira J, Conte G, Ciconte G, Chierchia G-B, Casado-Arroyo R, Baltogiannis G, Di Giovanni G, Saitoh Y, Juliá J, Mugnai G, et al. A score model to predict risk of events in patients with Brugada syndrome. *Eur Heart J*. 2017;38:1756–1763. DOI: 10.1093/eurheartj/ehx119.
30. Son MK, Byeon K, Park S-J, Kim JS, Nam G-B, Choi K-J, Kim Y-H, Park SW, Kim Y-H, Park HW, et al. Prognosis after implantation of cardioverter-defibrillators in Korean patients with Brugada syndrome. *Yonsei Med J*. 2014;55:37–45. DOI: 10.3349/ymj.2014.55.1.37.
31. Subramanian M, Prabhu MA, Rai M, Harikrishnan MS, Sekhar S, Pai PG, Natarajan KU. A novel prediction model for risk stratification in patients with a type 1 Brugada ECG pattern. *J Electrocardiol*. 2019;55:65–71. DOI: 10.1016/j.jelectrocard.2019.04.006.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188. DOI: 10.1016/0197-2456(86)90046-2.
33. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72:39. DOI: 10.1186/2049-3258-72-39.
34. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. DOI: 10.1136/bmj.327.7414.557.
35. Dickersin K, Berlin JA. Meta-analysis: state-of-the-science. *Epidemiol Rev*. 1992;14:154–176. DOI: 10.1093/oxfordjournals.epirev.a036084.
36. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol*. 2001;54:1046–1055. DOI: 10.1016/S0895-4356(01)00377-8.
37. Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int J Epidemiol*. 2008;37:1148–1157. DOI: 10.1093/ije/dyn065.
38. Simmonds M. Quantifying the risk of error when interpreting funnel plots. *Syst Rev*. 2015;4:24. DOI: 10.1186/s13643-015-0004-8.
39. Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: a comparison of new and existing tests. *Res Synth Methods*. 2018;9:41–50. DOI: 10.1002/jrsm.1266.
40. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res*. 2015;116:1887–1906. DOI: 10.1161/CIRCRESAHA.116.304521.
41. Wu W, Tian L, Ke J, Sun Y, Wu R, Zhu J, Ke Q. Risk factors for cardiac events in patients with Brugada syndrome: a PRISMA-compliant meta-analysis and systematic review. *Medicine*. 2016;95:e4214. DOI: 10.1097/MD.0000000000004214.
42. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol*. 2006;17:577–583. DOI: 10.1111/j.1540-8167.2006.00455.x.
43. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline 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 on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272–e391. DOI: 10.1161/CIR.0000000000000549.

SUPPLEMENTAL MATERIAL

Data S1.

Search Terms

(Search date January 3rd 2020)

PUBMED
Search: **brugada syndrome family history** Filters: **English**
(("brugada syndrome"[MeSH Terms] OR ("brugada"[All Fields] AND "syndrome"[All Fields])) OR "brugada syndrome"[All Fields]) AND ((((("medical history taking"[MeSH Terms] OR (("medical"[All Fields] AND "history"[All Fields]) AND "taking"[All Fields])) OR "medical history taking"[All Fields]) OR ("family"[All Fields] AND "history"[All Fields])) OR "family history"[All Fields])
Translations
brugada syndrome: "brugada syndrome"[MeSH Terms] OR ("brugada"[All Fields] AND "syndrome"[All Fields]) OR "brugada syndrome"[All Fields]
family history: "medical history taking"[MeSH Terms] OR ("medical"[All Fields] AND "history"[All Fields] AND "taking"[All Fields]) OR "medical history taking"[All Fields] OR ("family"[All Fields] AND "history"[All Fields]) OR "family history"[All Fields]

EMBASE
Brugada syndrome/ and family history/
Limited to English language

Included countries and studied centers

1. Kingdom of Saudi Arabia
    1.1. King Faisal Specialist Hospital and Research Center
    1.2. Aramco Dhahran Health Center Hospital
2. United Arab Emirates
    2.1. Sheikh Khalifa Medical City
3. Oman
    3.1. The Royal Hospital
4. Bahrain
    4.1. Mohammed Bin Khalifa Bin SulmanAl-Khalifa Cardiac Centre
5. Kuwait
    5.1. Chest Disease Hospital

6. France
    6.1. Aix-en-Provence
    6.2. Clermont-Ferrand
    6.3. Grenoble
    6.4. Lille
    6.5. Lyon Louis Pradel
    6.6. Nîmes
    6.7. Paris Georges Pompidou
    6.8. Saint-Etienne
    6.9. Villefranche-sur-Saône
    6.10. University Hospitals of Bordeaux
    6.11. University Hospitals of Brest
    6.12. University Hospitals of Rennes
    6.13. University Hospitals of Tours
    6.14. University Hospitals of Angers
    6.15. University Hospitals of Poitiers
    6.16. University Hospitals of Strasbourg
    6.17. University Hospitals of Nantes
7. Switzerland
    7.1. Geneva
    7.2. Lausanne Cecil Clinic
8. Romania
    8.1. TaˆrguMures
    8.2. Niculae Stancioiu Heart Institute
9. Spain
    9.1. Hospital Universitario Central de Asturias
    9.2. Instituto de Investigacion Sanitaria del Principado de Asturias
    9.3. Grupo Para la Modelizacion Matematica Avanzada
    9.4. Universidad Católica de Murcia
10. Mexico
    10.1. Hospital Civil de Guadalajara Fray Antonio Alcalde
11. India

11.1. Amrita Institute of Medical Sciences
11.2. KMC Mangalore
11.3. Jawaharlal Nehru Medical College

12. Australia
    12.1. Royal Prince Alfred Hospital
    12.2. Concord Repatriation General Hospital
    12.3. Blacktown Hospital
    12.4. Australian Genetic Heart Disease Registry
13. China
    13.1. First Hospital of Xiamen(Fujian Medical University)
    13.2. Union Hospital(Fujian Medical University)
    13.3. Renmin Hospital(Wuhan University)
    13.4. First Hospital (Fujian Medical University)
    13.5. Fujian Provincial Hospital
    13.6. Zhongshan Hospital(Xiamen University)
    13.7. Fuzhou General Hospital
    13.8. Princess Margaret Hospital
    13.9. Pamela Youde Nethersole Eastern Hospital
    13.10. Queen Mary Hospital
    13.11. North District Hospital
    13.12. Prince of wales Hospital
    13.13. United Christian Hospital
    13.14. Kwong wah Hospital
14. Taiwan
    14.1. National Taiwan University
    14.2. National Taiwan University Hospital
15. Iran
    15.1. Rajaie Cardiovascular Research and Medical Center
16. Korea
    16.1. Cardiac and Vascular Center
    16.2. Samsung Medical Center
    16.3. Asan Medical Center
    16.4. Korea University Cardiovascular Center
    16.5. Chonnam National University Hospital
17. United Kingdom
    17.1. National Heart and Lung Institute
    17.2. Imperial College Healthcare NHS Trust
18. Greece
    18.1. General Hospital of Athens
    18.2. University Hospital of Ioannina
    18.3. Hippokration Hospital of Thessaloniki
    18.4. Athens Naval Hospital
    18.5. Tzaneio General Hospital of Piraeus
    18.6. Henry Dunant Hospital
    18.7. General Hospital of Corfu
    18.8. Athens Red Cross Hospital

19. USA
    19.1. University of Oklahoma Health Sciences Center
20. Thailand
    20.1. Queen Sirikit Heart Center, Srinagarind Hospital
21. Italy
    21.1. University Hospital of Padova
    21.2. General Hospital of Conegliano
    21.3. Policlinico University Hospital San Donato
    21.4. University of Torino
    21.5. Cardinal Massaia Hospital of Asti
22. Germany
    22.1. University of Muenster
    22.2. University Hospital of Mannheim
23. The Netherlands
    23.1. Academic Medical center Amsterdam
24. Belgium
    24.1. Universitair Ziekenhuis Brussels
25. Japan
    25.1. Kyoto University Hospital
    25.2. National Cerebral and Cardiovascular Center
    25.3. Nihon University
    25.4. Okyama University Hospital
    25.5. Ritsumeikan university
    25.6. Shiga University of Medical Science
26. Tunisia
    26.1. Sahloul Hospital
    26.2. Military Hospital
    26.3. Habib Thameur Hospital
    26.4. Hedi Chaker Hospital
27. Canada
    27.1. Montreal Heart Institute
    27.2. Quebec Heart and Lung Institute
    27.3. Sherbrooke University Hospital

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	3-4
4	Type of exposure or intervention used	3-4
5	Type of study designs used	3-4
6	Study population	3-4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	3-4
8	Search strategy, including time period included in the synthesis and key words	3-4
9	Effort to include all available studies, including contact with authors	4
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	3
12	Use of hand searching (eg, reference lists of obtained articles)	4
13	List of citations located and those excluded, including justification	Supplement
14	Method of addressing articles published in languages other than English	4
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	4
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	4
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6
22	Assessment of heterogeneity	6
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6-7
24	Provision of appropriate tables and graphics	6-7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2-4
26	Table giving descriptive information for each study included	Table 1 and Supplement
27	Results of sensitivity testing (eg, subgroup analysis)	Supplement
28	Indication of statistical uncertainty of findings	9-10

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10-11
30	Justification for exclusion (eg, exclusion of non-English language citations)	4
31	Assessment of quality of included studies	8-9
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	13-14
34	Guidelines for future research	13-14
35	Disclosure of funding source	Title page

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.

Supplement Table 1: MOOSE checklist for meta-analyses of observational studies

Table S2. Newcastle-Ottawa quality assessment scale of included studies in meta-analysis.

	Selection				Comparability	Outcome			Total
	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Endpoint not present at start	Comparability (Confounding)	Assessment of outcome	Follow up duration	Adequacy of follow up	
Daoulah et al., 2012	*	*	*	*	*	*	*	*	8
Deliniere et al,2019	*	*	*	*	*	*	*	*	8
Garcia-Iglesias et al,2019	*	*	*	*	**	*	*	*	9
Gray et al, 2017	*	*	*	*	*	*	*	*	8
Huang et al., 2009	*	*	*	*	*	*	*	*	8
Juang et al., 2015	*	*	*	*	*	*	*	*	8
Kharazi et al, 2007	*	*	*	*	-	*	*	*	7
Leong et al., 2019	*	*	*	*	**	*	*	*	9
Letsas et al,2019	*	*	*	*	*	*	*	*	8
Makarawate et al,2017	*	*	*	*	**	*	*	*	9
Migliore et al,2019	*	*	*	*	*	*	*	*	8
Mok et al., 2004	*	*	*	*	-	*	*	*	7
Nagase et al., 2018	*	*	*	*	*	*	*	*	8
Ohkubo et al., 2007	*	*	*	*	-	*	*	*	7
Ouali et al, 2011	*	*	*	*	*	*	*	*	8
Pappone et al,2018	*	*	*	*	*	*	*	*	8
Probst et al,2010	*	*	*	*	*	*	*	*	8
Rivard et al., 2016	*	*	*	*	*	*	*	*	8
Sieira et al, 2017	*	*	*	*	*	*	*	*	8
Son et al, 2014	*	*	*	*	*	*	*	*	8
Subramanian et al, 2019	*	*	*	*	*	*	*	*	8
Tokioka et al., 2014	*	*	*	*	*	*	*	*	8

Table S3. Meta-regression of overall analysis with nonspecific age definition of SCD in the family.

Covariates	MAE OR			
	Coefficient (95% CI)	P value	Residual I^2 (%)	Tau^2
%Symptomatic	-0.1426385 (-1.893632 to 1.608354)	0.867	47.62	0.2691
Mean age (years)	0.0384038 (-0.0341872 to 0.1109948)	0.283	42.82	0.1966
%Male	-1.340309 (-4.250869 to 1.570252)	0.348	47.30	0.2328
Mean follow-up (years)	0.0083335 (-0.0066869 to 0.023354)	0.261	44.66	0.1681
%Positive SCN5A	1.884714 (-1.890666 to 5.660094)	0.292	37.24	0.2265
Uni- VS multivariate analysis	0.2066118 (-0.6972387 to 1.10094)	0.645	47.62	0.2696
Caucasian VS Asian	0.528531 (-0.3797091 to 1.436771)	0.239	40.92	0.1565
Study quality	-0.1723582 (-1.112925 to 0.7454263)	0.684	46.51	0.2797

Table S4. Meta-regression of analysis with <45 years old SCD in the family.

Covariates	MAE OR			
	Coefficient (95% CI)	P value	Residual I^2 (%)	Tau^2
%Symptomatic	0.4760355 (-1.662224 to 2.614295)	0.631	51.20	0.1891
Mean age (years)	0.1480045 (0.0260957 to 0.2699133)	0.022	22.62	0
%Male	-0.0120929 (-3.942071 to 3.917885)	0.995	49.21	0.2154
Mean follow-up (years)	0.0073439 (-0.0150698 to 0.0297577)	0.482	54.75	0.1759
%Positive SCN5A	1.799623 (-2.710865 to 6.310111)	0.352	37.73	0.1609
Uni- VS multivariate analysis	-0.2017126 (-1.165987 to 0.7625616)	0.651	47.18	0.2193
Caucasian VS Asian	0.4061039 (-.6650696 to 1.477277)	0.418	43.37	0.1269
Study quality	-0.5832752 (-1.448507 to 0.281957)	0.164	32.11	0.1275

Figure S1. Event rate in Brugada syndrome patient with family history of SCD

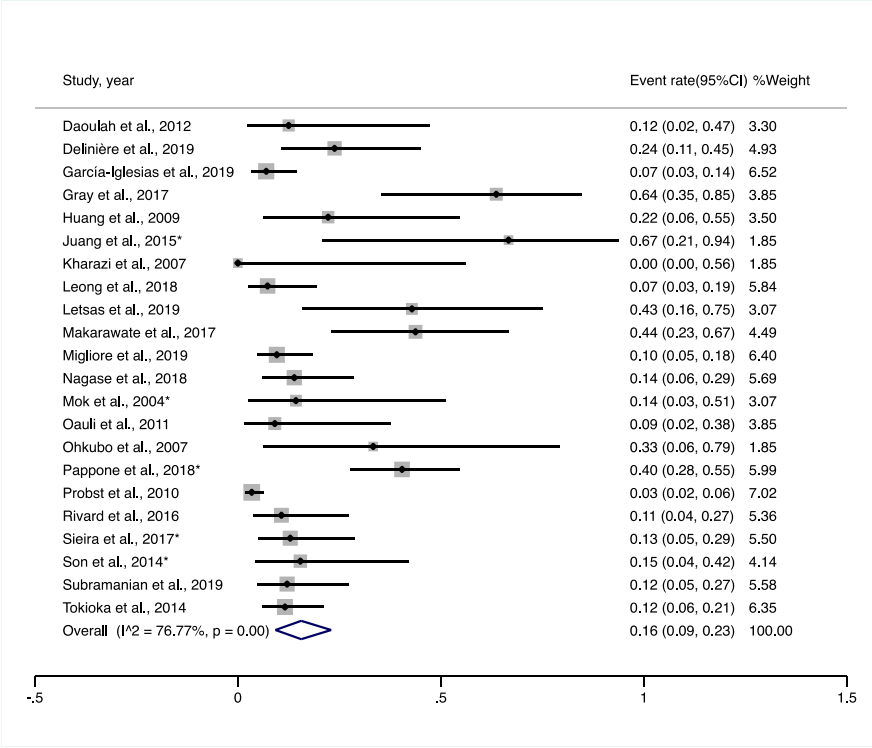


Figure S2. Event rate in Brugada syndrome patient without family history of SCD.

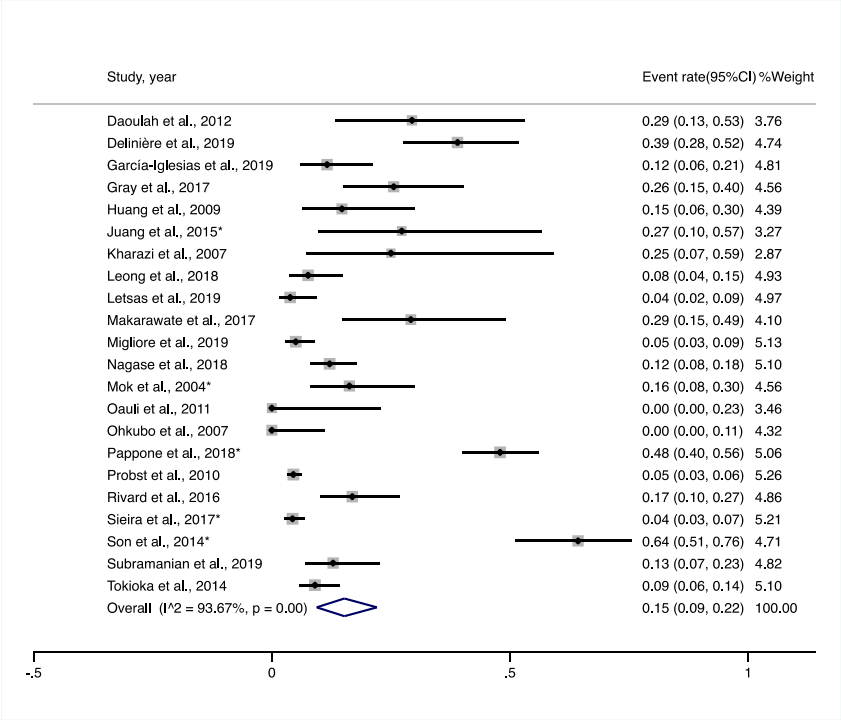


Figure S3. Event rate in Brugada syndrome patient with family history of <40 and <45 years old SCD.

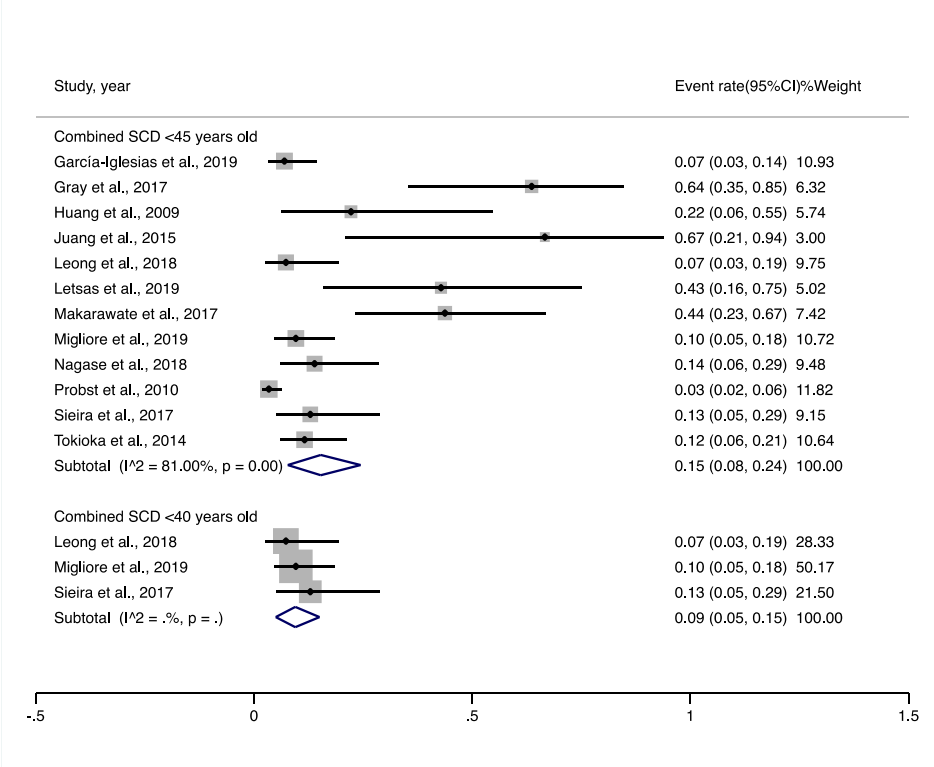


Figure S4. Event rate in Brugada syndrome patient without family history of <40 and <45 years old SCD.

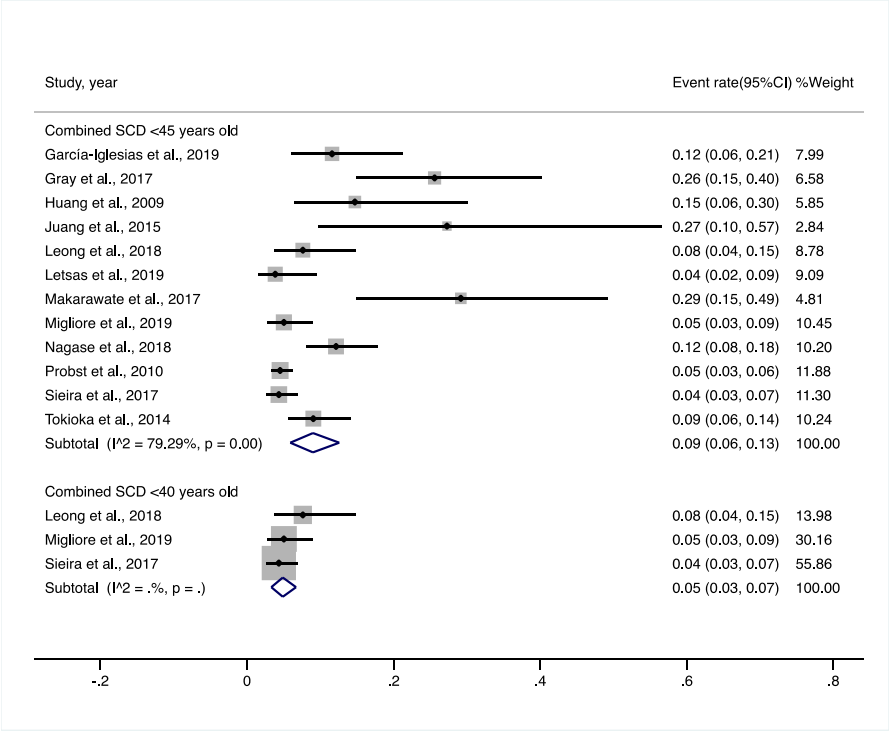


Figure S5. Subgroup analysis of univariate analysis and multivariate analysis in overall analysis.

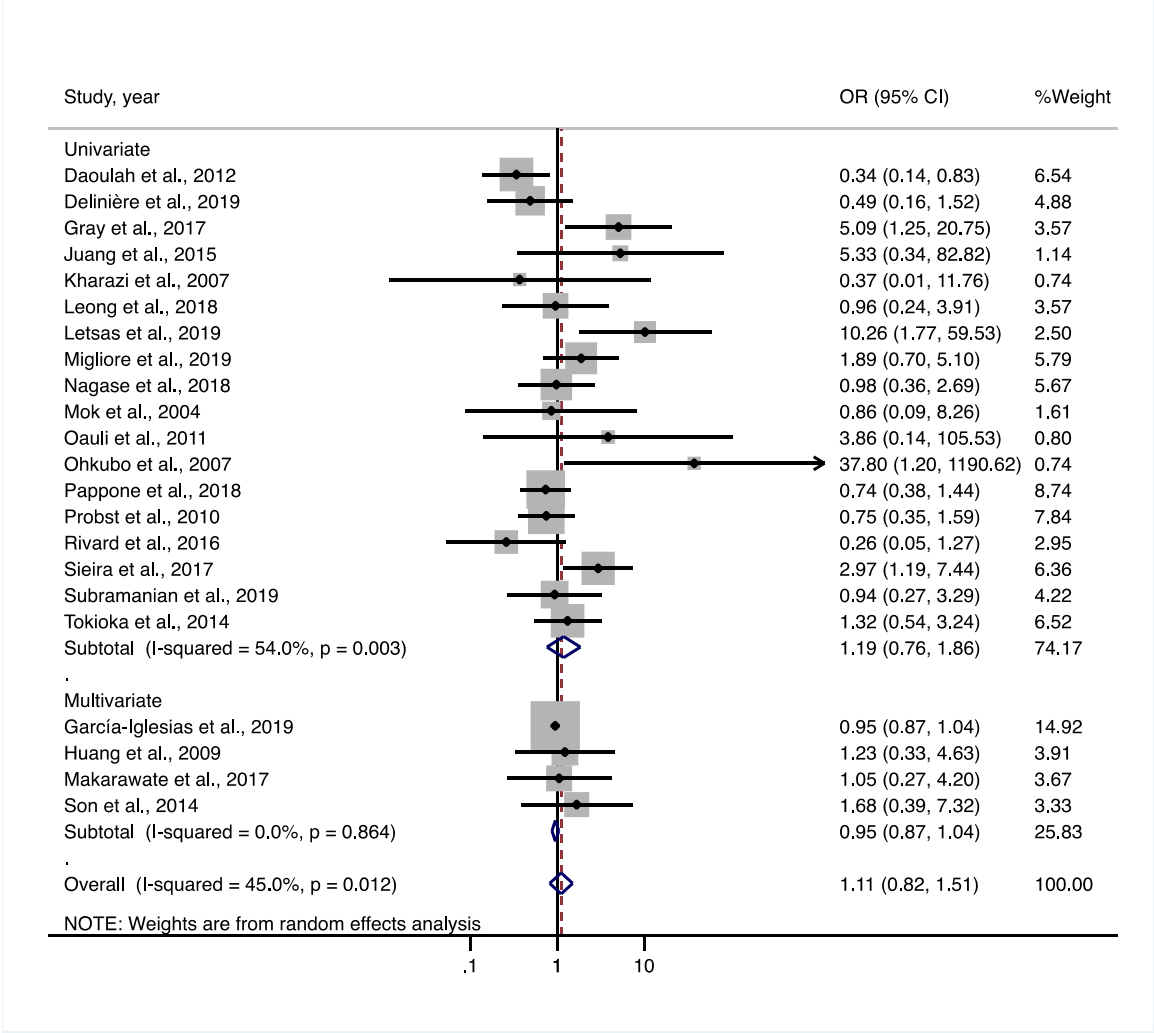


Figure S6. Subgroup analysis of univariate and multivariate analysis in <45 years old SCD.

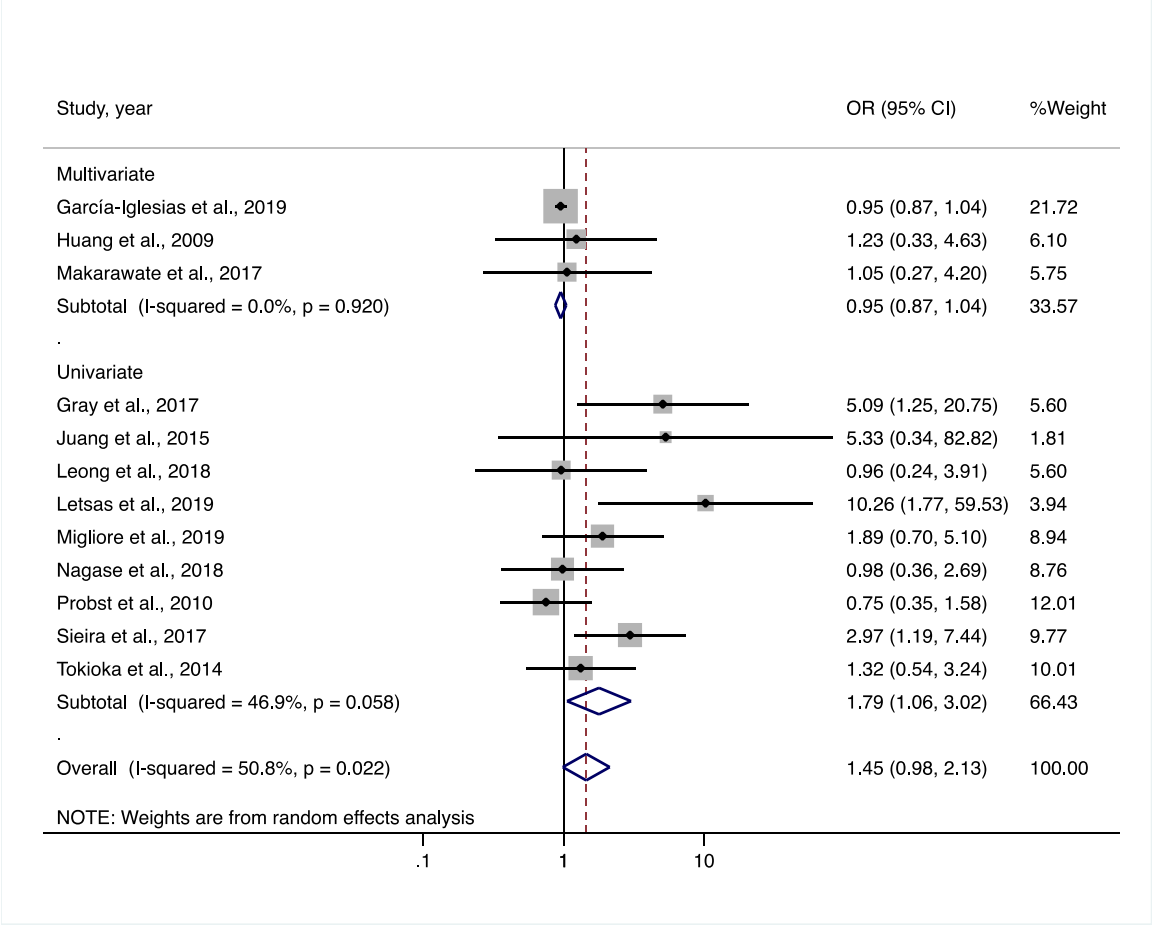


Figure S7. Subgroup analysis of ethnicity between Caucasian and Asian in overall analysis.

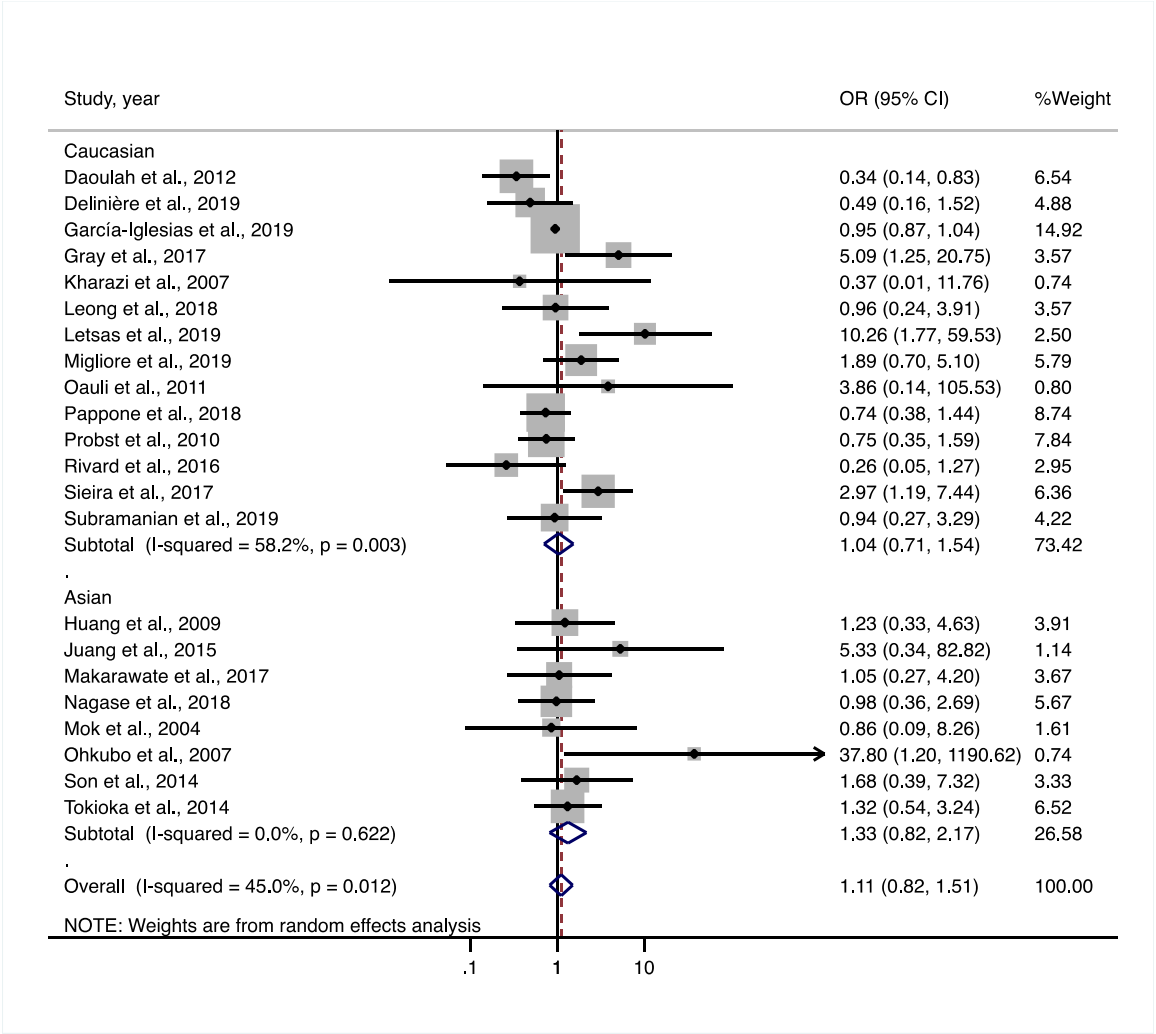


Figure S8. Subgroup analysis of ethnicity between Caucasian and Asian in <45 years old SCD.

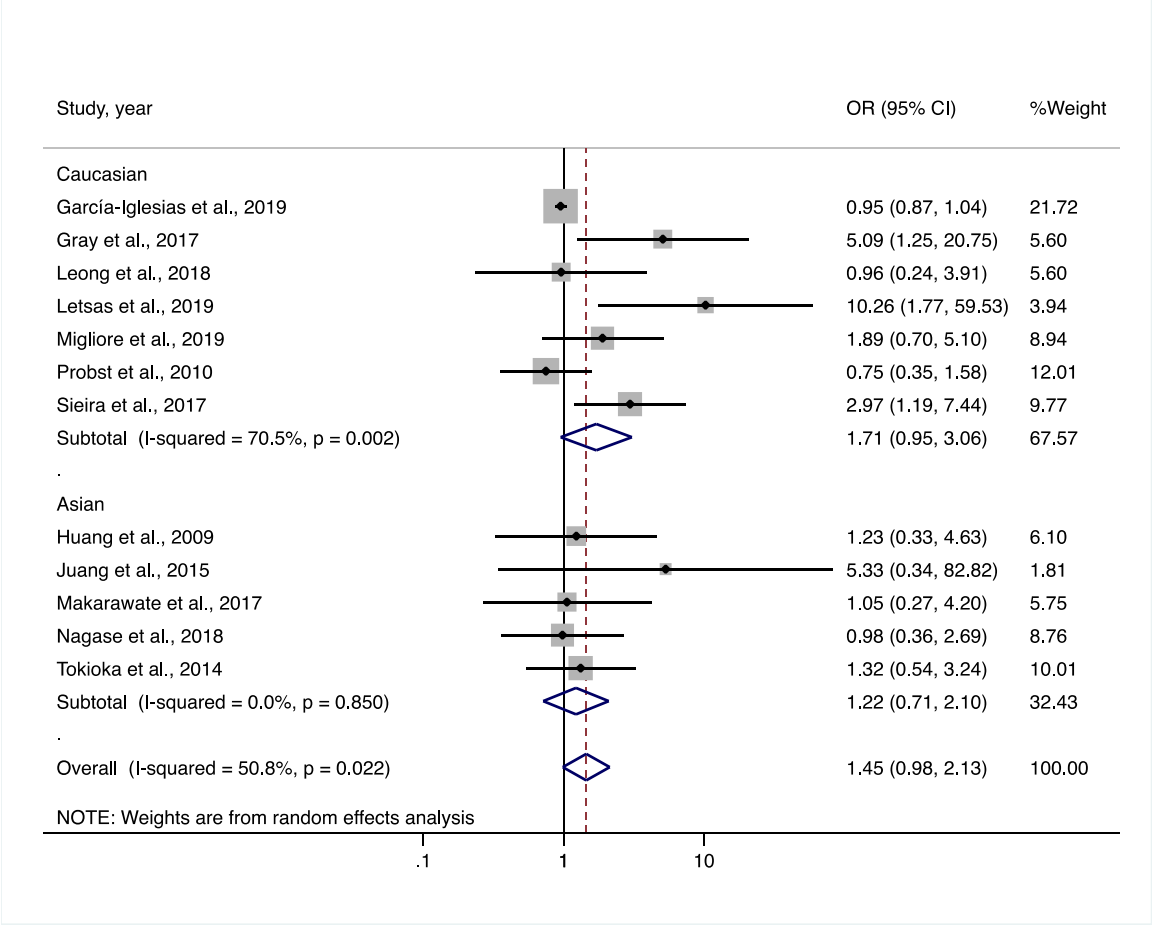


Figure S9. Overall sensitivity analysis.

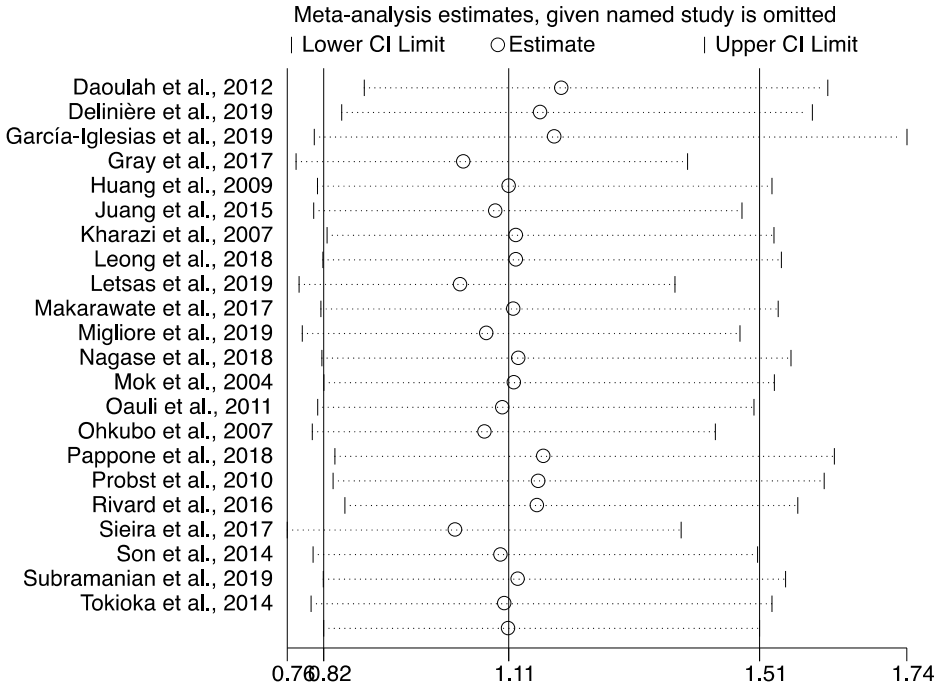
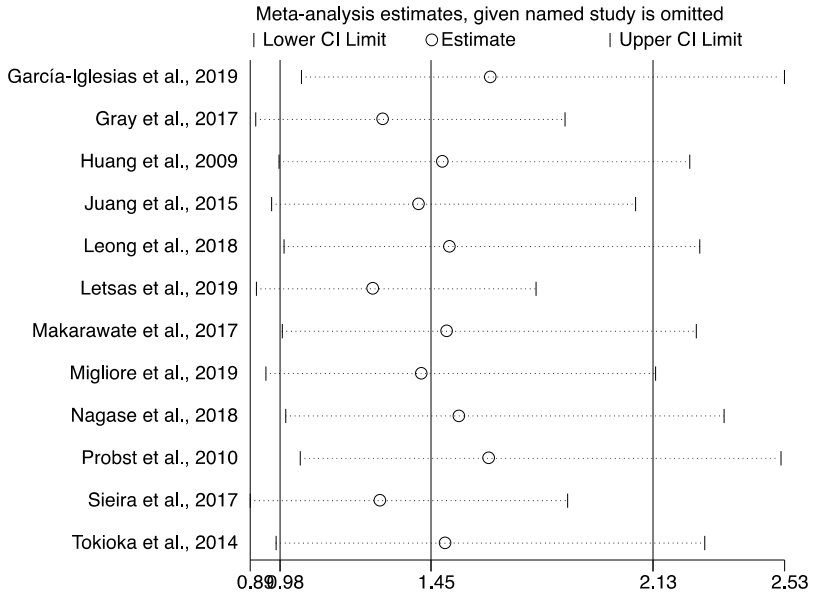


Figure S10. Family history of <45 (a) and <40 (b) years old SCD sensitivity analysis.

a)



b)

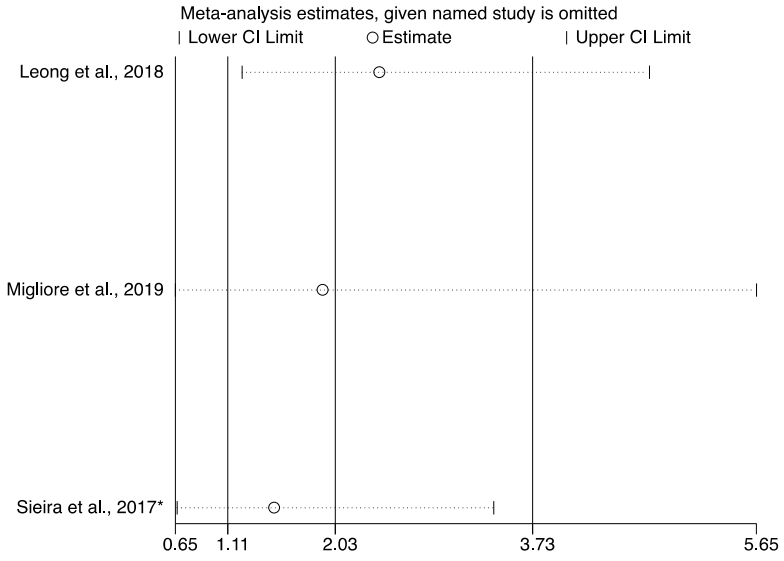


Figure S11. Egger's plot of overall analysis.

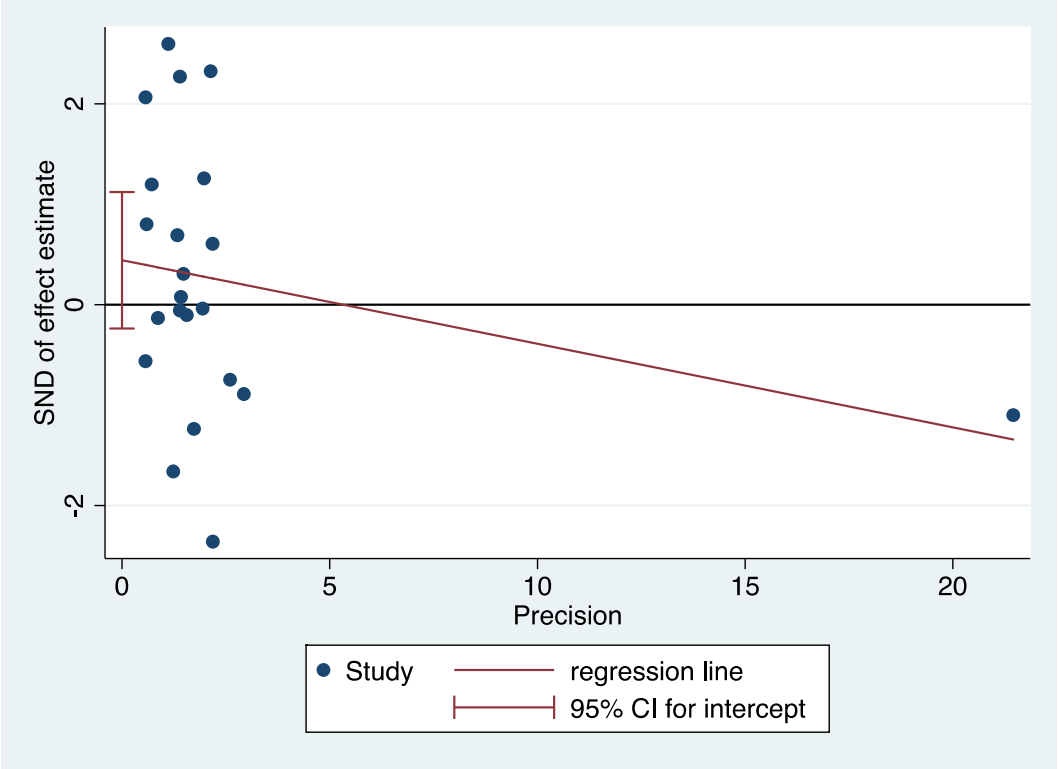
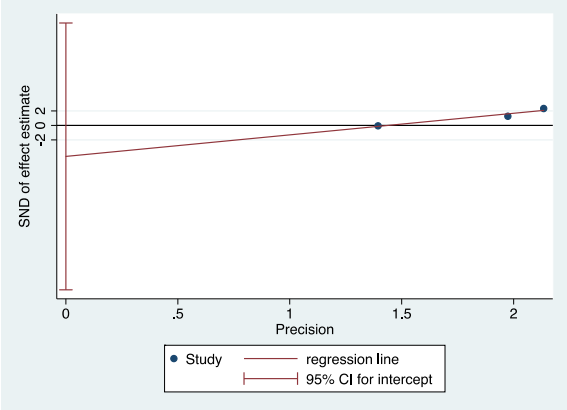


Figure S12. Egger's plot of <40 (a) and <45 (b) years old SCD analysis .

a)



b)

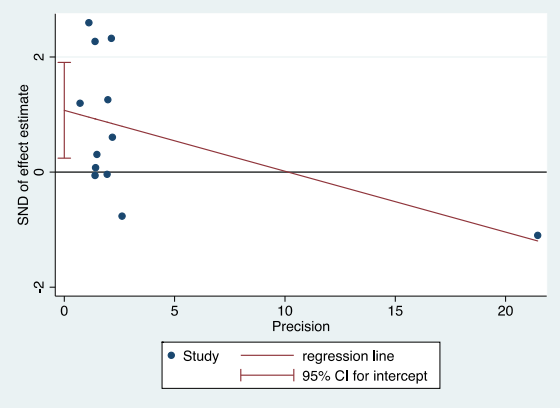
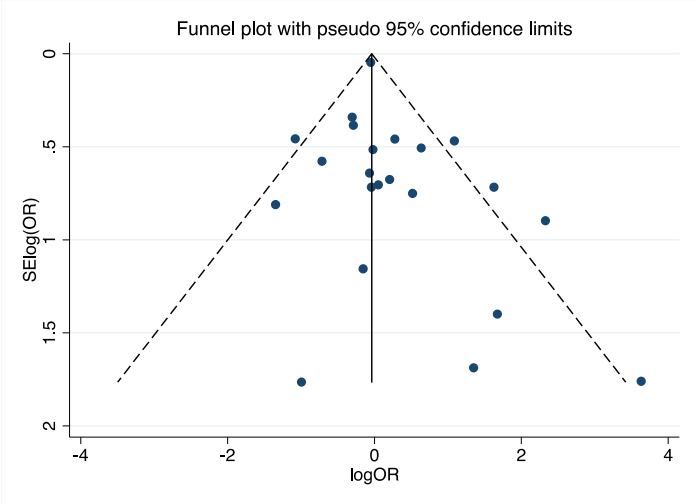
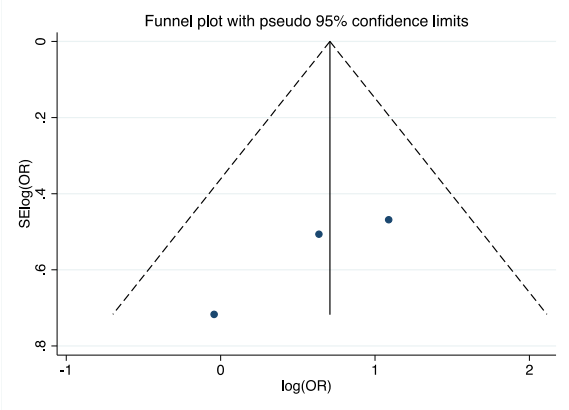


Figure S13. Funnel plot of the family history of SCD with non-specific age definition and MAE in patients with Brugada syndrome (a). Family history of SCD at age <40 (b) and <45 (c) years old and MAE in patients with Brugada syndrome.

a)



b)



c)