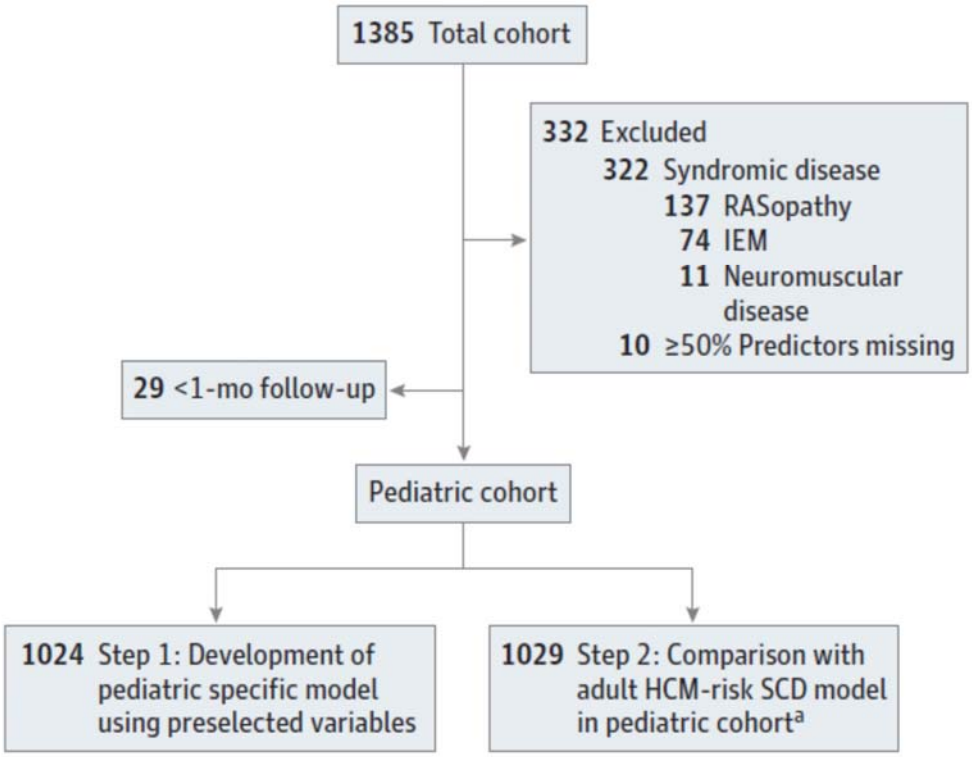
Supplementary Online Content

Norrish G, Ding T, Field E, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol*. Published online August 14, 2019. doi:10.1001/jamacardio.2019.2861

This supplementary material has been provided by the authors to give readers additional information about their work.

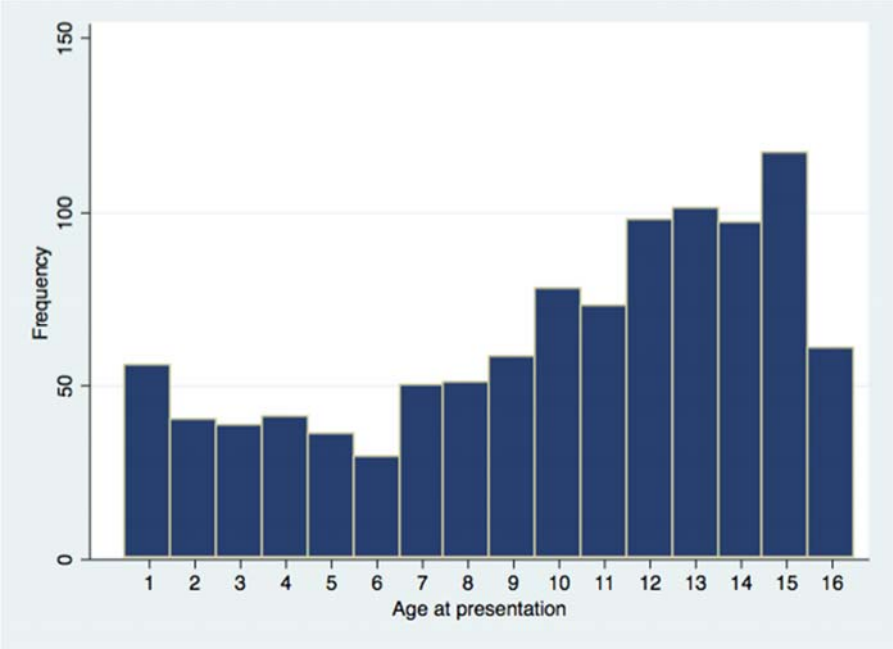
eFigure 1. Pediatric Risk Model for (SCD) in (HCM Risk-Kids)



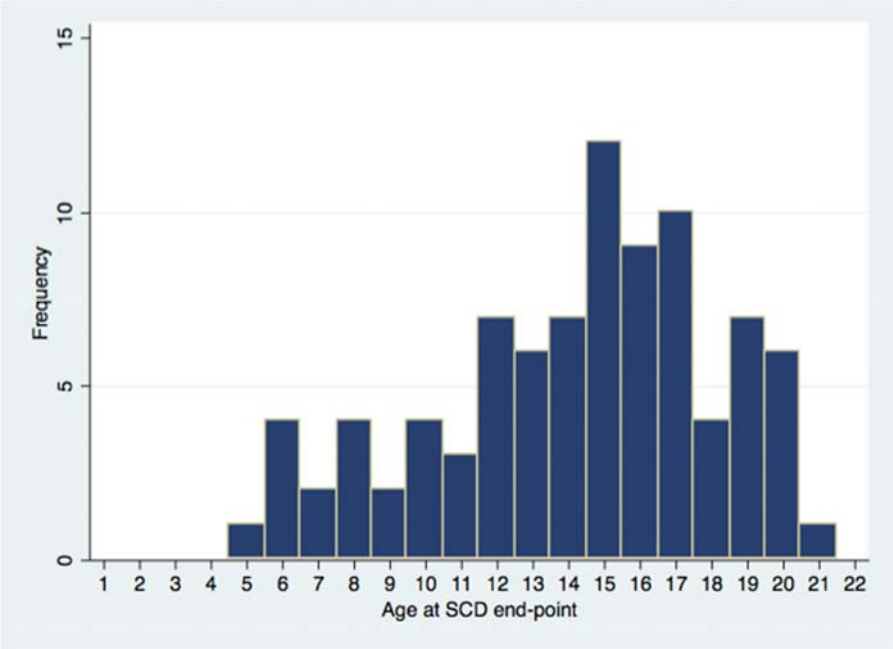
[a]Five additional patients were included in the comparison with adult model excluded from the pediatric development owing to more than 50% missing data for pediatric variables.

eFigure 2. Bar Chart Showing Age Distribution of Cohort

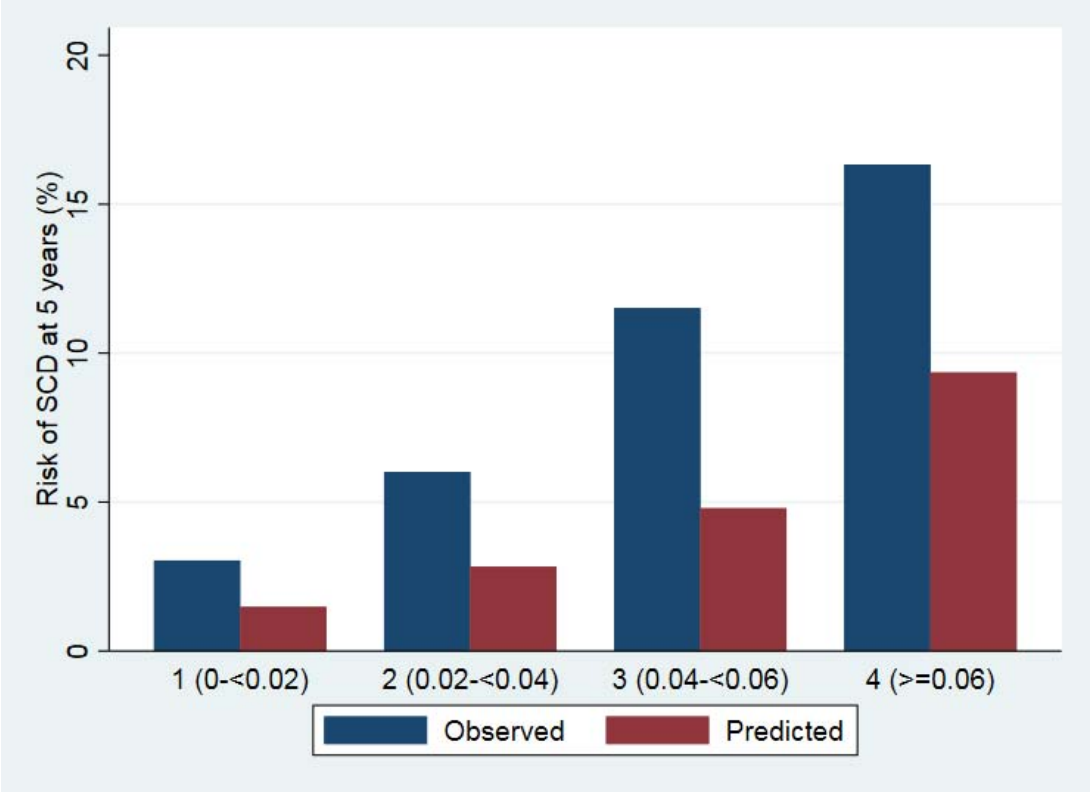
A age at baseline



B age at time of SCD-end point



eFigure 3. Comparison of Observed and Predicted Risk by Clinical Risk Group for External Validation of Adult HCM-Risk SCD Model.



Vertical bars represent observed (blue) and model-based predicted (red) probability of SCD by 5 years using one imputed data set.

eTable 1. Number of Patients Enrolled by Participating Center

	Centre	Number of patients enrolled	% of cohort
1	Great Ormond Street Hospital, London, UK	210	20.5
2	Children's Memorial Health Institute, Warsaw, Poland	101	9.9
3	Careggi University Hopsital, Florence, Italy	79	7.7
4	Monaldi Hospital, Naples, Italy	52	5.1
5	Onassis Cardiac Surgery Centre, Athens, Greece	45	4.4
6	The Royal Children's Hospital, Melbourne, Australia	44	4.3
7	S. Orsola-Malpighi Hospital, Bologna, Italy	41	4
8	Our Lady's Children's Hospital, Dublin, Ireland	36	3.5
9	Royal Hospital for Children, Glasgow, UK	34	3.3
10	Favaloro Foundation University Hospital, Buenos Aires, Argentina	32	3.1
11	Leiden University Medical Center, Leiden, Netherlands	30	2.9
12	Bambino Gesu Hospital, Rome, Italy	27	2.6
13	University Hospital Motol, Prague, Czech Republic	23	2.3
14	Royal Brompton and Harefield NHS Trust, London, UK	22	2.2
15	Hospital Sant Joan de Deu, Barcelona, Spain	20	2
16	Papa Giovanni XXIII hospital, Bergamo, Italy	19	1.9
17	Birmingham Children's Hospital, Birmingham, UK	15	1.5
18	Hospital General Universitario Gregorio Maranon, Madrid, Spain	15	1.5
19	University Hospital of Wales, Cardiff, UK	14	1.4
20	Leeds General Infirmary, Leeds, UK	14	1.4
21	Val d'Hebron University Hospital, Barcelona, Spain	14	1.4
22	University Hospital Virgen de la Arrixaca, Murcia, Spain	12	1.2
23	Bristol Royal hospital for Children, Bristol, UK	12	1.8
24	Niguarda Hospital, Milan, Italy	12	1.2

25	Complexo Hospitalario Universitario A Coruña, Spain	11	1.1
26	University Hospital La Paz, Madrid, Spain	10	1
27	John Radcliffe Hospital, Oxford, UK	10	1
28	Glenfield Hospital, Leicester, UK	9	0.9
29	Southampton General Hospital, Southampton, UK	9	0.9
30	Hospital Universitario Puerta de Hierro Majadahonda Madrid, Spain	7	0.7
31	Aarhus University Hospital, Aarhus, Denmark	7	0.7
32	University Hospitals Parma, Italy	7	0.7
33	Alder Hey Children's hospital, Liverpool, UK	6	0.6
34	Ghent University Hospital, Belgium	6	0.6
35	Kochi Medical School Hospital, Kochi University, Japan	4	0.4
36	Mater Dei Hospital, Malta	4	0.4
37	Odense University Hospital, Odense, Denmark	3	0.3
38	Evelina Children's Hospital, London, UK	3	0.3
39	Freeman Hospital, Newcastle, UK	2	0.2

eTable 2. Summary of Candidate Predictors Following Systematic Review of Literature[1]

Candidate predictor	Total number of studies using univariable/multivariable survival analysis with cardiac death as an end-point	Total number of studies using univariable/multivariable survival analysis with SCD as an end-point	Number of studies showing significant independent association with cardiac death univariable survival analysis	Number of studies showing significant independent association with SCD univariable survival analysis	Number of studies showing significant independent association with cardiac death in multivariable survival analysis	Number of studies showing significant independent association with SCD in multivariable survival analysis
Age	11[2-12]	6 [6, 8, 9, 11-13]1	3[5-7]	1 [6]	0	0
Gender	5 [3-5, 12, 14]	2 [12, 14] 0	1[3]	0	1[3]	0
NYHA/Ross	4[2, 3, 8, 9, 15]	2 [5, 9] 1	2 [9, 15]	1 [9]	1 [3]	0
Unexplained syncope	7 [7, 9, 11, 14-17]	6 [7, 9, 11, 14-16] 2	3 [7, 15, 16]	3 [7, 15, 16]	1 [15]	1 [15]
Family history of SCD	7 [3, 4, 7, 9, 11, 14, 17] 1	4 [7, 9, 11, 14] 1	0	0	1[14]	1[14]
Non-sustained VT on ambulatory ECG	6 [4, 7, 9, 11, 17, 18]	4 [7, 9, 11, 18] 2	2 [11, 18]	2 [11, 18]	0	0
Left ventricular hypertrophy+	13 [2-5, 7-9, 11, 12, 14, 17-19]	9 [5, 7-9, 11, 12, 14, 18, 19] 3	9 [2-5, 7, 12, 17-19]	6 [5, 7, 9, 12, 18, 19]	2 [4, 5]	1 [5]
Left atrial diameter	3 [8, 9, 19]	3 [8, 9, 19] 0	1 [9]	1 [9]	1[8]	1[8]

Left ventricular outflow tract obstruction*	6 [2, 4, 9, 11, 17, 20]	2 [9, 11] 0	1 [4]	1 (9)	0	0
Abnormal blood pressure response to exercise	4 [7, 9, 14, 17]	3 [7, 9, 14] 1	1 [17]	0	0	0

The following search strategy was used to identify studies:
MEDLINE search: MeSH terms "((hypertrophic cardiomyopathy) AND (death OR sudden death OR cardiac death OR outcome OR prognosis OR risk factors) AND (children OR childhood OR young OR paediatric)). Search was limited to: original articles written in English; patients aged < 18 years; published 1963 to December 2015. Initial search strategy was supplemented with manual searches

Risk factors examined in more than 2 survival studies using SCD as an end-point were considered as candidate predictors.

+ Measure of left ventricular hypertrophy varied between studies: extreme left ventricular hypertrophy (maximal wall thickness >30mm/Z score >6)[4, 9, 14, 17-19]; interventricular septal wall thickness (IVST) [3-5, 7-9, 11, 12, 19]; left ventricular posterior wall thickness (LVPWT) [2-4, 12, 19]; LVPWT:LV cavity [5, 9]

*Measure of LVOTO varied between studies: LVOT gradient, mmHg (9, 20), peak LVOTO gradient >20mmHg (11), peak LVOTO gradient >16mmHg (2, 4, 17)

eTable 3. Baseline Clinical Characteristics by Era

	Whole cohort	**Pre-1990 (n=29)**	**1990-1999 (n=129)**	**2000-2009 (n=416)**	**2010 onwards (n=450)**
Male gender	699 (68.3%)	18 (62.1%)	79 (61.2%)	289 (69.5%)	313 (69.6%)
Age (median, IGQ)	11 (7,14)	8 (5,13)	11 (5,13)	11 (7,14)	11 (7,14)
Family history of HCM (n=1006)	534 (53.1%)	11 (38%)	70 (54.7%)	220 (53.5%)	233 (53.2%)
Family history SCD (n=1020)	130 (12.8%)	4 (13.8%)	23 (18%)	54 (13%)	49 (11%)
Unexplained syncope (n=1023)	102 (9.9%)	5 (17.2%)	18 (14%)	44 (10.6%)	35 (7.8%)
NYHA/Ross >1 (n=1006)	223 (22.2%)	11 (40.3%)	36 (28.4%)	95 (23.6%)	81 (18.1%)
NSVT (n=856)	55 (6.4%)	11 (40.7%)	6 (5.3%)	28 (7.9%)	10 (2.8%)
MWT (mm) [mean, +/- SD] (n=997)	17.1 (7.4)	22 (+/-8.9)	19.4 (+/- 8.1)	17.4 (+/- 7.5)	16 (+/-6.7)
MWT z-score [mean, +/- SD] (n=906)	11.1 (7.1)	16.2 (+/- 8.5)	14.3 (+/- 8.0)	11.4 (+/- 7.3)	9.8 (+/- 6.4)
LA diameter (mm) [mean, +/- SD] (n=712)	33.4 (8.5)	33.6 (+/- 6.1)	34.1 (+/- 8.2)	35.8 (+/- 8.8)	31.3 (+/- 7.8)
LA z-score [mean, +/- SD] (n=675)	1.9 (2.3)	2.8 (+/-2.5)	2.4 (+/-2.1)	2.6 (+/-2.6)	1.3 (+/- 1.9)
LVOTg max [median, IQR] (n=871)	9 (6, 22)	10 (5,10)	12 (6, 46)	10 (6, 23)	8 (5, 16)

n=1024 unless otherwise indicated. NYHA = New York Heart Association, SCD = sudden cardiac death, MWT=maximal wall thickness, LA = left atrium, LVOTg max = Maximal left ventricular outflow tract gradient. NSVT = non-sustained ventricular tachycardia

eTable 4: Summary of Missing Data

		N (%)
Age (mean, 95% CI)		NA
Male gender		NA
Family history HCM		18 (1.7%)
Family history SCD		4 (0.4%)
Unexplained Syncope		1 (0.1%)
NYHA/Ross (n=1006)	**1**	18 (1.7%)
	2+	
NSVT on ambulatory ECG		168 (16.4%)
MWT (mm) [mean, +/- SD]		27 (2.6%)
Z score MWT [mean, +/- SD]		118 (11.5%)
LA diameter (mm [mean, +/- SD]		312 (30.4%)
Z score LA diameter [mean, +/- SD]		349 (34.1%)
LVOTg max [median, IQR]		153 (14.9%)
Number of predictors missing		
	0	527 (51.5%)
	1	252 (24.6%)
	2	176 (17.2%)
	3	69 (6.7%)

eTable 5. Sensitivity Analysis: Model Including Age and Family History of SCD

SCD risk prediction model + age + FH		
	Hazard ratio (95% CI)	P-value
Age	1.04 (0.99-1.09)	0.169
Unexplained syncope	1.48 (0.76-2.90)	0.251
NSVT	1.23 (0.56-2.72)	0.607
zscoreLA	1.14 (1.03-1.27)	0.010
zscoreMWT	1.23 (1.05-1.44)	0.009
$zscoreMWT^2$	0.995 (0.991-1.000)	0.058
LVOT	0.994 (0.986-1.002)	0.114
Family history of SCD	0.85 (0.51-1.43)	0.547
Uno's C statistic	0.69 (0.66, 0.72)	
Calibration slope	0.92 (0.53, 1.32)	

eAppendix. HCM Risk-Kids Calculator

HCM Risk-Kids calculator for the primary prevention of SCD

	Enter patient characteristics *	Coefficients	Coefficients
Sex (M=1, F=0)	0		
Weight (Kg)	10		
BSA	0.489638584		
MWT (mm)	7		
MWT z score	3.904719745	0.2171364	0.0047562
LA diammeter (mm)	23		
LA z score	1.737194333	0.130365	
LVOT gradient (mmHg)	20	0.0065555	
NSVT (yes=1, no=0)	1	0.1861694	
Unexplained syncope (yes=1, no=0)	0	0.429624	

Prognostic index	**-0.630415507**
Survival from SCD at 5 years	**0.972755824**
Estimated SCD risk at 5 years (%)	**2.72441755**

* calculated values

Definitions

MWT, Maximal LV wall thickness on TTE measurement -at time of evaluation (mm)

MWT z score, Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation (mm)

LA z score, The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients were determined using the modified Bernouilli equation:

LVOT gradient, Gradient= $4V^2$, where V is the peak aortic outflow velocity

NSVT, ≥3 consecutive ventricular beats at a rate of ≥120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation

Unexplained syncope, History of unexplained syncope at or prior to evaluation

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