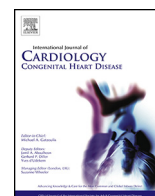


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The 100 most influential articles in congenital heart disease in 2000–2020: A bibliometric analysis



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ABSTRACT

Background: Congenital heart disease (CHD) is the most common type of major congenital malformations. CHD outcomes have improved in the past 20 years, and research efforts in the field have increased exponentially. The purpose of this investigation is to identify the most influential recent publications related to CHD, and reveal their shared features using bibliometric analysis.

Methods: Journal articles related to CHD published between 2000 and 2020 were retrieved from the Scopus database. In order of citation frequency, the 100 most-cited clinical original articles overall, the 20 most-cited clinical original articles of the years 2018–2020, and the top 10 most-cited review articles were compiled. The lists were analyzed to identify characteristics of highly cited publications. VOS Viewer was used to construct and visualize network maps based on co-authorship and co-occurring keywords.

Results: The total number of citations varied from 244 to 1741, and the number of citations per year varied from 13.2 to 121.9. Articles were most commonly published in *Circulation*, *Journal of the American College of Cardiology*, or *Journal of Thoracic and Cardiovascular Surgery*. Most originated from the USA, and had a sample size of 200 patients or less. A total of 46 authors had at least 3 publications among the list and were organized in 6 collaboration clusters. Tetralogy of Fallot, atrial septal defect, the perinatal period, Fontan, and cardiac surgery were identified as major areas of research.

Conclusions: This bibliographic analysis mapped two decades of research in CHD, highlighting important articles and defining major areas of research.

1. Introduction

Congenital heart disease (CHD) is the most common type of major congenital malformations, affecting approximately 1% of live births worldwide [1]. Of the estimated 30,000 to 40,000 children born with CHD in North America each year, one quarter require intervention in the first year of life [2]. Before cardiopulmonary bypass methods were established and CHD emerged as a subspecialty, most complex congenital heart defects were lethal. However, advances in cardiac surgery, cardiac

imaging, intensive care medicine, and interventional cardiology have resulted in better survival for children born with CHD. As a consequence, demographic shifts have occurred, so adult patients with CHD now outnumber children even with complex forms of CHD [3]. In the past two decades, further research efforts and clinical applications have been directed toward reducing CHD-associated mortality and morbidity.

Bibliometric analysis enables qualitative and quantitative evaluation of scientific literature, and allows assessment of productivity within specific areas. It can also reveal potential gaps in the current

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understanding of fields such as CHD. The purpose of this study was to evaluate the focus and recent direction of research in CHD using bibliometric analysis to identify the 100 most influential articles in CHD published between 2000 and 2020.

2. Methods

A bibliometric analysis of top-cited original clinical articles on CHD published between 2000 and 2020 was undertaken. Methods were adapted from a bibliometric analysis by O’Keeffe et al. [4]. All journals from Elsevier’s Scopus were eligible for inclusion, irrespective of country of origin, language, medical specialty, and the availability of articles or abstracts in electronic formats. Scopus was chosen as the source database because it has the widest coverage of publications in medicine, including over 22,000 of the most-cited journals in the world.

2.1. Main analyses

Relevant articles were retrieved from Scopus on January 12, 2021 using the following pre-formulated search string: TITLE-ABS-KEY (((“pediatric” OR “paediatric”) AND (“cardiology” OR “cardiac surgery”)) OR “congenital heart” OR “congenital cardiac” OR “tetralogy of fallot” OR “atrial septal defect” OR “ventricular septal defect” OR “atrioventricular septal defect” OR “ebstein anomaly” OR “fontan” OR “univentricular heart” OR “transposition of the great arteries” OR “truncus arteriosus” OR “tricuspid atresia” OR “coarctation of the aorta” OR “patent ductus arteriosus” OR “anomalous pulmonary venous return” OR “pulmonary atresia” OR “hypoplastic left heart” OR “interrupted aortic arch” OR “eisenmenger” AND PUBYEAR>1999 AND PUBYEAR<2021.

The 92,391 articles retrieved using this search were subsequently sorted by number of citations. From these, citation information from the 200 most-cited articles (including author name(s), publication year, journal name, and number of citations) were compiled in a single dataset. Articles were included if they presented original clinical research about CHD. All preclinical original articles and non-original articles on CHD, including review articles, meta-analyses, guidelines, consensus statements, statistics updates, conference abstracts, editorials, letters, news reports, and book reviews, were excluded. Articles that did not specifically focus on CHD were also excluded. Each article was independently screened for inclusion eligibility by two researchers. Differences in opinion regarding article inclusion were resolved by consensus among all study authors. This process was repeated until the 100 most-cited clinical original articles on CHD had been identified.

The final dataset contained the following elements: title, abstract, authors, number of authors, country of origin, number of institutional affiliations, collaborative authorship, publication date, journal, total Scopus citations, times cited per year, study design, sample size, study population, age group, topic, and keywords. Data were independently extracted by two researchers. Differences in opinion were resolved by consensus among all study authors.

The VOS Viewer Program (Leiden University, Leiden, The Netherlands), scientific software for visual representation of bibliometric analysis, was used to construct and visualize network maps based on co-authorship and co-occurring keywords of retrieved publications. Network maps show different parameters using nodes of differing colors linked by connecting lines. Node size is determined by number of documents, while the thickness of connecting lines represents “link strength”, a numerical value proportional to the number of publications that two researchers have co-authored or the number of publications that have reported the same keyword.

2.2. Sensitivity analyses

To overcome an inherent limitation of bibliographic analyses, where more recent (but similarly impactful) articles have not yet accrued high

numbers of citations, we performed a sensitivity analysis. A search was performed using the same terms as in the original analysis of 100 articles, but using a more recent time period (2018–2020). The 12,877 results of this search were subjected to eligibility screening in the same manner as the 2000–2020 dataset. The top 20 most-cited original clinical articles were identified and analyzed. In addition, the 10 most-cited review articles (2000–2020) were listed and are presented separately.

3. Results

3.1. Clinical articles

3.1.1. Article characteristics

The 100 most-cited original clinical articles are presented in Supplementary Material, Table S1, together with their total number of citations and average number of citations per year. The average number of citations per year ranged from 13.2 to 121.9, with mean \pm standard deviation 28.3 ± 17.4 , and median 23.6. To determine whether a linear correlation existed between the average number of citations per year and the cumulative total number of citations, both parameters were logarithmically transformed and a scatterplot was generated (Supplementary Material, Fig. S1). Spearman’s rank correlation coefficient between the average number of citations per year and the total number of citations was 0.677 ($p < 0.001$), suggesting a moderately strong linear correlation.

The 100 most-cited articles were published within the period from 2000 to 2014. Fig. 1A presents the distribution of the number of articles per year. Approximately a third (34 articles) were published within a continuous 3-year period between 2000 and 2002, with a further 41 articles published between 2004 and 2008. The articles were distributed across 22 different journals (Fig. 1B), with *Circulation* containing more than a third (35 articles), followed by *Journal of the American College of Cardiology* (19 articles) and *The Journal of Thoracic and Cardiovascular Surgery* (8 articles).

3.1.2. Author characteristics

There were 709 unique authors contributing to the 100 most-cited articles. The 10 most-cited authors contributed a total of 35 articles. The number of authors per paper ranged from 2 to 28, with a mean of 9.2; 71 articles had 6 or more authors (Supplementary Material, Table S2). In 12 articles, collaborative authorship was used. Mean number of institutional affiliations was 4.2. The greatest number of publications originated from the USA (44 articles) or from multi-national groups (25 articles).

Fig. 2 presents a network map of collaboration among authors with a minimum of 3 publications included in the 100 most-cited articles. The visualization shows 46 authors distributed in 6 clusters, each cluster with a unique color representing a close working network.

3.1.3. Study characteristics

The characteristics of the studies included in the 100 most-cited articles are described in Supplementary Material, Table S3. These publications covered a broad range of congenital cardiac conditions, with tetralogy of Fallot (14 studies), populations undergoing cardiac surgery (9 studies), hypoplastic left heart syndrome (6 studies), and atrial septal defect (5 studies) being the most well-represented. In 37 papers more than one type of CHD was studied. Half of the studies included adult subjects, while children were included in 42 studies, infants in 22, neonates in 9, and fetuses in 4. Retrospective cohort was the most common study design (40 studies), followed by prospective cohort (28 studies) and cross-sectional study design (11 studies). A total of 34 studies included between 1 and 199 patients with CHD, whereas more than 1000 patients were included in 18 studies.

To identify major topics of research, we performed two additional analyses. First, we manually assigned a topic to each study. Two independent reviewers each assigned 3 descriptive terms to each study, that were considered as being representative for the study content. Subsequently, from these descriptive terms, the reviewers decided about one

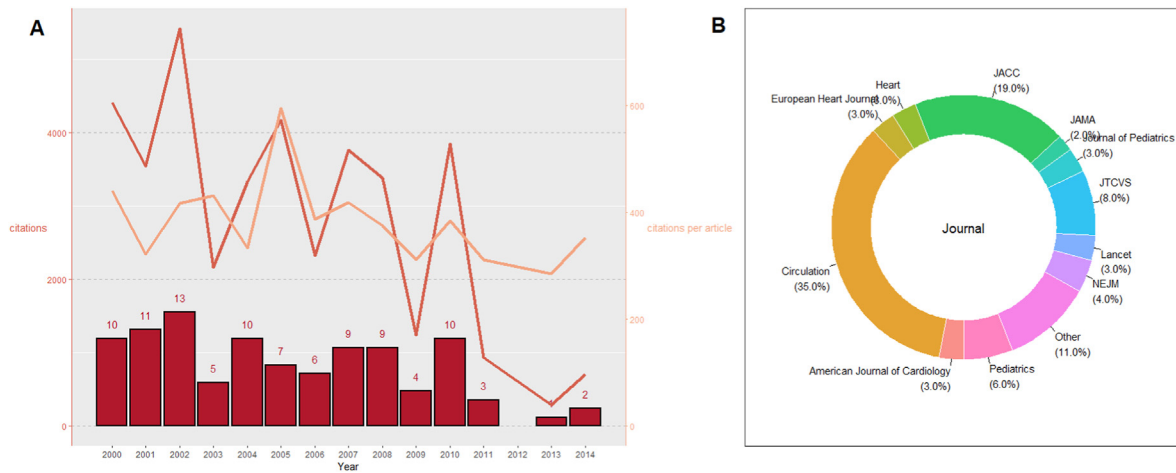


Fig. 1. (A) Number of articles (red bars), citations (red line), and citations (orange line) per article for each year. (B) Donut chart with the distribution of journals for the 100 most-cited articles. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

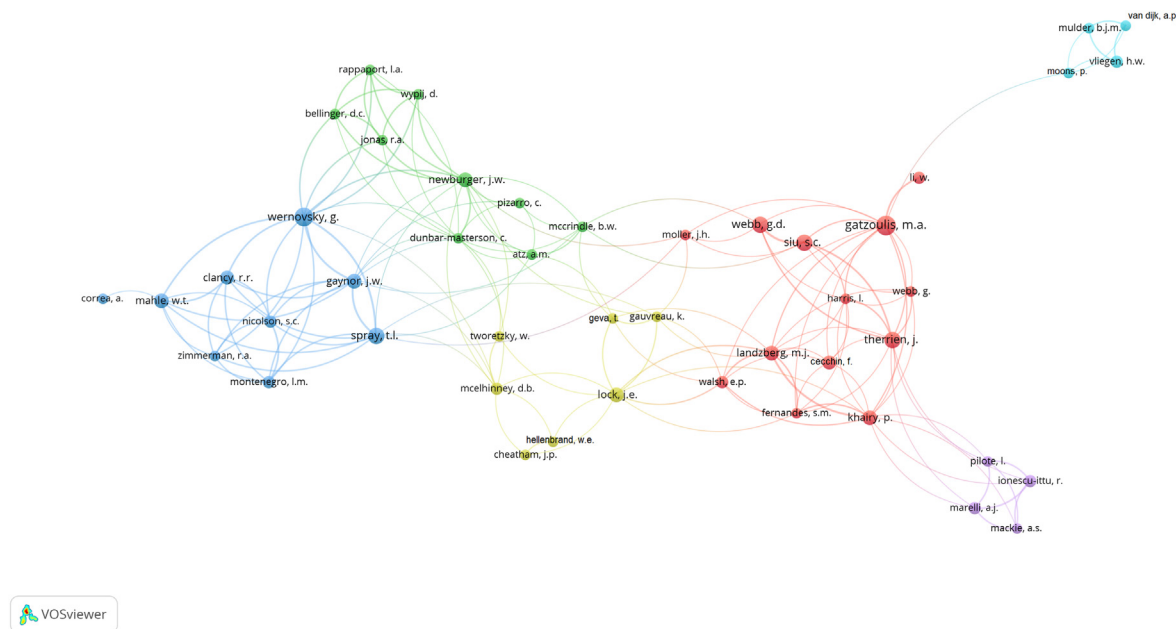


Fig. 2. Network visualization map of collaboration among authors in the 100 most-cited articles. All authors with a minimum of 3 publications are shown in the map. Node size is determined by number of documents, while the thickness of connecting lines represents “link strength”, which is a numerical value proportional to the number of publications that two researchers have co-authored. The same colors represent researchers from one cluster. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

term that was considered as the study “topic” based on its co-occurrence in multiple studies and its relevance. This revealed that most studies looked at long-term outcomes, survival and mortality data (18 studies), neurodevelopmental outcome (11 studies), perioperative/surgical considerations (11 studies), epidemiology (9 studies), and pulmonary valve replacement (9 studies). Second, a network map of the co-occurrence of keywords with minimum occurrence of 5 times was generated (Fig. 3). The visualization shows 68 keywords distributed in 5 clusters: tetralogy of Fallot, atrial septal defect, perinatal period, Fontan, and cardiac surgery (Supplementary Material, Table S4).

3.2. Sensitivity analysis

The top 20 most-cited original clinical articles on CHD published from 2018 to 2020 are listed in Supplementary Material, Table S5. A description of the bibliometric analysis for these articles is given in

Supplementary Material, Tables S6 and S7.

3.3. Review articles

Based on the same search strategy as in the original analysis of 100, the most-cited review articles were selected. The top 10 review articles in CHD are shown in Supplementary Material, Table S8.

4. Discussion

This study was conducted to analyze article, author and study characteristics, as well as collaborations between authors and major areas of research in CHD. Collectively, our bibliographic analysis mapped two decades of research in CHD, providing an overview of the 100 most influential original clinical articles published in this period. There were 5 major topics revealed by the network map of keywords: tetralogy of

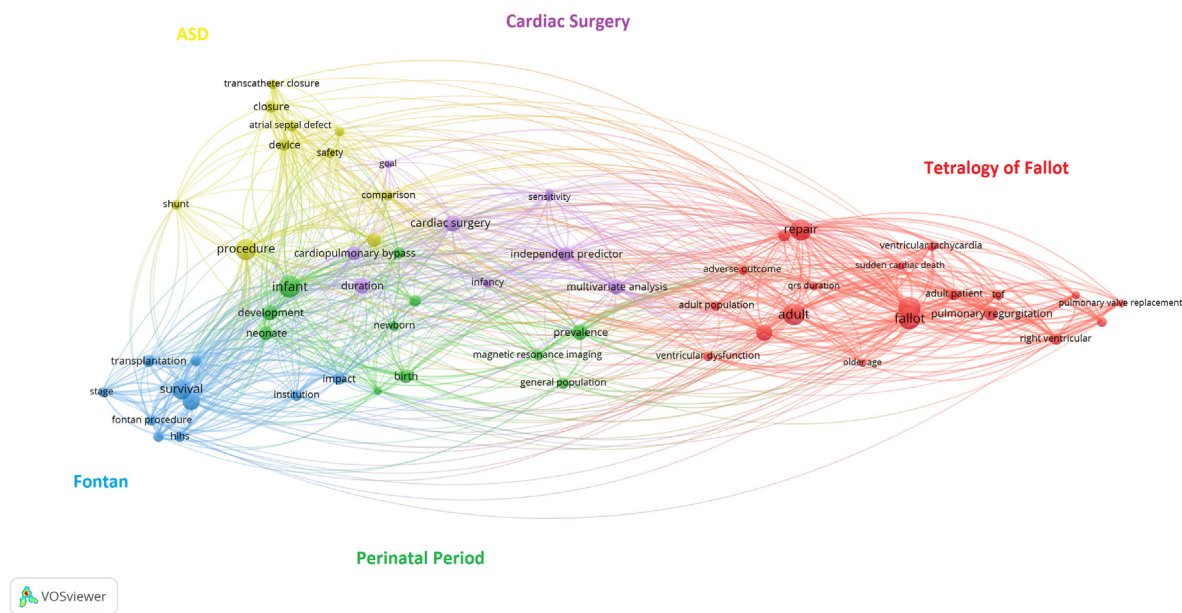


Fig. 3. Network visualization map of co-occurrence of keywords. Keywords with minimum occurrence of 5 times are shown in the map. Node size is determined by number of documents, while the thickness of connecting lines represents “link strength”, which is a numerical value proportional to the number of publications that have reported the same keyword. Keywords with the same color are closely related and form 5 main clusters together. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fallot, atrial septal defect, perinatal period, Fontan, and cardiac surgery.

4.1. Tetralogy of fallot

Surgical management of tetralogy of Fallot (ToF) has a long history, starting with palliation using the pioneering Blalock-Thomas-Taussig shunt in 1944. It was also the first complex lesion to undergo successful open repair, so the care for patients tetralogy of Fallot (ToF) has had time to evolve significantly [5]. Surgical mortality at initial repair is now less than 3%, but it is becoming increasingly clear that many survivors are hemodynamically compromised and carry an elevated risk of heart failure, arrhythmia, and sudden cardiac death [6].

Pulmonary valve replacement reduces arrhythmia risk [7] and favorably influences ventricular morphology and function [8], yet optimal timing of the procedure remains an important matter of debate [9,10]. Nine publications on this topic are found on the list, emphasizing the importance of pulmonary valve management in ToF and introducing hope that transcatheter valve replacement procedures will reduce the surgical burden for patients with ToF [11]. Other research efforts have been dedicated to predicting late-onset ventricular tachyarrhythmias and developing evidence-based indications for implantable cardioverter [12]. Work continues to gain better understanding of pathophysiology and its association with functional impairment, to develop risk assessment tools such as magnetic resonance imaging with late gadolinium enhancement [13], and to mitigate risk through valve-sparing primary repair.

4.2. Atrial septal defect

Atrial septal defect (ASD) accounts for approximately 10% of all CHD [1]. Surgical ASD closure has, for most of the 45 years it has been in use, been the preferred treatment for patients with secundum ASD [13]. More recently, transcatheter ASD occlusion has become an accepted therapeutic procedure for selected patients. The widely used Amplatzer septal occluder has demonstrated low complication rates and shorter hospital length of stay when compared to surgical repair [13,14].

Three of the studies included in our list investigated early and late complications associated with catheter-mediated ASD closure [14–16].

Chessa et al. [15] demonstrated that 34 (8.2%) out of 417 patients receiving an ASD occlusion device experienced complications during hospitalization, including device malposition, device embolization, pericardial effusion, and thrombus formation. Moreover, data by Krumsdorf et al. [16] show that thrombus formation might occur until up to 6 months after the procedure in 1.2%. The risk of late thrombus forming on the implant, systemic embolization, and, most concerning, sudden death, therefore require ongoing investigation. Proper patient selection and physician experience are critical to safe and effective transcatheter ASD closure, so better screening techniques to establish device candidacy are needed. These will require more definitive identification of risk factors for device failure.

4.3. Perinatal period

This broad category includes a diverse collection of publications representing 4 major topics: (1) Prenatal CHD diagnosis; (2) Postnatal patent ductus arteriosus; (3) Neurodevelopmental consequences of CHD surgery early in infancy; (4) Childbearing risks among women with CHD. With improvements in prenatal diagnosis, the field of congenital cardiology now includes fetal life. Detection of CHD before birth presents opportunities for fetal interventions and facilitates planning for care of the child with CHD at delivery, which promotes survival and reduces morbidity [17,18]. Nonetheless, fetal CHD detection rate remains low and overall diagnostic accuracy is imperfect and dependent on the type of CHD [19].

Patent ductus arteriosus (PDA) frequently complicates the clinical course in premature infants. Often causing a substantial left-to-right shunt, PDA increases the risk of intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and death [20]. Treatment is evolving from the prostaglandin inhibitor indomethacin to ibuprofen, which exhibits similar efficacy with less oliguria [21], and percutaneous [22] or surgical [23] closure.

Eleven articles in our list were related to neurodevelopmental impairment in infants undergoing surgery to correct CHD, highlighting how great this concern remains. Mild ischemic lesions of the brain occur frequently in postoperative patients [24], but not all neuropathology is surgical in origin. In fact, abnormalities of brain size, structure, and

function are found in a substantial proportion of third-trimester fetuses with CHD, suggesting antenatal factors contribute to childhood neurodevelopmental morbidity [25].

Research interest in perinatal consequences of CHD is not limited to the newborn members of the maternal-fetal dyad. Cardiac, obstetric, and neonatal complication rates are considerable in pregnant women with CHD. In particular, cyanotic CHD, left heart obstruction, ventricular dysfunction, and severe pulmonary regurgitation have been associated with adverse outcomes [26,27]. Recognizing the vulnerability of these expectant mothers, a multidisciplinary approach is now recommended for women with CHD contemplating pregnancy.

4.4. Fontan

The Fontan procedure was first described in 1971 as a means to palliate pediatric patients with univentricular hearts [28]. Fifty years later, the Fontan procedure is now a mainstay in the management of left or right ventricular hypoplasia, atrioventricular or semilunar valve atresia, and other complex congenital heart conditions. Outcomes are, however, not ideal, so efforts to study and improve the procedure are featured in 11 articles on our most-cited list.

In recent years, hospital survival rates have improved for operations intended to prepare for eventual Fontan [29,30]. Despite this success and improved acute survival for the Fontan itself, a discouraging proportion of patients experience late failure of the Fontan circulation, with 70% freedom from failure rate at 20 years [28]. Nearly half of all patients experience a major adverse event within 15 years post-Fontan [31]. These patients are at risk of cardiovascular complications, including supraventricular arrhythmias, thromboembolic and bleeding events, and heart failure, as well as non-cardiovascular comorbidities such as kidney disease, liver disease, neurodevelopmental conditions [32]. The volume of research into Fontan failure and Fontan-associated morbidity disclosed in this analysis is understandable given the burden of disease and its impact on health-related quality of life.

4.5. Cardiac surgery

Once developments in cardiopulmonary bypass and cardioplegia made it possible, intracardiac repair of CHD became increasingly successful in the second half of the 20th century. This bibliometric analysis reveals that further improvement of surgical outcomes continued to be of prime interest as the 21st century began. Specific topics addressed include predictors of morbidity and mortality following cardiopulmonary bypass [33], predictive biomarkers and prevention of postoperative acute kidney injury [34], the effects of deep hypothermic circulatory arrest on neurodevelopment [35], and risk stratification and adjustment [36]. Although attentive to identification of risk and prediction of outcome, there was notably little focus within the highly cited papers on the development of novel techniques or approaches to mitigate these risks.

The future of cardiac surgical research innovation may therefore need to shift to the cellular and molecular levels. Optimization of cardioplegia, myocyte preconditioning, and modulation of postoperative inflammatory mediators and leukocyte-endothelial interactions may come to the forefront [37]. Congenital heart surgeons and researchers are also still in the pursuit of ideal valve substitutes, and bioengineers have set their sights on accurate diagnosis, tissue collection and the development of living conduits for implantation that grow as the patient does [38]. The therapeutic potential of xenotransplantation may also become a high profile area of investigation.

4.6. Limitations

This study was limited to publications published between 2000 and 2020. Scopus includes literature in English and lacks non-English publications. Some English language publications that are indexed in

databases other than Scopus might have been omitted. Relatively new articles would not have accrued high numbers of citations in the defined two-decade time frame of the present analysis. Although we attempted to account for this using a sensitivity analysis, the possible underexposure of newly published work in recent years is a limitation. The current study focused on the absolute number of citations; different results might have been observed if a selection was made based on the average number of citations. Furthermore, shifts in journal impact factors in the past few years might have led to changes in the patterns of publishing. As an example, journal impact factors for *Circulation* and *European Heart Journal* were 14.429 and 10.046, respectively, in 2010, but increased to 18.880 and 23.425 in 2017. Lastly, new articles are published every day, implying that the order of the included studies might change once they obtain more citations.

5. Conclusions

This bibliometric analysis, mapping two decades of research in CHD, has highlighted the 100 most influential original clinical articles and defined major areas of recent investigation. Several overlapping themes are identified among these publications, including efforts to test less invasive forms of treatment, identify and stratify therapeutic risks, especially for the most vulnerable populations, and for those with types of CHD for which current approaches leave considerable opportunity for outcome improvement.

CRedit author statement

JVDE: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing – original draft; Writing – review & editing. TF: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing. YCF: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing. BM: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing. SA: Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing. WB: Conceptualization; Investigation; Supervision; Writing – review & editing. MG: Conceptualization; Investigation; Supervision; Writing – review & editing. DD: Conceptualization; Investigation; Supervision; Writing – review & editing. SK: Conceptualization; Investigation; Supervision; Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: W. Budts is proctor for Abbott and Occlutech. M. Gewillig is proctor for Edwards and Medtronic. SK is consultant for GE Healthcare. All other authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcchd.2021.100156>.

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