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Electrocardiogram Screening for Disorders That Cause Sudden Cardiac Death in Asymptomatic Children: A Meta-analysis

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KEY WORDS
sudden cardiac death, ECG screening, hypertrophic cardiomyopathy, long QT syndrome, Wolff-Parkinson-White syndrome

ABBREVIATIONS
AUC—area under the HSROC curve
CI—confidence interval
ECG—electrocardiogram
ECHO—echocardiogram
HCM—hypertrophic cardiomyopathy
HSROC—hierarchical summary receiver operating characteristic
LQTS—long QT syndrome
NPV—negative predictive value
PPV—positive predictive value
SCD—sudden cardiac death
WPW—Wolff-Parkinson-White syndrome

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abstract

BACKGROUND AND OBJECTIVES: Pediatric sudden cardiac death (SCD) occurs in an estimated 0.8 to 6.2 per 100 000 children annually. Screening for cardiac disorders causing SCD in asymptomatic children has public appeal because of its apparent potential to avert tragedy; however, performance of the electrocardiogram (ECG) as a screening tool is unknown. We estimated (1) phenotypic (ECG- or echocardiogram [ECHO]-based) prevalence of selected pediatric disorders associated with SCD, and (2) sensitivity, specificity, and predictive value of ECG, alone or with ECHO.

METHODS: We systematically reviewed literature on hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Wolff-Parkinson-White syndrome, the 3 most common disorders associated with SCD and detectable by ECG.

RESULTS: We identified and screened 6954 abstracts, yielding 396 articles, and extracted data from 30. Summary phenotypic prevalences per 100 000 asymptomatic children were 45 (95% confidence interval [CI]: 10–79) for HCM, 7 (95% CI: 0–14) for LQTS, and 136 (95% CI: 55–218) for Wolff-Parkinson-White. The areas under the receiver operating characteristic curves for ECG were 0.91 for detecting HCM and 0.92 for LQTS. The negative predictive value of detecting either HCM or LQTS by using ECG was high; however, the positive predictive value varied by different sensitivity and specificity cut-points and the true prevalence of the conditions.

CONCLUSIONS: Results provide an evidence base for evaluating pediatric screening for these disorders. ECG, alone or with ECHO, was a sensitive test for mass screening and negative predictive value was high, but positive predictive value and false-positive rates varied. *Pediatrics* 2012;129:e999–e1010

Although sudden cardiac death (SCD) in children and adolescents (hereafter "children") is rare (0.8–6.2 per 100 000 annual incidence[1,2]), the sudden death of a child is tragic and has widespread repercussions. Concern about SCD has raised calls for screening in primary care or school-based settings for all children; others have recommended screening for subgroups of children starting stimulants or participating in competitive athletics, both of which increase heart rate and may theoretically precipitate SCD.[1,3,4]

Population-based screening programs that identify children at risk for SCD have broad public appeal, as common sense suggests that presymptomatic diagnosis saves lives, and the societal cost is presumed to be the cost of the screening test itself. Japan is the sole country with published data on mass screening of school-aged children, including a targeted cardiac history and physical and electrocardiogram (ECG).[5] No data regarding mass pediatric screening and associated costs are available in the United States.[6]

In 2008, the American Heart Association released a statement[7] broadly interpreted as recommending an ECG before initiating stimulants for children with attention-deficit/hyperactivity disorder, estimated at 4% to 12% of children.[8] The American Academy of Pediatrics later released a statement, in collaboration with the American Heart Association, recommending that children with attention-deficit/hyperactivity disorder be assessed with a targeted history and cardiac examination but that further evaluation, including an ECG, be obtained only if indicated.[9] A recent decision analysis recommended that children participating in competitive sports undergo mass screening.[3] Several studies have described screening programs for athletes. Italy uses preparticipation screening, including ECGs, for athletes aged 12 to 35[1] and some American universities use preparticipation screening and ECGs for college athletes. Because 10 million people in the United States may be classified as "young competitive athletes,"[10] calls for screening have far-reaching implications.

Screening programs are most effective if (1) preclinical prevalence is sufficiently high in the screened population, (2) a highly discriminatory screening test is available, (3) the disease or disorder is serious, and (4) treatment while asymptomatic decreases morbidity and mortality more than treatment after symptoms develop.[11] These criteria enable evaluation of the efficiency of ECG to detect the disorders that may cause SCD in asymptomatic children.

Several rare disorders cause pediatric SCD, but not all have ECG findings.[12] The most common disorders detectable by ECG are hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), and Wolff-Parkinson-White syndrome (WPW). Their estimated prevalence rates are low in otherwise healthy, asymptomatic children; moreover, the value of the ECG as a "highly discriminatory" test is not well established. The ECG should selectively identify disorders responsible for SCD in all affected patients (ie, sensitivity) and rule out these disorders in healthy children (ie, specificity). Together, low prevalence and imperfect sensitivity and specificity estimates could result in inefficient screening strategies with unanticipated societal and economic costs.

We undertook a systematic review and meta-analysis of the literature of these 3 disorders that cause SCD. Our first aim was to summarize how often ECG- or echocardiogram (ECHO)-based testing (phenotypic prevalence) suggests HCM, LQTS, or WPW among asymptomatic and undiagnosed children who could be identified by mass screening. We focused on phenotypic prevalence, rather than genetic prevalence, because genetic testing is currently impractical in mass screening programs and is limited to diagnosis or risk stratification. Our second aim was to examine the reported sensitivity and specificity of the ECG, alone or with ECHO, to detect these disorders and calculate predictive values. Together, this information on phenotypic (ECG- or ECHO-based) prevalence, sensitivity, specificity, and predictive value form an evidence base that will facilitate further evaluation of the efficiency and downstream implications of ECG screening programs for SCD.

METHODS

We focused on HCM, LQTS, and WPW because they are the most common disorders potentially detectable by ECG among children. Because ECG findings in HCM are age sensitive (ie, may not be detected until late adolescence or early adulthood) and can be nonspecific, thus requiring an ECHO for diagnostic guidance, we chose to include articles that examined test characteristics of ECG alone, ECHO alone, or ECG combined with ECHO (ECG/ECHO).

Literature Searches

We performed a systematic review and searched the Medline database (1950 to December 2010) for studies reporting on HCM, LQTS, WPW, and SCD or on ECG and/or ECHO detection of these disorders. We combined keywords and Medical Subject Heading terms for hypertrophic cardiomyopathy, long QT syndrome, Wolff-Parkinson-White syndrome, sudden cardiac death, electrocardiography, echocardiography, sensitivity, and specificity. The search was limited to English-language publications of primary studies in humans with no geographic restrictions. Six reviewers screened titles and abstracts to identify relevant studies and then examined full-text articles for eligibility.

Eligibility Criteria

To summarize how often ECG- or ECHO-based testing (phenotypic prevalence) suggests HCM, LQTS, or WPW in asymptomatic children or young adults (3–25 years old), we included cross-sectional or cohort studies from the general population that used ECG or ECHO diagnostic criteria for each disorder consistent with clinical standards. Studies in which the mean age was >2 SDs from 25 years were excluded, including a recent study focused on neonates.[13] We also excluded studies of highly selected subgroups that were not representative of the general population. For example, "elite" athletes who competed in competitive regional, national, or international events were excluded, but studies of normally active high school athletes were included. Studies that used sampling techniques that might result in a nonrepresentative sample (eg, convenience sampling, studies requiring informed consent from participants) were excluded. Studies assessing the frequency of genetic variations related to HCM, LQTS, or WPW were excluded, given our focus on ECG screening in asymptomatic and previously undiagnosed children.

For our second aim we included studies with data on the sensitivity or specificity of ECG (with or without ECHO) to identify children who would have a diagnosis of HCM, LQTS, or WPW according to clinical criteria. Specifically, we deemed that an adequate reference ("gold") standard for HCM is ECHO, genotyping, or a well-documented HCM diagnosis. For LQTS, we accepted as reference standard testing for pathogenic variations (eg, the *KCNQ1*, *KCNH2*, and *SCN5A* genes) or a combination of personal and family history, clinical follow-up, and ECG. For WPW, ECG is the reference standard, so sensitivity and specificity information were not collected. Based on these criteria, studies with incorporation bias (where the index test comprises part of the reference standard against which it is measured) were eligible. We included studies in which only those with positive ECG and/or ECHO were verified with the reference standard (verification bias, which may overestimate sensitivity and underestimate the specificity of the index test). For those studies that had multiple alternative sets of ECG and/or ECHO criteria, we selected the most widely used or most sensitive criteria to avoid duplication of information.

Data Extraction

Four reviewers extracted data with at least 2 independently extracting or reviewing each article. All 4 reviewers discussed and resolved any discrepancies by consensus. From studies informing on phenotypic (ECG- or ECHO-based) prevalence, we extracted information on study population (description, country), study design (prospective, retrospective), sampling technique (representative or not), age of the study sample, sample size, diagnostic criteria, and number of participants with each disorder.

From studies on the sensitivity and specificity of ECG and/or ECHO to identify HCM or LQTS, we extracted information on study population (description, country), age of the study sample, type of test (ECG and/or ECHO), diagnostic criterion and thresholds for the test, reference standard definition, true-positive, false-negative, false-positive, true-negative, and presence of verification bias. If the study provided only sensitivity and specificity, we used this information to calculate the true-positive, false-negative, false-positive, and true-negative values.

Analysis

Because of the complexities of our methods, we briefly discuss analyses in the following paragraphs and provide detailed Supplemental Information that discusses characteristics of screening tests in general (eg, sensitivity, specificity, predictive value) and analytic methods used (eg, creation of hierarchical summary receiver operating characteristic [HSROC] curve).

Analysis of Phenotypic Prevalence

Phenotypic (ECG- or ECHO-based) prevalence (per 100 000) estimates and 95% confidence intervals (CIs) for HCM, LQTS, and WPW were calculated by using the exact binomial distribution. We obtained summary estimates of phenotypic prevalence by using random effects meta-analysis of logit-transformed phenotypic prevalence.[14] To assess the extent to which variation in the reported outcomes may be a result of chance alone, we used Cochran Q to test for heterogeneity (significant when $P < .10$) and quantified its magnitude in terms of I^2,[15] which ranges between 0% and 100% and expresses the proportion of between-study variability attributable to heterogeneity rather than chance. We considered I^2 values exceeding 75% suggestive of substantial heterogeneity. These calculations were performed by using Stata, version 11 (StataCorp LP, College Station, TX).

Analysis of Sensitivity and Specificity

For each disorder, we summarized the relationship between sensitivity (ie, the probability of having a positive test among those with the disorder) and specificity (ie, the probability of having a negative test among those without the disorder) of ECG and/or ECHO with an extension of the HSROC model.[16–18] For each disorder and screening tool combination, we plotted the HSROC curve for individual studies and the HSROC curve for the summary of the reviewed studies. These curves allow visual comparison between individual studies and the summary curve. Points along the summary curves incorporate different diagnostic criteria and do not correspond directly to specific observed study cut points for ECG and/or ECHO. Restricting the range to that observed in the data, the area under the posterior estimate

of the HSROC curve (AUC) calculated by numeric integration indicates test performance. An AUC of 1.0 represents a perfect test, whereas an AUC of 0.5 represents a test that performs no better than chance.

For each summary curve, we identified 2 illustrative examples to demonstrate how changes in sensitivity and specificity resulted in different predictive values, number needed to screen, false-positives, and false-negatives. We selected 2 points on the HSROC curve: (1) the point with "maximal accuracy" (ie, maximizing the sum of the sensitivity and specificity), thereby giving equal weight to ruling in people with disease (sensitivity) and ruling out those without disease (specificity); and (2) the point with "maximal specificity" where specificity was near 1 and the corresponding sensitivity, thereby giving more weight to ruling out those without the disease (specificity). We did not select a point on the curve where sensitivity was maximized because the corresponding specificity was low (0.001). By using the 2 illustrative points, we calculated 5 parameters: (1) positive predictive value (PPV, ie, the probability of having the disorder given a positive test), (2) negative predictive value (NPV, ie, the probability of not having the disorder given a negative test), (3) number needed to screen to detect 1 case, (4) number of false-positives when detecting 1 case, and (5) number of false-negatives per 100 000 children screened. To explore the effect of alternative prevalence rates, we repeated these calculations by using oft-cited prevalences of 200 per 100 000 for HCM,[19] 50 per 100 000 for LQTS,[13] and 200 per 100 000 for WPW (See Supplemental Information, Supplemental Figures 4-8, and Supplemental Tables 1-3 for more information on screening trade-offs in general.).[20]

Sensitivity Analysis

To determine whether alternative assumptions substantially affected the meta-analysis results, we performed extensive sensitivity analyses.[21] For key questions related to phenotypic (ECG- or ECHO-based) prevalence, we repeated the analyses excluding studies where (1) diagnostic criteria were not specified, (2) reported phenotypic prevalence exceeded the range of often-cited prevalence rates, or (3) phenotypic prevalence was based on previously diagnosed cases and not asymptomatic cases. For key questions addressing the ability of ECG- or ECHO-based testing to diagnose people with the conditions of interest, we repeated the analyses by excluding studies that did not apply the reference standard to participants with a nonsuggestive ECG and/or ECHO (ie, verification bias).

For additional sensitivity analyses, we back-calculated disease prevalence when applying a non-ECG reference standard to define disease. A positive screening ECG (eg, a result suggesting LQTS) can be either a true-positive (the person has LQTS) or a false-positive (the person does not and will not have LQTS). Thus, the frequency of "suggestive ECGs" is not the same as the prevalence of the disease. One can back-calculate the prevalence of LQTS from an acceptable alternative non-ECG reference standard to diagnose LQTS (eg, genetic testing for deleterious mutations in LQTS genes[13]), and from the proportion of positive ECG tests in a population. We performed such analyses only for LQTS, as an example to contextualize our discussion comments. As described in the Supplemental Information, we extended the Bayesian method of Joseph and colleagues.[22]

RESULTS

From 6954 titles and abstracts screened for eligibility, we retrieved and evaluated the full text in 396 articles, with 30 meeting eligibility criteria (Fig 1).[1,19,23–50]

Characteristics of Reviewed Studies

In the 11 primary studies[1,19,23–31] that reported phenotypic (ECG- or ECHO-based) prevalence findings, study populations ranged from general to subgroups of high school athletes and military conscripts. Studies were conducted in North America, Europe, and Asia and had sample sizes ranging from 1369 to 1 336 377 (Table 1).

Twenty primary studies[28,32–50] reported sensitivity and specificity estimates by using ECG to detect LQTS and/or HCM,

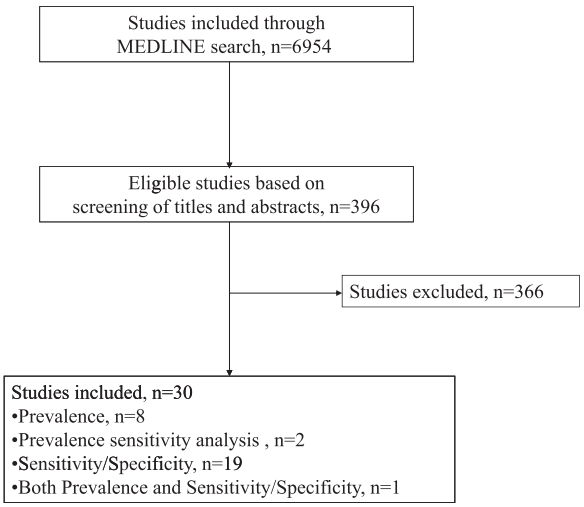

FIGURE 1
Literature search strategy.

TABLE 1 Articles Reporting Phenotypic (ECG- or ECHO-based) Prevalence of HCM, LQTS, and WPW

Author	Population and Source	Location	Study Design	Sampling Technique	Age, y	Sample Size	Diagnostic Criteria
HCM, *n* = 9							
Arola (1997)[23a]	Medical chart review within hospitals	Finland	RC	Representative	Range: 0–20	1 336 377	Interventricular septum or LV wall thickness ≥2 SD of normal
Colivicchi (2004)[24]	Pre-participation athletic screening	Italy	PC	Representative	Mean=16.2 SD=2.4	7568	LV wall thickness ≥13 mm
Corrado (1998)[25]	Pre-participation athletic screening	Italy	PC	Representative	Mean=19 SD=5	33 735	LV wall thickness ≥13 mm
Corrado (2006)[1]	Pre-participation athletic screening	Italy	PC	Representative	Range: 12–35	42 386	LV wall thickness ≥13 mm
Maron (1995)[19]	Epidemiology study with subjects selected from general population	USA	PC	Representative	Range: 23–35	4111	LV wall thickness ≥15 mm
Maron (1999)[26a]	Diagnostic testing requested by primary physician in rural community	USA	PC	Representative	Range: 16–87	15 137	LV wall thickness >13 mm
Niimura (1989)[27]	Screening of "presumably healthy" nursery school and junior high school children	Japan	PC	Representative	Ranges: 3–5, 12–14	930 939	Not specified
Nistri (2003)[28]	Screening of military recruits (males only) before mandatory military service	Italy	RC	Representative	Mean=19 SD=2	34 910	LV wall thickness ≥15 mm
Zou (2004)[29]	Epidemiology study in random sample of general population	China	PC	Representative	Range: 18–29	1369	LV wall thickness ≥13 mm
LQTS, *n* = 4							
Chiu (2008)[30]	Citywide survey of general population	Taiwan	PC	Representative	Range: 6–20	430 391	QTc >450 ms
Corrado (2006)[1]	Pre-participation athletic screening	Italy	PC	Representative	Range: 12–35	42 386	Male: QTc >440 ms, Female: QTc >460 ms
Kobza (2009)[31a]	Screening of military recruits (mostly male) before mandatory military service	Switzerland	PC	Representative	Mean=19.2 SD=1.4	40 917	Male: QTc >450 ms, Female: QTc >460 ms
Niimura (1989)[27]	Screening of "presumably healthy" nursery school and junior high school children	Japan	PC	Representative	Ranges: 3–5, 12–14	930 939	Not specified
WPW, n = 3							
Chiu (2008)[30]	Citywide survey of general population	Taiwan	PC	Representative	Range: 6–20	430 391	PR interval <120 ms; slurred upstroke of the QRS complex; QRS >120 ms
Corrado (1998)[25]	Pre-participation athletic screening	Italy	PC	Representative	Mean=19 SD=5	33 735	PR interval <0.12 s; QRS ≥0.12 s
Corrado (2006)[1]	Pre-participation athletic screening	Italy	PC	Representative	Range: 12–35	42 386	PR interval <0.12 s; QRS ≥0.12 s

LV, left ventricular; PC, prospective cohort; QTc, corrected QT interval; RC, retrospective cohort.
[a] These studies were included in sensitivity analysis only.

ECHO to detect HCM, or ECG/ECHO to detect HCM. Populations in these studies were mainly disease probands and their relatives. The studies were conducted in North America, Europe, and Asia and had sample sizes ranging from 23 to 2770 (Table 2).

Hypertrophic Cardiomyopathy

Based on 7 studies,[1,19,24,25,27–29] HCM phenotypic (ECG- or ECHO-based) prevalence ranged from 0 to 170 per 100 000 (Fig 2) with a summary phenotypic prevalence rate of 45 per 100 000 (95% CI: 10–79) but with substantial variation between studies (I^2 = 91%, $P < .001$). Inclusion of the study with a phenotypic prevalence estimate of zero[29] helped inform the upper bounds of the estimate. Although 1 study[27] did not specify diagnostic criteria, we included it because its exclusion had no effect on phenotypic prevalence (remained at 45 per 100 000) and this study was based on a well-established screening program in Japan. When adding 2 nonrepresentative studies[23,26] for sensitivity analysis, the summary phenotypic prevalence rate decreased to 13 per 100 000 (95% CI: 7–19) with substantial heterogeneity (I^2 = 92%, $P < .001$). Turning to screening for HCM, Fig 3 illustrates a set of HSROC curves for detection by ECG (10 studies),[28,32–40] ECHO (6 studies),[33–35,37,40,41] and ECG/ECHO (4 studies).[33–35,40] Based on the summary HSROC curves, the AUC values were high.

To provide clinical context for interpreting these results, we used the summary phenotypic prevalence estimate for HCM and the 2 previously described illustrative points (the maximal accuracy point and the maximal specificity point) on the HSROC curves for detection of HCM by using ECG, ECHO, and ECG/ECHO (Table 3). Regardless of whether an ECG, ECHO, or ECG/ECHO was used, both illustrative points yielded an

TABLE 2 Articles Reporting Sensitivity and Specificity for Screening ECG and/or ECHO to detect HCM and LQTS

Disorder & Screening Test	Author (year)	Sample	Location	Age, y	Screening Test Criteria	Definition of Reference ("Gold") Standard	Verification Bias	Sample Size
HCM, *n*=11								
ECG, *n*=10	Autore (1988)[32]	First-degree relatives of patients with HCM	Italy	Mean=36 SD=20	LV hypertrophy; abnormal Q waves; negative T waves; atrial fibrillation; left or right bundle branch block	ECHO	No	72
	Charron (1997)[33]	Genotyped probands and first-degree relatives	France	Range: 18–29	Q waves; LV hypertrophy, repolarization alterations; isolated left atrial enlargement; short PR interval; microvoltage; minor Q waves; bundle-branch block or hemiblock	Genotyping	No	58
	Charron (1998)[34]	Children of HCM genotyped families	France	<18	Q waves; voltage; repolarization alterations; abnormal PR interval, left and/or right atrial enlargement; atrial fibrillation; abnormal QRS axis; increased QRS duration; increased ventricular activation time; T waves; R/S ratio, rSr' aspect; bundle branch block or hemiblock; microvoltage	Genotyping	No	35
	Charron (2003)[35]	Genotyped probands and first-degree relatives	France	Mean=37.7 SD=17.9	abnormal Q waves; T-wave inversion; LV hypertrophy	Genotyping	No	109
	Dipchand (1999)[36]	Children with HCM and healthy controls	Canada	Median=3, Range: 0–19	Q waves; R waves; S waves; T waves; QTc interval; voltage	ECHO, LV angiography	Yes	73
	Fragola (1993)[37]	First-degree relatives of patients with HCM	Italy	Mean=34 SD=19	LV and RV hypertrophy; atrial enlargement; rhythm disturbances; atrioventricular and intraventricular conduction; ST-T displacement; Q waves; R waves; QRS	ECHO	No	116
	Konno (2004)[38]	Genotyped relatives of patients with HCM	Japan	<30	Q wave; LV hypertrophy; ST-segment depression; T-wave inversion	Genotyping	No	45
	Nistri (2003)[28]	Screening of military recruits (males only)	Italy	≥17	LV wall thickness; Q waves; ST-T waves	ECHO	No	2770
	Potter (2010)[39]	Patients with HCM and healthy controls	UK, Sweden, US	Mean=48.7 SD=14.0	RR, PR, P-wave, QRS and QT and JT intervals; P, QRS, and T-wave amplitudes; frontal plane QRS and T-wave axes; and ST-segment levels	ECHO	Yes	181
	Ryan (1995)[40]	Probands and relatives	UK, Poland	Mean=47 SD=19	R waves; S waves; Q waves; ST-T waves	Genotyping or clinical diagnosis	No	506
ECHO, *n*=6	Charron (1997)[33]	Genotyped probands and first-degree relatives	France	Range: 18–29	MWT	Genotyping	No	58
	Charron (1998)[34]	Children of HCM genotyped families	France	<18	MWT; intraventricular septum/posterior wall; left atrium diameter; systolic anterior motion of mitral valve; mid-systolic aortic closure; gradient >30 mmHg; mitral valve regurgitation; E/A wave ratio	Genotyping	No	35
	Charron (2003)[35]	Genotyped probands and first-degree relatives	France	Mean=37.7 SD=17.9	MWT in anterior septum or posterior wall; MWT in posterior septum or free wall; systolic anterior motion of the mitral valve, redundant leaflets	Genotyping	No	109
	Fragola (1993)[37]	First-degree relatives of patients with HCM	Italy	Mean=34 SD=19	Increased interventricular septal thickness; posterior wall thickness	ECHO	No	122
	Ho (2002)[41]	Genotyped relatives of patients with HCM and healthy controls	USA	Mean=35.6 SD=12.6	LV ejection fraction; early diastolic myocardial velocities	Genotyping	No	72

TABLE 2 Continued

Disorder & Screening Test	Author (year)	Sample	Location	Age, y	Screening Test Criteria	Definition of Reference ("Gold") Standard	Verification Bias	Sample Size
	Ryan (1995)[40]	Probands and relatives	UK, Poland	Mean=47 SD=19	LV wall thickness	Genotyping or clinical diagnosis	No	506
ECG/ECHO, *n*=4	Charron (1997)[33]	Genotyped probands and first-degree relatives	France	Range: 18–29	See above Charron 1997 ECG and ECHO criteria	Genotyping	No	58
	Charron (1998)[34]	Children of HCM genotyped families	France	<18	See above Charron 1998 ECG and ECHO criteria	Genotyping	No	35
	Charron (2003)[35]	Genotyped probands and first-degree relatives	France	Mean=37.7 SD=17.9	See above Charron 2003 ECG and ECHO criteria	Genotyping	No	109
	Ryan (1995)[40]	Probands and relatives	UK, Poland	Mean=47 SD=19	See above Ryan 1995 ECG and ECHO criteria	Genotyping or clinical diagnosis	No	506
LQTS, *n*=9								
ECG, *n*=9	Benhorin (1990)[42]	Participants in the International LQTS Registry and healthy controls	USA, Italy	Range: 17–60	ST segment; repolarization area; T wave area symmetry	ECG: QTc > 440 ms	Yes	352
	Kaufman (2001)[43]	Genotyped relatives of patients with LQTS	USA	≤13	QTc	Genotyping	No	38
	Miller (2001)[44]	Genotyped proband and first-degree relatives	USA	Range: 2–85	QTc	Genotyping	No	23
	Moennig (2001)[45]	Genotyped probands and relatives	Germany	Mean=38 Range: 31–50	QTc	Genotyping	No	116
	Neyroud (1998)[46]	Genotyped patients with LQTS and matched controls	France	Mean=31 SD=17	QTc	Genotyping	Yes	50
	Swan (1998)[47]	Genotyped probands and relatives	Finland	Range: 7–72	QTc	Genotyping	No	73
	Vincent (1992)[48]	Genotyped probands and relatives	Not specified	Range: 1.5–39.0	QTc	Genotyping	No	198
	Viskin (2010)[49]	Patients with LQTS and healthy controls	Not specified	Mean=32 SD=15	QTc	LQTS registry or genotyping	Yes	150
	Wong (2010)[50]	Genotyped probands and relatives	UK	Mean=26 SD=31	QTc	Genotyping	No	159

ECG/ECHO, ECG combined with ECHO; LV, left ventricular; MWT, maximal wall thickness; QTc, corrected QT interval; RV, right ventricular.

NPV that was near 100%, but PPV, number needed to screen, false-positives, and false-negatives differed substantially. At the maximal accuracy point, the PPVs fell below 1% compared with PPVs from 2% to 21% at the maximal specificity point. The maximal accuracy point led to fewer false-negatives (16%) and a lower number needed to screen to detect 1 case of HCM (2600). In contrast, the maximal specificity point led to 40% to 96% false-negative rates and 4000 to 57 000 needed to screen to detect 1 case of HCM. Last, the maximal accuracy point led to more false-positives per true HCM case detected (400 vs 4–57) than the maximal specificity point. By using the often-cited prevalence of 200 per 100 000[19] (4 times our estimate) resulted in similar NPV, a fourfold increase in PPV and false-negatives per 100 000 screened, and a decrease in the number needed to screen to detect 1 case and number of false-positives when detecting 1 case.

Long QT Syndrome

Phenotypic (ECG-based) prevalence rates of the 3 studies reporting on LQTS ranged from 1 to 12 per 100 000 (Fig 2),[1,27,30] with a summary phenotypic prevalence rate of 7 per 100 000 (95% CI: 0–14) and substantial heterogeneity (I^2 = 93%, $P < .001$). Although 1 study[27] did not specify diagnostic criteria, we included it because its exclusion increased phenotypic prevalence to only 9 per 100 000 and this study was based on a well-established screening program in Japan. The Kobza study[31] was excluded because its prevalence rate (550 per 100 000) exceeded often-cited prevalence rates of LQTS (40–50 per 100 000).[13] When incorporating Kobza, the summary prevalence increased fivefold to 38 per 100 000 (95% CI: 19–58) and heterogeneity increased (I^2 = 99%, $P < .001$).[42–50] The Bayesian sensitivity analysis giving the Schwartz[13] prior a low weight (1/2500) resulted in similar

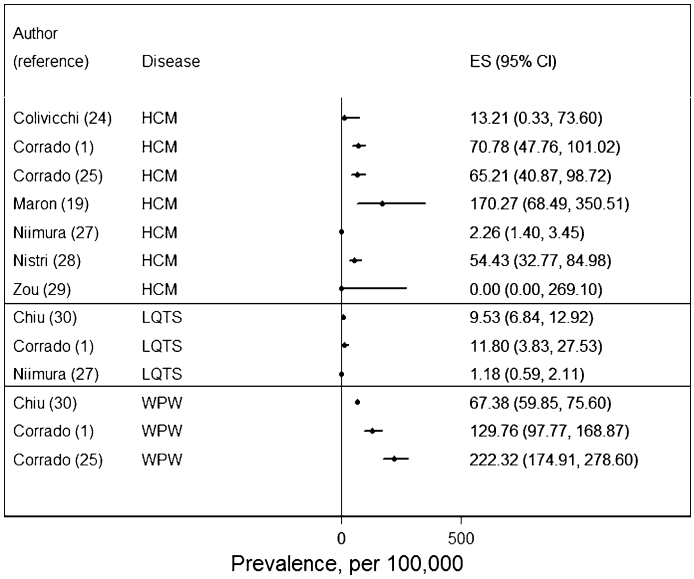

FIGURE 2

Forest plot of phenotypic (ECG- or ECHO-based) prevalence of HCM, LQTS, and WPW from reviewed studies. ES, effect size.

phenotypic prevalence of 7 per 100 000 (95% CI: 1–30), whereas giving the Schwartz prior more weight increased the phenotypic prevalence to 34 per 100 000 (95% CI: 20–54). For detecting LQTS (9 studies), Fig 3 illustrates a set of HSROC curves for ECG with a summary AUC of 0.92.

To provide clinical context, we used the summary phenotypic prevalence estimate for LQTS and 2 illustrative points (the maximal accuracy point and the maximal specificity point) on the HSROC curve for detection of LQTS by using ECG (Table 3). For both points, the NPV was near 100%. The PPV was very low (0.04% [1 in 2324]) at the maximal accuracy point, but increased slightly at the maximal specificity point (0.7% [1 in 136]). With maximal accuracy, the number needed to screen to detect 1 case of LQTS with an ECG was more than 16 000 with only 14% of those with LQTS missed (false-negatives), but more than 2000 false-positives per LQTS case detected. With maximal specificity, the number needed to screen to detect 1 case increased to 135 000 and 91% of those with LQTS would be missed, but there would be only 135 false-positives per LQTS case detected. By using the often-cited prevalence of 50 per 100 000[13] (7 times our estimate) resulted in a similar NPV, a sevenfold increase in PPV and false-negatives per 100 000 screened, and a decrease in number needed to screen to detect 1 case and number of false-positives when detecting 1 case.

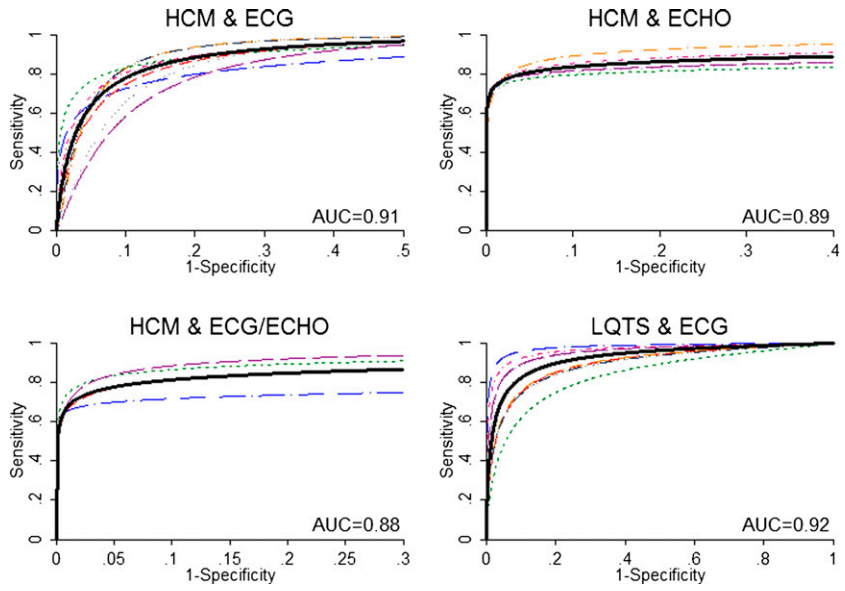

FIGURE 3

HSROC and AUC of reviewed studies for HCM and ECG, HCM and ECHO, HCM and ECG/ECHO (ECG combined with ECHO), and LQTS and ECG. Solid black lines represent summaries of reviewed studies and other lines represent individual studies. The lines describe the relationship between (average) sensitivity and (average) specificity for varying diagnostic thresholds (eg, increasingly stringent ECG or ECHO criteria in the 2 top panels, respectively). These lines describe average test performance. It is generally not straightforward to correspond specific points on the curve to specific cut points for ECG or ECHO. The x-axis is restricted to the range of the data.

WPW Syndrome

Three studies[1,25,30] reported phenotypic (ECG-based) prevalence rates for WPW ranging from 68 to 222 per 100 000 with a summary phenotypic prevalence rate of 136 per 100 000 (95% CI: 55–218) (Fig 2) and substantial heterogeneity (I^2 = 95%, $P < .001$). Because ECG is considered the reference standard and no studies reported estimates of sensitivity and specificity for any other screening tests to detect WPW, we assumed that its sensitivity and specificity were one and the PPV and NPV estimates were perfect and are not discussed further. By using the often-cited prevalence estimate of 200 per 100 000[20] did not substantially alter the number needed to screen.

DISCUSSION

By using published literature, we report on phenotypic (ECG- or ECHO-based)

TABLE 3 Implications of Screening ECG and/or ECHO on PPV, NPV, Number Needed to Screen, False-Positives, and False-Negatives for Illustrative Points on the HSROC Curve

	Prevalence per 100 000	Sensitivity	Specificity	PPV	NPV	Number Needed to Screen to Detect 1 Case	Number of False-Positives When Detecting 1 Case	Number of False-Negatives per 100 000 Screened
Illustrative point where sensitivity and specificity are equally weighted (maximal accuracy) with prevalence from meta-analysis								
HCM & ECG	45	0.847	0.848	0.0025 (1/400)	0.9999	2624	399	7
HCM & ECHO	45	0.851	0.851	0.0026 (1/390)	0.9999	2611	389	7
HCM & ECG/ECHO	45	0.837	0.837	0.0023 (1/434)	0.9999	2655	433	7
LQTS & ECG	7	0.861	0.860	0.0004 (1/2324)	0.9999	16 592	2323	1
WPW & ECG	136	1.000	1.000	1.0000	1.0000	735	0	0
Illustrative point where specificity is given more weight (maximal specificity) with prevalence from meta-analysis								
HCM & ECG	45	0.039	0.999	0.0173 (1/58)	0.9996	56 980	57	43
HCM & ECHO	45	0.607	0.999	0.2146 (1/5)	0.9998	3661	4	18
HCM & ECG/ECHO	45	0.514	0.999	0.1879 (1/5)	0.9998	4323	4	22
LQTS & ECG	7	0.106	0.999	0.0074 (1/136)	0.9999	134 771	135	6
WPW & ECG	136	1.000	1.000	1.0000	1.0000	735	0	0
Illustrative point where sensitivity and specificity are equally weighted (maximal accuracy) with oft-cited prevalence								
HCM & ECG	200[19]	0.847	0.848	0.0110 (1/91)	0.9996	590	90	31
HCM & ECHO	200[19]	0.851	0.851	0.0113 (1/88)	0.9996	588	87	30
HCM & ECG/ECHO	200[19]	0.837	0.837	0.0102 (1/98)	0.9996	597	97	33
LQTS & ECG	50[13]	0.861	0.860	0.0031 (1/326)	0.9999	2323	325	7
WPW & ECG	200[20]	1.000	1.000	1.0000	1.0000	500	0	0
Illustrative point where specificity is given more weight (maximal specificity) with oft-cited prevalence								
HCM & ECG	200[19]	0.039	0.999	0.0725 (1/14)	0.9981	12 821	13	192
HCM & ECHO	200[19]	0.607	0.999	0.5488(1/2)	0.9992	824	1	79
HCM & ECG/ECHO	200[19]	0.514	0.999	0.5074 (1/2)	0.9990	973	1	97
LQTS & ECG	50[13]	0.106	0.999	0.0504 (1/20)	0.9996	18 868	19	45
WPW & ECG	200[20]	1.000	1.000	1.0000	1.0000	500	0	0

ECG/ECHO, ECG combined with ECHO.

prevalence rates of HCM, LQTS, and WPW in asymptomatic children and the test characteristics of ECG and/or ECHO in detecting these disorders. Based on our prespecified inclusion/exclusion criteria and methodology, phenotypic prevalence estimates demonstrated wide variation across studies and were lower than those in neonates (eg, Schwartz et al[13]) or studies examining genotypic prevalence. Consequently, we explored the effects of alternative prevalence estimates in our results. Although the AUC ranged from 0.88 to 0.92, indicating that ECG and/or ECHO are statistically acceptable screening tests for detecting the most common disorders that cause SCD, the low phenotypic prevalence substantially affected the predictive value.

Because these disorders have a very low phenotypic prevalence, choosing a point on the HSROC curve that maximizes accuracy or maximizes specificity had little impact on NPV (nearly 100% NPV for HCM and LQTS); however, the maximal specificity point resulted in improved PPV (0.74% [1 in 136] to 21%) at the cost of needing to screen more individuals to detect 1 case and missing more diseased individuals because of reduced sensitivity. With maximal accuracy, the number needed to screen to detect 1 case fell and fewer cases were missed, but at the cost of lower PPV (0.04% [1 in 2324] to 0.26% [1 in 390]) and more false-positives per case detected. These findings help define boundaries of the theoretical utility of ECG and/or ECHO as screening tests for these disorders, but are difficult to comprehend in isolation. Unlike "typical" screening programs that value ruling in those who may have the disease (ie, sensitivity), these illustrative points demonstrate that when phenotypic prevalence is low, prioritizing specificity over sensitivity can improve PPV while not affecting the NPV (similar to HIV screening[51]).

We performed calculations to understand how these estimates might apply to population-based ECG screening. First, assuming independence, the combined prevalence estimate of HCM, LQTS, and WPW from our meta-analysis is 188 per 100 000. When maximizing accuracy, the NPV approaches 100%, indicating a low false-reassurance rate. However, the PPV of using an ECG to screen for any of the 3 disorders is 1%, indicating a high false-alarm rate (99% of children with a positive ECG would not have any of the disorders). Conversely, when maximizing specificity, the NPV still approaches 100% (false-reassurance rate remains near 0%), but the PPV is 41% (false-alarm rate decreases to 59%). A sensitivity analysis using often-cited prevalence rates (40–50 per 100 000 for LQTS,[13] 200 per 100 000 for HCM,[19] 100–200 per 100 000 for WPW[20]) showed a more favorable outlook for screening (higher PPV, fewer need to screen to

detect 1 case, fewer false-positives when detecting 1 case, but more false-negatives per 100 000 screened).

Although these results suggest that ECG may be considered for mass screening from a statistical perspective and from the US Preventive Services Task Force criteria,[52] it does not address other components of screening programs, including changes in mortality, morbidity, cost, quality of life, and functioning that need to be weighed. Because of the very low phenotypic prevalence and inherent inaccuracy in nearly all medical tests (including pediatric cardiologists reviewing ECGs[53]), screening for rare disorders will lead to many false-positive tests that trigger additional diagnostic evaluations and, possibly, unnecessary therapies and physical activity restrictions. In addition, false-positives may lead to unwarranted child and parent anxiety; previous work suggests this anxiety may not dissipate immediately following a cardiac evaluation and may influence lifelong lifestyle decisions.[54]

Concern has been raised about increased rates of diagnosed heart disease where diagnosis may not be helpful (resulting in diagnosis of cardiac nondisease and overtreatment[55]). Some children may ultimately be diagnosed by other means (eg, family history, emergence of sublethal symptoms, diagnostic testing for unrelated indications) even in the absence of mass screening, and earlier diagnosis of the disorder may not provide survival benefit. Among those children detected by screening, the safety, efficacy, and acceptability of specific therapies and recommendations for prophylaxis of SCD in asymptomatic children is sometimes uncertain and often based on expert consensus as opposed to clinical evidence.[6]

In addition, families need to be aware that a negative ECG does not definitively rule out risk for SCD. Other rare cardiac disorders cause SCD, such as anomalous origin of the coronary artery, arrhythmogenic right ventricular cardiomyopathy, catecholaminergic ventricular tachycardia, and Brugada syndrome. With the exception of Brugada syndrome, which manifests in late adolescence, these disorders are not typically diagnosed by ECG. Also, given that clinical and ECG findings may not manifest in HCM until adolescence, programs that screen young children may miss those genetically predisposed to developing HCM, which may necessitate repeat ECGs during adolescence.

This study has several limitations. First, our search was restricted to literature cataloged by Medline. Medline indexes most biomedical articles, making it unlikely that we omitted important findings. Second, our estimates may reflect publication bias, as it is conceivable that "unsuccessful" studies of diagnostic or detection interventions may not have been published. This phenomenon, if it took place, would inflate our test accuracy estimates. Third, heterogeneity existed between studies. Populations varied by age and studies varied in their screening approach and their diagnostic criteria. Fourth, our calculations omitted a targeted history and physical. Although we included medical history, physical examination, and family history in our search, we found insufficient data for further analyses. Published studies suggest that history and physical examination have low sensitivity,[25] low PPV,[56] and limited value from a health economics perspective.[3,4] Fifth, we defined phenotypic prevalence based on results from ECG or ECHO (not genotyping) because these were the screening options considered in our analysis and because genotyping has only recently become available and is still evolving. In estimating the sensitivity and specificity of ECG and/or ECHO, however, we allowed genotypically identified cohorts because genetic testing will likely play a more prominent role in screening and diagnosing disorders that cause SCD. By using genotyping as the reference standard allows us to incorporate some variability in penetrance (leading to false-positives), which will likely be important for screening test interpretation. Finally, this study is limited by considering only 3 disorders, but these are the 3 most common disorders detectable by ECG and/or ECHO.

Despite these limitations, this study provides an important starting point for evaluating SCD screening programs. Screening programs may be gaining popularity because of availability bias in risk perception (ie, recent publicized events result in the overestimated likelihood of a similar event occurring). Given our results on the low phenotypic (ECG- or ECHO-based) prevalence and the variation in false-positive rate based on different sensitivities and specificities, further cost- or comparative-effectiveness analyses will be necessary to determine whether screening programs to detect SCD in asymptomatic children should be promoted as public health policy.

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Electrocardiogram Screening for Disorders That Cause Sudden Cardiac Death in Asymptomatic Children: A Meta-analysis

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