Routinely collected health data to study inherited heart disease? A systematic review (2000-2016)

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Article type: Systematic review (Supplementary File)

Supplementary Table 1A. Medline search strategy (N = 2 816) [a,b]

Data	Methodological approach	Condition of interest
Autopsy	Case-control studies	Arrhythmogenic right ventricular tachycardia
Death	Cohort studies	Bicuspid aortic valve disease
Death certificate	Epidemiology	Brugada syndrome
Drug prescriptions	Epidemiological methods	Catecholaminergic polymorphic ventricular tachycardia
Drug utilisation	Molecular epidemiology	Familial dilated cardiomyopathy
Emergency service, hospital	Observational study	Familial hypercholesterol*
Factual database	Pharmacoepidemiology	Familial restrictive cardiomyopathy
Hospitalisation	Prospective study	Hypertrophic cardiomyopathy
Medical records	Retrospective study	Long QT syndrome
Pregnancy		Left ventricular noncompaction
Pregnancy outcomes		Marfan syndrome
Prescription drugs		Sudden cardiac death
		Sudden unexplained death

[a]The terms in each column are linked by 'or'. Terms between columns are linked by 'and'. Therefore to be included in the search results an article needed to have at least one term from each column.

[b]Search completed 31 October 2016; results limited to English language; publication date between 2000-2016; excluded evidence based medicine reviews, article reviews (DARE), article reviews (ACP journal club), review articles, topic reviews (Cochrane).

Supplementary Table 1B. Pre-Medline search strategy (N = 375) [a,b]

Data	Condition of interest
Autopsy	Arrhythmogenic right ventricular tachycardia
Death certificate	Bicuspid aortic valve
Emergency	Brugada syndrome
Hospital*	Catecholaminergic polymorphic ventricular tachycardia
Medical record	Familial dilated cardiomyopathy
Pregnan*	Familial hypercholesterol*
Prescription	Familial restrictive cardiomyopathy
Routinely collected data	Hypertrophic cardiomyopathy
	Left ventricular noncompaction
	Long QT syndrome
	Marfan syndrome
	Sudden cardiac death
	Sudden unexplained death

[a]The terms in each column are linked by 'or'; the terms between columns are linked by 'and'. Therefore to be included in the search results an article needed to have at least one term from each column. We did not include a methodological approach in this search strategy due to the low yield from this data source and these articles have not been linked with MESH subject headings.

[b]Search completed 31 October 2016; results limited to English language; publication date between 2000-2016; exclude review articles.

Supplementary Table 1C. EMBASE search strategy (N = 2 309)[a,b]

Data	Methodological approach	Condition of interest
Factual database	Case control study	Arrhythmogenic right ventricular tachycardia
Hospitalisation	Cohort analysis	Bicuspid aortic valve
Hospital admission	Epidemiology	Brugada syndrome
Death certificate	Genetic epidemiology	Catecholaminergic polymorphic ventricular tachycardia
Emergency ward	Observational study	Familial dilated cardiomyopathy
Autopsy	Pharmacoepidemiology	Familial hypercholesterol*
Drug utilisation	Prospective study	Familial restrictive cardiomyopathy
Prescription drug	Retrospective study	Hypertrophic cardiomyopathy
Prescription		Long QT syndrome
Medical record		Marfan syndrome
Pregnancy		Sudden cardiac death
Pregnancy outcomes		Sudden unexplained death

[a]The terms in each column are linked by 'or'; the terms between columns are linked by 'and'. Therefore to be included in the search results an article needed to have at least one term from each column.

[b]Search completed 31 October 2016; results were limited to English language; publication date between 2000-2016; human studies; exclude Cochrane library.

Supplementary Table 1D. CINAHL search strategy (N = 185) [a,b]

Data	Methodological approach	Condition of interest
Autopsy	Case control study	Arrhythmogenic right ventricular tachycardia
Death certificate	Data collection methods	Bicuspid aortic valve
Drug prescriptions	Epidemiological research	Brugada syndrome
Drug utilisation	Epidemiology	Catecholaminergic polymorphic ventricular tachycardia
Emergency service	Hospital-based case control	Familial dilated cardiomyopathy
Hospital admission	Matched case control	Familial hypercholesterol*
Hospitalisation	Molecular epidemiology	Familial restrictive cardiomyopathy
Medical record linkage	Nonexperimental studies	Hypertrophic cardiomyopathy
Medical records	Observational methods	Left ventricular noncompaction
Medical records personal	Pharmacogenetics	Long QT syndrome
Pregnancy	Pharmacovigilance	Marfan syndrome
Pregnancy outcomes	Population-based case control	Sudden cardiac death
Prescription drug	Prospective studies	Sudden unexplained death
	Retrospective design	

[a]The terms in each column are linked by 'or'; the terms between columns are linked by 'and'. Therefore to be included in the search results an article needed to have at least one term from each column.

[b] Search completed 31 October 2016; results limited to: English language; published between 2000-2016; included academic journals.

Supplementary Table 2A. A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist

Section/topic	#	Checklist item	Reported on page #	Comments
INTRODUCTION				
Was an "a priori" design provided?	1	The research question and inclusion criteria should be established before the conduct of the review.	3-4	
METHODS				
Was there duplicate study selection and data extraction?	2	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	5	
Was a comprehensive literature search performed?	3	At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	4	
Was the status of publication (i.e., grey literature) used as an inclusion criterion?	4	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	4	
Were the methods used to combine the findings of studies	5	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it	X	Not a meta-analysis: Qualitative synthesis

appropriate?		sensible to combine?).		
RESULTS				
Were the characteristics of the included studies provided?	6	In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Supplementary Table 5	
Was the scientific quality of the included studies assessed and documented?	7	''A priori'' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	10-11, and Supplementary Table 6	
Was the scientific quality of the included studies used appropriately in formulating conclusions?	8	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	X	Not a meta-analysis: Qualitative synthesis
Was the likelihood of publication bias assessed?	9	An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	X	Not a meta-analysis: Qualitative synthesis
FUNDING				
Was the conflict of interest included?	10	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	15, Table 1	
APPENDIX				

Was a list of studies (included and excluded) provided?	11	A list of included and excluded studies should be provided.	Supplementary Tables 3 and 4	

Supplementary Table 2B. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #	Comments
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1	
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2	No registration number
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	3	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3	
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X	No registered protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, Figure 1	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Tables 1A-D	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6, Supplementary Figures 1 and 2	

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X	Not a meta-analysis: Qualitative synthesis
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	X	Not a meta-analysis: Qualitative synthesis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	X	Not a meta-analysis: Qualitative synthesis
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary Table 5, 16-17	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	X	Not a meta-analysis: Qualitative synthesis
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	X	Not a meta-analysis: Qualitative synthesis
Synthesis of	21	Present the main results of the review. If meta-analyses are done, include for each, confidence	7-11	

results		intervals and measures of consistency.		
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11, Supplementary Table 6	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	X	Not a meta-analysis: Qualitative synthesis
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14	
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15, Table 1	

Supplementary Table 3. List of studies included in review

1. Achelrod D, Blankart CR, Linder R, Von Kodolitsch Y, Stargardt T. The economic impact of Marfan syndrome: a non-experimental, retrospective, population-based matched cohort study. *Orphanet Journal of Rare Diseases.* 2014; 9(1): 90.
2. Carley ME, Schaffer J. Urinary incontinence and pelvic organ prolapse in women with Marfan or Ehlers-Danlos syndrome. *American Journal of Obstetrics and Gynecology.* 2000; 182(5): 1021-1023.
3. Chan YC, Ting CW, Ho P, Poon JT, Cheung GC, Cheng SW. Ten-year epidemiological review of in-hospital patients with Marfan syndrome. *Annals of Vascular Surgery.* 2008; 22(5): 608-612.
4. Chiu HH, Wu MH, Chen HC, Kao FY, Huang SK. Epidemiological profile of Marfan syndrome in a general population: a national database study. *Mayo Clinic Proceedings.* 2014; 89(1): 34-42.
5. Chothani A, Panaich SS, Patel N, et al. Septal ablation and hypertrophic obstructive cardiomyopathy: 7 years US experience. *Journal of Interventional Cardiology.* 2016; 29(5): 505-512.
6. Collins RT, Phomakay V, Zarate YA, Tang X. Impact of aortic aneurysm on hospitalizations in patients with Marfan syndrome: a multi-institutional study. *Pediatric Cardiology.* 2015; 36(1): 132-139.
7. Hassan N, Patenaude V, Oddy L, Abenhaim HA. Pregnancy outcomes in Marfan syndrome: a retrospective cohort study. *American Journal of Perinatology.* 2015; 30(2): 123-129.
8. Hreybe H, Zahid M, Sonel A, Good CB, Shaver J, Saba S. Noncardiac surgery and the risk of death and other cardiovascular events in patients with hypertrophic cardiomyopathy. *Clinical Cardiology.* 2006; 29(2): 65-68.
9. Kim LK, Swaminathan RV, Looser P, et al. Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US Nationwide Inpatient database, 2003-2011. *JAMA Cardiology.* 2016; 1(3): 324-332.
10. Panaich SS, Badheka AO, Chothani A, et al. Results of ventricular septal myectomy and hypertrophic cardiomyopathy (from Nationwide Inpatient Sample [1998-2010]). *The American Journal of Cardiology.* 2014; 114(9): 1390-1395.
11. Roll K. The influence of regional health care structures on delay in diagnosis of rare diseases: the case of Marfan syndrome. *Health Policy (Amsterdam, Netherlands).* 2012; 105(2-3): 119-127.
12. Takiguchi M, Knight T, Bguyen TT, et al. Underdiagnosis of conditions associated with sudden cardiac death in children – is it the absence of a comprehensive screening program or a true low prevalence? *Hawai'i Journal of Medicine & Public Health*. 2016; 75(2): 42-45.

Supplementary Table 4. List of studies excluded from review with reason for exclusion

Reference		Reason for exclusion
1.	Ahmad MN, Ahmad MM, Hussaini SF, et al. Aortopathy in hypertrophic cardiomyopathy; the association with sinus of valsalva versus mid ascending aorta: an epidemiological study. *Journal of the American College of Cardiology.* 2016; 1): 1613.	1
2.	Al-Ghamdi B, Shafquat A, Mallawi Y. Arrhythmogenic right ventricular cardiomyopathy/dysplasia in Saudi Arabia: a single-center experience with long-term follow-up. *Annals of Saudi Medicine.* 2014; 34(5): 415-426.	3
3.	Barbara DW, Hyder JA, Behrend TL, Abel MD, Schaff HV, Mauermann WJ. Safety of noncardiac surgery in patients with hypertrophic obstructive cardiomyopathy at a tertiary care center. *Journal of Cardiothoracic and Vascular Anesthesia.* 2016; 30(3): 659-664.	3
4.	Besseling J, Hovingh GK, Huijgen R, Kastelein JJ, Hutten BA. Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality. *Journal of the American College of Cardiology.* 2016; 68(3): 252-260.	3
5.	Brescia ST, Rossano JW, Pignatelli R, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. *Circulation.* 2013; 127(22): 2202-2208.	3
6.	Chan SS, Chan DK, Pang SM, Lam ST, Lao TT, Choy KW. Urinary incontinence should be added to the manifestation in women with Marfan syndrome. *International Urogynecology Journal.* 2010; 21(5): 583-587.	3
7.	Chang KH, Sano E, Saitoh Y, Hanaoka K. Anesthetic management of patients with hypertrophic obstructive cardiomyopathy undergoing non-cardiac surgery. *Masui: The Japanese Journal of Anesthesiology.* 2004; 53(8): 934-942.	2
8.	Chong E, Lin YJ, Chen SA. Circadian and seasonal variations of cardiac arrest and ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy. *Europace.* 2013; 15: ii41.	1
9.	Collins RT, Fram RY, Tang X, Robbins JM, St John Sutton M. Hospital utilization in adults with single ventricle congenital heart disease and cardiac arrhythmias. *J Cardiovascular Electrophysiology.* 2014; 25(2): 179-186.	3
10.	Colquitt JL, Noonan JA. Cardiac findings in Noonan syndrome on long-term follow-up. *Congenital Heart Disease.* 2014; 9(2): 144-150.	3
11.	Cook C, Farber-Eger E, Wang T, Wells Q. Prevalence of clinically apparent hypertrophic cardiomyopathy in 32 patients with the GL a A143T mutation: implications for genetic screening for Fabry disease in patients with hypertrophic cardiomyopathy. *Journal of the American College of Cardiology.* 2015; 1): A953.	1
12.	Curry RA, Gelson E, Swan L, et al. Marfan syndrome and pregnancy: maternal and neonatal outcomes. *BJOG: An International Journal of Obstetrics and Gynaecology.* 2014; 121(5): 610-617.	3
13.	Dimas VV, Denfield SW, Friedman RA, et al. Frequency of cardiac death in children with idiopathic dilated cardiomyopathy. *American Journal of Cardiology.* 2009; 104(11): 1574-1577.	3
14.	Docimo R, Maturo P, D'Auria F, et al. Association between oro-facial defects and systemic alterations in children affected by Marfan syndrome. *Journal of Clinical Diagnostics Research.* 2013; 7(4): 700-703.	3

15.	Elizondo Lopez De Landache I, Braceras Izaguirre L, Gardeazabal Romillo MJ, Acevedo Heranz P. Prevalence of heterozygous familial hypercholesterolemia in the autonomous community of the Basque country. *Atencion Farmaceutica.* 2013; 15(6): 446.	1
16.	Groth KA, Hove H, Kyhl K, et al. Prevalence, incidence, and age at diagnosis in Marfan Syndrome. *Orphanet Journal of Rare Diseases.* 2015; 10: 153.	3
17.	Guerrero JCC, Jimenez-Baena E, Martinez-Martinez A, et al. Revisiting prognostic impact of atrial fibrillation in hypertrophic cardiomyopathy. *Journal of the American College of Cardiology.* 2016; 1: 1515.	1
18.	Harikrishnan P, Gupta T, Kolte D, et al. Association of arrhythmias with outcomes in patients with hypertrophic cardiomyopathy: an analysis of the Nationwide Inpatient Sample 2003-2011. *Journal of the American College of Cardiology.* 2015; 1): A296.	1
19.	Hassan N, Patenaude V, Oddy L, Abenhaim H. Pregnancy outcomes in Marfan's syndrome: a retrospective cohort study. *Obstetrics and Gynecology.* 2014; 123: 148S.	1
20.	Khouw NK, Wasim M, Uppal H, Chandran S, Potluri R. Predictors of mortality in patients with hypertrophic cardiomyopathy - a hospital admissions study: 2000-2013. *Global Heart.* 2014; 1): e271.	1
21.	Knickelbine T, Lui M, Garberich R, Miedema M, Strauss C. Under diagnosis and suboptimal treatment of familial hypercholesterolemia in a large ambulatory population. *Journal of the American College of Cardiology.* 2014; 1): A1380.	1
22.	Knickelbine T, Strauss C, Hauser R, Garberich R. Familial hypercholesterolemia in a large ambulatory population: use of the electronic record and relationship to clinical disease. *Journal of Clinical Lipidology.* 2013; 7 (3): 255-256.	1
23.	Leonardi RA, Townsend JC, Patel CA, et al. Alcohol septal ablation for obstructive hypertrophic cardiomyopathy: outcomes in young, middle-aged, and elderly patients. *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions.* 2013; 82(5): 838-845.	3
24.	Lipschultz SE, Sleeper LA, Towbin JA et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *New England Journal of Medicine.* 2003; 348(17): 1647-1655.	3
25.	Lipworth L, Shirey-Rice J, Wei WQ, et al. Identification and characterization of heterozygous familial hypercholesterolemia patients using the Vanderbilt University medical center synthetic derivative database. *European Heart Journal.* 2015; 36: 927.	1
26.	Manning S, Lanigan B, O'Keefe M. Outcomes after lensectomy for children with Marfan syndrome. *Journal of American Association for Pediatric Ophthamology and Strabismus.* 2016; 20(3): 247-251.	3
27.	McLeod CJ, Ommen SR, Ackerman MJ, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *European Heart Journal.* 2007; 28(21): 2583-2588.	3
28.	Oluleye O, Duval S, Jain R. Sex differences in heart failure hospitalizations in patients with hypertrophic cardiomyopathy. *Journal of the American College of Cardiology.* 2014; 1): A846.	1
29.	Rohatgi RK, Bos JM, Ackerman MJ. Stimulant therapy in children with attention-deficit/hyperactivity disorder and concomitant long QT syndrome: a safe combination? *Heart Rhythm.* 2015; 12(8): 1807-1812.	3
30.	Sikka P, Suri V, Aggarwal N, Chopra S, Bahl A, Vijayverghia R. Are we missing	3

	hypertrophic cardiomyopathy in pregnancy? Experience of a tertiary care hospital. *Journal of Clinical Diagnostic Research.* 2014; 8(9): OC13-15.	
31.	Soska V, Freiberger T, Cifkova R, et al. Plasma HDL-cholesterol and triglyceride levels in familial hypercholesterolemia: data from the MedPed CZ database and the Czech population. *International Journal of Clinical Chemistry.* 2011; 412(11-12): 920-924.	3
32.	Sze E, Moss AJ, Goldenberg I, et al. Long QT syndrome in patients over 40 years of age: increased risk for LQTS-related cardiac events in patients with coronary disease. *Annals of Noninvasive Electrocardiology.* 2008; 13(4): 327-331.	3
33.	Veselka J, Zemanek D, Jahnlova D, et al. Risk and causes of death in patients after alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *Canadian Journal of Cardiology.* 2015; 31(10): 1245-1251.	3
34.	Waddell-Smith KE, Li J, Smith W, Crawford J, Skinner JR, Cardiac Inherited Disease Group New Zealand. Beta-blocker adherence in familial long QT syndrome. *Circulation.* 2016; 9(8).	3

1 = conference abstract/editorial; 2 = non-English manuscript; 3 = inherited heart disease of interest not defined using routinely collected health data exclusively

Supplementary Table 5. Summary of reviewed studies

Study details[a]	Aim(s) and cohort details[b]	Relevant findings/conclusions[c]
Achelrod (2014) Germany 2006-2008	*Aim* Estimate health resource utilization and costs attributable to Marfan syndrome from sickness fund and societal perspectives *Condition and definition* Marfan syndrome: ≥1 ICD-10-GM inpatient diagnosis of Q87.4 or ≥2 ICD-10-GM diagnoses of Q87.4 as an outpatient within 180 days. *Cohort details* **A) Control** Enrolled in sickness fund continuously from 2007-2008 except due to death. Random selection of 150 males and females per age from 0 to 100 years then matched to B) by sex, age, pharmacy-based measures and comorbidities. N = 892; age (mean) = 28.9 years; 41% female **B) Marfan syndrome** Enrolled in sickness fund continuously from 2007-2008 except due to death; diagnosed with Marfan syndrome N = 892; age (mean) = 29.0 years; 41% female	**1)** Health resource utilization: compared to controls, Marfan syndrome cohort has 38.8% more physician contacts; 153.3% longer length of stay if hospitalized; 119.0% more inpatient stays; 33.4% more prescriptions; 236.3% more MRT/CTs; 19.7% higher average prescription costs *Sickness fund perspective (excess cost per capita)* **2)** Direct medical costs: in-patient and outpatient treatments, care by non-physicians, pharmaceuticals, devices/medical appliances, rehabilitation and medical services **A)** €1 695; **B)** €4 024 (€2 329 higher than control) **3)** Direct non-medical costs per capita: administration costs, sick leave costs, travel expenses for physician appointments, ambulance transport **A)** €226; **B)** €392 (€166 higher than control) *Societal perspective (excess cost per capita)* **4)** Direct medical costs: copayments for adults for outpatient consultations, pharmaceuticals, medical appliances, hospital stays and rehabilitation services **A)** €1 739; **B)** €4 105 (€2 366 higher than control) **5)** Direct non-medical costs: administrative costs, cost of informal care provided by family caregivers **A)** €1 556; **B)** €7 431 (€5 875 higher than control) **6)** Indirect costs: costs of being absent from work, premature death, reduced work productivity **A)** €2 842; **B)** €10 329 (€7 487 higher than control) *From a sickness fund perspective, the main drivers of cost for Marfan syndrome are inpatient treatment (accounts for 38.4% of costs), care by non-physicians (33.8%), outpatient visits (10.7%) and pharmaceuticals (5.8%)

		*Extrapolating costs to entire German population, the cost of Marfan syndrome ranged from €24-61 million (sickness fund perspective) to €151-387 million (societal perspective)
Carley (2000) Setting and observation period not specified	*Aim* Determine prevalence of urinary incontinence, pelvic organ prolapse and rectal prolapse in women with Marfan syndrome *Condition and definition* Marfan syndrome: ICD-9 code (not further specified) *Cohort details* **A) Marfan syndrome** Alive females with Marfan syndrome aged ≥18 years and available for telephone interview N = 12; age (mean, SD): 49±12 years; 100% female	**1)** Frequency of any urinary incontinence N = 5 (42%) **2)** Frequency of any pelvic organ prolapse N = 4 (33%) **3)** Frequency of rectal prolapse N = 0 (0%) *Females with Marfan syndrome have high rates of urinary incontinence and pelvic organ prolapse indicating connective tissue disorders may be a factor in the pathogenesis of these medical conditions
Chan (2008) Hong Kong, China 1997-2006	*Aim* Determine epidemiology and demographics of patients admitted to hospital with Marfan syndrome *Condition and definition* Marfan syndrome: hospitalized with cardiovascular disease (ICD-9-CM code not specified) *Cohort details* **A) Marfan syndrome** Patients with Marfan syndrome and hospitalized between 1997 and 2006 N = 525; age (mean): 18.7-19.8 years; 41% female	**1)** Frequency of aortoiliac aneurysm and/or aortoiliac dissection N = 112 (21.3%) **2)** Frequency of major cardiac or aortoiliac operations N = 49 (9.3%) **3)** Frequency of mortality in persons who had a major cardiac or aortoiliac operation N = 5/49 (10.2%) **4)** Frequency of beta-blockade medication use N = 128 (24.4%) *Aortoiliac aneurysm/dissection associated with a worse survival outcome *Persons taking beta-blockers have a worse survival outcome *Overall mortality over 10 years is 7%
Chiu (2014) Taiwan 2000-2012	*Aim* Explore epidemiological profile of persons with Marfan syndrome *Condition and definition* Marfan syndrome: ICD-9-CM diagnosis code of 759.82 *Cohort details* **A) Marfan syndrome** Admitted to	**1)** Number of deaths N = 69 (3.0%) **2)** Frequency of aortic dissection N = 226 (9.7%) **3)** Frequency of mortality after dissection

	hospital with Marfan syndrome or attended an outpatient clinic with Marfan syndrome ≥3 times N = 2 329; age details not specified; 42% female	N = 24 (10.6%) **4)** Frequency of cardiovascular intervention N = 360 (15.5%) *Average annual mortality rate was 0.23% *Significant predictors of death include: aortic dissection and emergent intervention *Likelihood of aortic dissection increased with age, particularly after age 20, but plateaued from 60 years *Age-specific prevalence was highest in persons aged 15-19 years likely due to progressively apparent clinical symptoms
Chothani (2016) US 2005-2011	*Aim* Evaluate post-procedural mortality, complications, length of stay and cost of hospitalisation following septal ablation (SA) *Condition and definition* HCM: ICD-9-CM diagnosis code of 425.1 *Cohort details* **A) HCM** ICD-9 procedure code of 37.34 for ablation of heart tissue in adult patients with HCM. Cases were excluded in patients with arrhythmia diagnosis or open surgical ablation procedure code; or, principal diagnosis is an SA-associated complication N = 358 procedures; age (mean, SD) 58.4±14.9 years; 58% female	**1)** Frequency of post-procedural mortality N = 0 (0%) **2)** Frequency of post-procedural complications N = 83 (23.2%) *≥1 comorbidities significant predictor of any post-surgical complication (OR: 3.62 95%CI: 1.32-9.92) increased length of hospital stay (1.32 days, 95%CI: 0.09-2.55) and increased hospitalisation costs ($9 521, 95%CI: 2 727-16 316) *Surgery at a hospital where a large volume of SA procedures occurred was protective against any post-surgical complication *62% of patients had a history of hypertension
Collins (2015) US 2004-2011	*Aim* Evaluate hospital resource utilization in patients with Marfan syndrome either with or without aortic aneurysm (AA) admitted to a pediatric hospital *Condition and definition* Marfan syndrome: ICD-9 diagnosis code of 759.82 as a principal or secondary diagnosis *Cohort details* **A) Aortic aneurysm** Patient admitted to pediatric hospital between 2004 and 2011 with ICD	**1)** Hospital length of stay (average number of days) **A)** 8.0±10.2 **B)** 7.4±15.1 **2)** Cost per hospital admission ($US) **A)** 118 117±156 949 **B)** 80 319±146 945 **3)** Cost per day in hospital ($US) **A)** 16 050±10 964 **B)** 12 694±11 408 **4)** Proportion of persons admitted to intensive care unit **A)** 66% **B)** 33%

	diagnosis code 759.82 and ICD-9 code 441.00-441.9 (diagnosis of aortic aneurysm with or without dissection or rupture) N = 188; age (mean, SD) 13.8±5.9 years; 37% female **B) No aortic aneurysm** A) but no ICD-9 code for AA dissection or rupture (441.00-441.9) N = 1 120; age (mean, SD) 11.8±6.7 years; 43% female	**5)** Proportion of persons requiring mechanical ventilation **A)** 40% **B)** 14% **6)** Proportion of persons requiring an operating room **A)** 67% **B)** 52% **7)** Frequency of cardiac diagnosis associated with admission **A)** 71% **B)** 44% **8)** Frequency of common cardiac procedures in admissions **A)** 29% **B)** 7% **9)** Frequency of common cardiothoracic procedures in admissions **A)** 53% **B)** 21% **10)** Frequency of common vascular procedures in admissions **A)** 9% **B)** 1% *Aortic aneurysm with dissection occurs in 0.75% of admissions *It appears that aortic aneurysm is a marker for more severe cardiovascular phenotype in Marfan syndrome
Hassan (2015) US 2003-2010	*Aim* Evaluate pregnancy and cardiovascular outcomes in pregnant women with Marfan syndrome *Condition and definition* Marfan syndrome: ICD-9 code diagnosis of 759.82 *Cohort details* **A) Control** ICD-9 code for a birth between 2003 to 2010 N = 7 094 061; 34% aged <25 years, 54% aged 25-34 years, 12% aged ≥35 years; 100% female **B) Marfan syndrome** A) plus ICD-9 code for Marfan syndrome N = 339; 47% aged <25 years, 46% aged 25-34 years, 7% aged ≥35 years; 100% female	*Maternal delivery outcomes (reference group is cohort A; adjusted OR [aOR], 95%CI)* **1)** Use of forceps: 6.35 (4.10-9.83) **2)** Use of vacuum: 2.01 (1.36-2.96) **3)** Caesarean section: 1.91 (1.53-2.38) **4)** Spontaneous vaginal delivery: 0.36 (0.29-0.45) *Fetal outcomes (reference group is cohort A; aOR, 95%CI)* **5)** Fetus being small for gestational age: 2.06 (1.24-3.43) **6)** Fetus weight <500 grams: 1.95 (1.13-3.35) **7)** Pre-term birth (prior to 37 weeks): 2.15 (1.60-2.89) *Maternal morbidity/mortality outcomes (reference group is cohort A; aOR, 95%CI)* **8)** Maternal death: 22.38 (2.92-171.81) **9)** Aortic repair: 42.54 (3.62-500.33) **10)** Pneumothorax: 51.95 (6.18-437.10) **11)** Hospital stay ≥6 days: 2.79 (1.93-4.04)

		*No statistically significant differences between groups for maternal pregnancy outcomes during antepartum or intrapartum periods
Hreybe (2006) US 1996-2002	*Aim* Evaluate the incidence of acute myocardial infarction (MI) and all-cause, in-hospital mortality following noncardiac surgery in patients admitted to hospital with a diagnosis of HCM. *Condition and definition* HCM: ICD-9-CM diagnosis code of 425.1 *Cohort details* **A) Control** Patients admitted to hospital b/w 1996 and 2002; matched to B) based on age, sex, year of surgical procedure on a ratio of 2 controls: 1 HCM patient. Exclude patients with either no cardiac or surgical procedures performed; patients with MI as a primary diagnosis; or, ICD-9-CM procedure codes ≥8700 rather than surgical procedures. N = 554; age (mean, SD): 68.8±17.4 years; 68% female **B) HCM** A) without matching and diagnosed with HCM N = 227; age (mean, SD): 67.6±18.8 years; 62% female.	**1)** Frequency of death **A)** 2.5% **B)** 6.7% **2)** Frequency of myocardial infarction **A)** 0.3% **B)** 2.2% **3)** Frequency of death or myocardial infarction **A)** 2.7% **B)** 8.8% **4)** Frequency of death or myocardial infarction in low-risk surgeries **A)** 2.9% **B)** 10.6% **5)** Frequency of death or myocardial infarction in high-risk surgeries **A)** 1.1% **B)** 16.4% *After controlling for age, sex, race, presence of hypertension, diabetes mellitus, history of coronary artery disease, history of CHF, atrial fibrillation and ventricular arrhythmias; presence of HCM increases odds of death by 61% (OR 1.61) and odds of death or MI by 182% (OR 2.82). *Absolute mortality rate is 4.2% higher in patients with HCM compared to controls.
Kim (2016) US 2003-2011	*Aim* Evaluate trends, characteristics and in-hospital outcomes after septal myectomy (SM) and alcohol septal ablation (ASA) and examine the association between institutional procedural volume and outcomes after each procedure. *Condition and definition* HCM: ICD-9-CM diagnosis code of 425.1 as a primary diagnosis *Cohort details* **A) Septal myectomy** ICD-9-procedure code 36.33 in any procedure field and adults with HCM as primary diagnosis. N = 6 386; age (mean) 55.7-59.9 years; 58% female.	**1)** Annual rate of surgeries (2003 to 2011) **A)** SM surgeries decreased by 24.5% (2 to 1.51 procedures/1 million persons/year) **B)** ASA procedures increased by 56.2% (1.6 to 2.49 procedures/1 million persons/year) **2)** Patient- and institution factors associated with procedure and outcomes **A)** Persons with procedures at high volume SM procedure centers were more likely to be younger and undergo concomitant coronary artery bypass graft valve operations. High volume centers are more likely to be larger and teaching institutions. Compared to low

	B) Alcohol septal ablation ICD-9-procedure code 36.34 in any procedure field and adults with HCM as primary diagnosis. N = 4 862; age (mean) 59.2-62.4 years; 53% female.	volume centers, procedures are associated with shorter length of stay and lower costs **B)** High volume ASA procedure centers are more likely to be larger and teaching institutions; compared to low volume centers, procedures are associated with shorter length of stay and lower costs **3)** Complications post SM (OR, 95%CI): compared to high volume centers, procedures occurring at low volume centers associated with increased odds of all-cause mortality (3.11, 1.98-4.89) and bleeding complications (3.77, 2.12-6.70) **4)** Median length of hospitalisation **A)** 7.0 days **B)** 3.0 days *SM procedures had 2.3 times higher median hospital costs compared to ASA *Majority of US hospitals performing SM or ASA procedures are below the threshold recommended by guidelines
Panaich (2014) US 1998-2010	*Aim* Evaluate post-surgical outcomes of ventricular septal myectomy (VSM) and examine potential predictors of post-operative outcomes and resource utilization. *Condition and definition* HCM: ICD-9-CM diagnosis code of 425.1 *Cohort details* **A) HCM** ICD-9-CM procedure code 37.33 (for VSM) and HCM. Exclude cases with ICD-9-CM code for a specific complication listed as a principal diagnosis. N = 665 procedures; age (mean, SD): 56.9±0.6 years; 60% female	**1)** Rate of post-procedural complications **A)** N = 201 (30.2%) **2)** Rate of post-procedural mortality **A)** N = 39 (5.9%) *Predictors of mortality or complications (OR, 95%CI): age (1.04, 1.01-1.07) and at least one comorbidity (2.41, 1.17-4.98) *Predictors of increased cost of hospitalisation and length of stay: any complication increased the average length of stay by 6.08 days (mean: 8.89 days) and the cost by $33 870 (mean: $41 175±1 611) *****Most common cardiac complications include iatrogenic cardiac complications (10.5%) and complete heart block requiring pacemaker insertion (8.7%)
Roll (2012) Germany 2004-2009	*Aim* Investigate the association between regional availability of healthcare resources on health care quality based on data for Marfan syndrome.	**1)** Mean Elixhauser comorbidity score **A)** 2.33 **B)** 6.15 **2)** Number of physicians visits in 3 months prior to symptom onset

	Condition and definition Marfan syndrome: ≥1 ICD-10-GM inpatient diagnosis code of Q87.4 OR ≥2 outpatient diagnoses within 6 months. *Cohort details* **A) Immediate diagnosis** Continuously enrolled in fund for ≥3 years prior to Marfan syndrome diagnosis; diagnosed same day as first Marfan syndrome symptom presentation. Excluded persons if postcode changed in observation period or multiple postcodes recorded at one time. N = 174; age (mean, SD): 23.7±14.1 years; 41% female **B) Delay in diagnosis** A) except diagnosed after first day of Marfan syndrome symptoms presenting. N = 215; age (mean, SD): 24.8±16.0 years; 38% female	**A)** 11.78 **B)** 19.57 *Persons living in an area of increased density of specialists were more likely to have a delay in diagnosis; however results were not statistically significant *Mean days to diagnosis: 607 days (median: 641 days; maximum: 1 095 days) *Distance to healthcare centers was not associated with immediacy of diagnosis
Takiguchi (2016) Hawaii, US 2000-2013	*Aim* Assess the prevalence of diagnosed conditions associated with sudden cardiac death (SCD) among infants and children. *Condition and definition* ARVC: ICD-9 diagnosis code of 425.4; BrS: ICD-9 diagnosis code of 746.89; CPVT: ICD-9 diagnosis code of 427.1; HCM: ICD-9 diagnosis code of 425.18; long QT syndrome: ICD-9 diagnosis code of 426.82; LVNC: ICD-9 diagnosis code of 425.4. *Cohort details* **A) SCD in children** Person aged 0-18 years at time of SCD; SCD occurred between 2000 and 2013 inclusive. N = not reported; age: not reported; sex: not reported.	**1)** Children diagnosed with a condition associated with sudden cardiac death **A)** N = 51 **2)** Diagnosed with cardiomyopathy **A)** N = 28 (55%); 13 (46%) diagnosed with HCM and 7 (25%) diagnosed with dilated cardiomyopathy **3)** Diagnosed with channelopathy **A)** N = 21 (41%); 20 (95%) diagnosed with long QT syndrome and 1 (5%) diagnosed with Brugada syndrome *HCM and LVNC were most the commonly diagnosed cardiomyopathies *No sudden infant death syndrome (SIDS) cases were diagnosed with a condition associated with SCD *No children were diagnosed with CPVT

95%CI = 95% confidence interval; AA = aortic aneurysm; aOR = adjusted odds ratio; ARVC = arrhythmogenic right ventricular tachycardia; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; CT = computerized tomography; HCM = hypertrophic cardiomyopathy; ICD = International Statistical Classification of Diseases and Related Health Problems; CM = clinical modification; GM = German

modification; LVNC = left ventricular noncompaction; MI = myocardial infarction; MRT = magnetic resonance tomography; OR = odds ratio; SA = septal ablation; SD = standard deviation; SM = septal myectomy; VSM = ventricular septal myectomy.

[a]First author surname (publication year); setting; observation start and final year

[b]Aim(s); cohort inclusion criteria; cohort demographics

[c]For studies that conducted statistical analyses, we only report statistically significant results

Supplementary Table 6 Assessment of study quality: Strengthening in Observational studies in Epidemiology (STROBE) checklist for observational studies

Item #	Description of item	Number of studies reporting item (%)[a,b]
1a	Indicate study design with a commonly used term in title or abstract	5 (42)
b	Abstract has an informative and balanced summary of methods and results	12 (100)
2	Explains the scientific background and rationale for the investigation being reported	12 (100)
3	States specific objectives, including any pre-specified hypotheses	11 (92)
4	Presents key elements of study design early in the paper	4 (33)
5a	Describes the: setting	12 (100)
b	Region	11 (92)
c	Relevant dates: including periods of recruitment, exposure, follow-up and data	11 (92)
6a	Gives the eligibility criteria; sources and methods of selection of participants; describes methods of follow up	12 (100)
b	For matched studies, gives matching criteria and number of exposed and unexposed	2/2 (100)
7	Clearly defines all outcomes, exposures, predictors, potential confounders, and effect modifiers; gives diagnostic criteria if applicable	11 (92)
8	For each variable of interest, gives data sources and details of methods of assessment	12 (100)
9	Describes any efforts to address potential sources of bias	4 (33)
10	Explains how the study size was arrived at	3 (25)
11	Explains how quantitative variables were handled in the analyses; if applicable, describes which groupings were chosen and why	11 (92)
12a	Describes all statistical methods	12 (100)
b	Describes any methods used to examine subgroups and interactions	5 (42)
c	Explains how missing data were addressed	1 (8)
d	Explains how loss to follow-up was addressed	5 (42)
e	Describes any sensitivity analyses	2 (17)
13a	Reports the number of individuals at each stage of study	4 (33)
b	Give reasons for nonparticipant at each stage	2 (17)
c	Considers use of a flow diagram	0 (0)
14a	Gives characteristics of study participants and information on exposures and potential confounders	11 (92)
b	Indicates the number of participants with missing data for each variable of interest	2 (17)
c	Summarizes follow-up time	0 (0)
15	Reports numbers of outcome events or summary measures over time	11 (92)
16a	Gives unadjusted estimates and, if applicable, confounder-	7/11 (64)

	adjusted estimates and their precision	
b	Reports category boundaries when continuous variables were categorized	7/7 (100)
c	If relevant, considers translating estimates of relative risk into absolute risk for a meaningful interval	0/0 (0)
17	Reports other analyses done	8 (67)
18	Summarizes key results with reference to study objectives	12 (100)
19	Discusses limitations of the study, taking into account sources of potential bias or imprecision	11 (92)
20	Gives a cautious overall interpretation of results	10 (83)
21	Discusses generalizability of study results	10 (83)
22	Gives funding sources	4 (33)

[a] Every item subcategory is worth one point; maximum score = 36

[b] Denominator = 12 unless otherwise specified

Supplementary Figure 1 Initial data extraction form: eligibility criteria

*Reviewer initials:*_____

Defining IHD in RCD systematic review: initial data extraction

PAPER DETAILS
First author surname:_____
Year of publication: 20_____

INCLUSION CRITERIA: answer yes (Y) or no for each question below.	**Y/N**
1. Does the manuscript include original research?	
2. Is the manuscript written in English?	
3. Is the manuscript published between January 2000 and October 2016?	
4. Is routinely collected data used to identify an inherited heart condition? If yes, specify dataset(s):_____ And condition(s):_____	
5. Is routinely collected data used exclusively to define condition of interest? *Answer no if any measurements of the heart are included in the definition, e.g. physical or functional test results such as echocardiogram or electrocardiogram results.*	

Routinely collected data definition: data obtained for administrative and clinical purposes without specific a priori research goals.

INCLUDE IN SECOND DATA EXTRACTION?

- ○ **Y** – if answered 'yes' to questions 1 through 5
- ○ **N** – if answered 'no' to any question from 1-5

Study inclusion criteria:

- Study includes original research and published in a peer-reviewed journal
- Study published between 2000 and October 2016
- Study manuscript written in English language
- Study defines an inherited heart disease using routinely collected data alone

Supplementary Figure 2 Main data extraction tool

*Reviewer initials:*_____

Defining IHD in RCD systematic review: Main data extraction

1. BIBLIOGRAPHIC DETAILS

First author surname:_____ Year of publication: 20___

Journal:_____

Study funding source (tick all that apply): ___ Grant (government/research)

___ No funding ____ Not recorded Other: _____

Study location(s) – State and country:_____

2. STUDY AIM AND CONDITION(S) OF INTEREST:

Aim of study (verbatim):_____

_____

_____

_____

_____

Inherited heart condition(s) of interest: ___ ARVC ___ Bicuspid valve disease

___ BrS ___CPVT ___ FDC ___ FH ___ Familial restrictive cardiomyopathy

___ HCM ___ LVNC ___ Long QT ___ Marfan Syndrome

3. ROUTINELY COLLECTED DATA DETAILS

Number of datasets used to define inherited heart disease population:_____

Type of dataset(s) used: ___ Medical records ___ Hospitalisation

___ Health insurance ___ Other:_____

Name of dataset(s) used to define inherited heart disease population:

_____

Study observation period (report first and last year of observation):

_____

1

*Reviewer initials:*_____

Definition of inherited heart condition: _____

_____

Data coverage: ____ National ___ Single state/province

___Multiple states/provinces ___ Other:_____

Data enhancements: Was additional information linked to the routinely collected data? ___ Yes ____ No

Were any family members linked to persons with IHD? ___ Yes ____ No

4. COHORT DETAILS

Number of cohorts reported in study (including any comparison groups):_____

*Cohort 1: Name*_____ *Number of people:*_____

Cohort inclusion/exclusion criteria: _____

_____

_____

Age: _____ ___ Mean (SD) ___ Median (range) Sex: ___% female

*Cohort 2: Name*_____ *Number of people:*_____

Cohort inclusion/exclusion criteria: _____

_____

_____

Age: _____ ___ Mean (SD) ___ Median (range) Sex: ___% female

*Cohort 3: Name*_____ *Number of people:*_____

Cohort inclusion/exclusion criteria: _____

_____

_____

Age: _____ ___ Mean (SD) ___ Median (range) Sex: ___% female

*Reviewer initials:*_____

5. OUTCOMES/RESULTS

Describe the primary outcome measure (related to inherited heart disease):

_____

_____

Result: _____

_____

Describe any relevant secondary outcome measures (related to inherited heart disease): _____

_____

Result: _____

_____

Describe any relevant secondary outcome measures (related to inherited heart disease): _____

_____

Result: _____

_____

Describe any other relevant findings/conclusions (related to inherited heart disease):

_____

_____

_____

_____

_____

_____

3