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Changing epidemiology of congenital heart disease: effect on outcomes and quality of care in adults

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Abstract

The epidemiology of congenital heart disease (CHD) has changed in the past 50 years as a result of an increase in the prevalence and the survival rate of CHD. In particular, mortality of CHD populations has changed dramatically since the latter half of the 20th century given the more timely diagnosis of patients and the development of interventions for CHD that have prolonged life. As patients with CHDs age, the disease burden shifts away from the heart and towards acquired cardiovascular and systemic complications throughout the lifespan. The societal costs of CHD are high, not just in terms of health-care utilization, but also with regards to quality of life. Lifespan disease trajectories for populations with a high disease burden measured over prolonged time periods are becoming increasingly important in order to define long-term outcomes that can be improved. Quality improvement initiatives including advanced physician training for adult CHD in the past 10 years have begun to improve outcomes. As we seek to transform lifespan into health span, research efforts need to incorporate big data to allow high-value**,** patient-centred and artificial intelligence-enabled delivery of care. Such efforts will facilitate improved access to care in remote areas and inform the horizontal integration of services needed to manage CHD for the prolonged duration of survival among adult patients.

The 20th century has witnessed major changes in the epidemiology of congenital heart disease (CHD). Benefiting from advances in paediatric medicine, therapeutics and surgery, the majority of patients with CHD survive well into adulthood.[1] The changing epidemiology CHD, with regards to mortality and the shifting distribution of age, sex and lesion, has resulted in a lifelong burden of high-cost disease that requires interdisciplinary ongoing surveillance and care to ensure that the prolonged lifespan of patients with CHD coincides with sustained health.

In this Review, we update the reader on the changing demographics and disease distribution of CHD populations and describe the effect of the changing epidemiology of CHD on outcomes and health-care delivery in adults, highlighting novel concepts in lifespan disease management. The studies that we discuss have used standard statistical approaches on the observed demographic shifts and disease distribution of CHD, with a focus on each of the building blocks of the epidemiology framework we present (Fig. 1)[2]. Moreover, we underscore the limitations in measuring the changing epidemiology of CHD. Finally, we describe the changes in disease burden of CHD, introduce novel approaches for the analyses of outcomes and examine quality-of-care initiatives that have the potential to change CHD outcomes along the horizontal time frame that prolonged survival now permits.

[H1] Changing epidemiology of CHD

[H2] Birth prevalence of CHD

Since CHD develops during embryonic growth, the true incidence of CHD cannot be measured without an accurate ascertainment of rates of spontaneous and planned pregnancy termination. Therefore, the best proxy measure for incidence of CHD is the birth prevalence of CHD. To avoid potential bias in measures of CHD prevalence resulting from the varying methodologies, populations or observation periods used in different studies, we assessed the time trend within each

study. Although variations in birth prevalence of CHD have been reported, some consistent observations are documented. When discussing overall time trends in CHD prevalence, we described data from five studies that reported periodic birth prevalence based on registry data over a minimum of 5 years to avoid bias in time-trend measures (Table 1[3]**)**. All these studies demonstrated a progressive increase in the birth prevalence of CHD from the 1970s to 2000[4-8], whereby the average yearly increase in birth prevalence ranged from 0.1 to 0.3 per 1000 population. This finding was similar to the results reported by a 2011 systematic review and meta-analysis, which showed an increase in CHD birth prevalence from 5.3 per 1000 population in late 1970s to 9.1 per 1000 population in 1995[9]. However, inconsistent trends have been reported for periodic birth prevalence obtained from registry data since 2000 (Table 2[3])[5,10-13]. A 2019 systematic review and meta-analysis of 260 studies on birth prevalence of CHD demonstrated a similar pattern in the time trend in 1970–2017, showing an overall significant increase in birth prevalence from 4.5 per 1000 population in 1970–1974 to 9.4 per 1000 population in 2010–2017, with a plateau from 1995 to 2009[3].

Regional variations in birth prevalence of CHD have also been reported, with the lowest rates in Africa and the highest rates in Asia[3,9]. According to data from a 2019 systematic review, the birth prevalence of CHD in Africa is 2.1 per 1000 population, which is a quarter of that found in Asia, Europe, North American, South America and Oceania. The birth prevalence in these latter regions ranges from 7.2 to 9.2 per 1000 population, with no significant differences between regions[3]. Regional variations also exist in the distribution of CHD lesions. Globally, including in Africa where data are sparse, the five most common CHD lesions are ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), pulmonary stenosis and tetralogy of Fallot (TOF)[3,9,14-21], with VSD, ASD, and PDA constituting 57.9% of the total cases of CHD[3]. The increase in birth prevalence of CHD over the past 5 decades is largely accounted for by

mild lesions[3,9]. A 6-fold increase in the birth prevalence of ASD has been reported from the time periods of 1970–1974 to 2010–2017, whereas the birth prevalence of VSD and PDA increased 2–3-fold in the same time frame[3]. Over the same observation period, the birth prevalence of severe lesions remained constant. Different trends were see between right and left ventricular outflow tract obstructive lesions where the former showed a progressive increase whereas the latter showed one-third decrease[3].

The observed increase in birth prevalence of CHD before 2000, as well as the regional variations in time trends and CHD lesions distribution might be attributable, at least in part, to ascertainment bias. Echocardiography was used more frequently for CHD diagnosis and screening in the latter third of the 20th century in industrialized countries, but disparities in global access to diagnostic tools remain. The use of pulse oximetry as a more affordable means of CHD screening[22] has been promoted through policy change in the USA[23], Canada[24], Europe[25] and Asia[26], and pulse oximetry has also been made more readily available in Africa[27,28]. These factors might contribute to changes in prevalence of CHD that are likely to be observed in the next decade.

[H2] Changing mortality of CHD in children

As mentioned above, an improvement in the non-invasive diagnosis of CHD probably accounts for changes in CHD prevalence over time, particularly with milder forms of CHD. Furthermore, substantial shifts in mortality have been observed owing to major progress in diagnostics and the development of surgical and percutaneous interventions for neonates and infants with severe CHD across the world, which have resulted in prolonged survival of these patients[29].

In the USA, the Metropolitan Atlanta Congenital Defects programme reported a significant improvement in the survival rates of infants with critical CHD from 67.4% in the 1979–1993 birth cohort to 82.5% in the 1994–2005 cohort[30]. Furthermore, a study that examined multiple-cause

mortality files using death certificates from the USA reported a decrease of 39.3% (1.9% per year) in overall CHD-related mortality from 1979 to 1997[31]. The decrease in CHD mortality was more pronounced in infants and young children (< 5 years old), in which the average yearly decrease was 2.7% and 4.5%, respectively[31]. Another study using same data source reported a decline in mortality for all CHD lesions from 1979 to 2005, with the greatest reduction in mortality observed among patients with transposition of the greater arteries (TGA; 71%)[32]. A 40% decline in death associated with TOF during the same period was also reported. Finally, a population-based cohort study of patients with CHD in Quebec, Canada, showed a significant increase in the median age of death in patients with CHD from 2 years in 1997–1998 to 23 years in 2004–2005[1].

Data from Europe also show prolonged survival among patients with CHD in the past 5 decades. A Finnish population registry study found that the rate of sudden death after surgery for ASD, TGA, TOF or VSD decreased substantially from 1990 to 2009 in patients aged <15 years[33]. Furthermore, data from Belgian children with CHD showed significantly prolonged survival into adulthood: the probability of survival into adulthood was 88.6% for patients born between 1990 and 1992, which was 7.6% higher than the probability for patients born between 1970 and 1974[34]. A registry-based, prospective, matched-cohort study in Sweden also reported improvements in survival trends in children and young adults with CHD compared with the general population[35]. Survival was prolonged in children younger than 5 years, whereby the probability of survival increased from 96% in those born between 1970 and 1979 to 98% in those born between 1990 and 1993. Furthermore, the hazard ratios of death compared to that in control individuals decreased from 225.84 (95% CI 136.84–372.70) to 33.47 (95% CI 22.54–49.70). Data from the Dutch National CONCOR registry demonstrated that adult patients with a mild CHD lesion who had undergone surgery had a similar life expectancy as the general population (median survival 84.1 years (95% CI 81.9–87.0)). However, adults with a moderate or severe CHD lesion still had a lower

life expectancy compared with the general population (median survival 75.4 years (95% CI 72.9–79.1) and 53.4 years (95% CI 49.9–60.7), respectively[36]).

Of note, mortality data from patients with CHD in developing regions of the world are sparse. A systematic analysis of the Global Burden of Disease Study 2017 reported a 34.5% decline in the global CHD-associated mortality rates from 1990 to 2017 for patients of all ages and a decline of 39.7% for infants[37]. The analysis also demonstrated an association between the sociodemographic index and changes in mortality during this time period, whereby countries with a low sociodemographic index reported the smallest decrease in mortality. The decline in mortality for infants was 6.5% in countries with a low sociodemographic index, which was much lower than the rates reported by countries with a low-middle sociodemographic index (34.5%), a middle sociodemographic index (51.8%), a high-middle sociodemographic index (62.0%) and a high sociodemographic index (64.0%)[37].

[H2] Trends in prevalence across the lifespan

Measuring the prevalence of CHD across the lifespan is challenging. Empirically measured prevalence rates of CHD are a function of biological, diagnostic and therapeutic determinants that can vary with geography, population and observation times. The well-characterized Quebec CHD database was constructed using comprehensive population-based denominators from 1983 to 2010[38], currently updated to 2017 with up to 35 years of longitudinal observation on approximately 140,000 patients with CHD from birth to death[38]. Notwithstanding the inherent limitations of single jurisdiction data sources, the data from the Quebec CHD database can be used to observe changing prevalence rates of CHD across the lifespan and over calendar time in an internally well-validated single data source. **Fig. 2** illustrates the empirical measures of CHD prevalence in children and adults in 2000, 2005 and 2010 calculated using data from the Quebec CHD database, whereby

CHD prevalence increased by 11% in children and 57% in adults from 2000 to 2010. By 2010, two-thirds of the entire CHD population were adults, the prevalence of severe CHD lesion increased by 19% in children and 55% in adults[38]. Ultimately, the absolute numbers of patients in each age group will be determined by the age distribution of the underlying population. Therefore, in industrialized countries where adults outnumber children, there are now more adults than children with CHD despite the lower overall prevalence rate.

A study that assessed data from the National Vital Statistics System and the National Health Interview Survey in the USA reported a 2.3-fold increase in the prevalence of CHD in adults (aged 20–64 years) from 1968 to 2010[39]. The reported prevalence of adult CHD (ACHD) in 2010 was 1.46 per 1000 population, which was considered as a conservative estimate given that CHD identification was based on self-reported recalling of ever receiving a CHD diagnosis from a doctor. With the assumption that the birth prevalence and excess mortality were constant after 2010, the study modelled the prevalence of self-reported CHD in adults since 1970 and projected that the prevalence would start to plateau around 2050. Of note, the prevalence of ACHD was projected to increase by 57% from 2010 onwards before reaching a plateau.[39] A systematic review that summarized data from 10 studies reported an estimated prevalence of ACHD of 3.23 per 1000 population, with moderate and severe lesions accounting for 15% and 3% of ACHD population, respectively[40].

Similar results have also been reported in East Asia. A study of adult patients (aged 18–59 years) with CHD reported that the prevalence of ACHD increased from 1.41 per 1000 population in 2000 to 2.17 per 1000 population in 2014, with an overall increase of 54% over the first 15 years of the 21st century. The study also reported that the prevalence of patients with severe CHD increased from 0.14 to 0.25 per 1000 population over the same observation period[41].

The Global Burden of Disease Study 2017 provided regression model-based, cross-sectional estimates on global CHD prevalence between 1990 and 2017 by incorporating multiple data sources on mortality and prevalence rates[37]. However, the interpretation this data should take into account the design of the study. As the ascertainment of the diagnoses of CHD is likely to be different across different age groups, direct comparison of CHD prevalence between different age groups should be avoided. When assessing time trends in CHD prevalence, we calculated and presented the relative increase in CHD prevalence overall and in each age group. The Global Burden of Disease Study reported an 18.7% increase in the prevalence of CHD from 1990 to 2017, resulting in an estimate of 11,998,283 people living with CHD globally in 2017[37]. With the numbers from this study, we calculated the relative change in CHD prevalence by age groups (**Fig. 3**). Our calculations indicate that among all the age groups, the relative increase was the greatest in the group aged ≥50 years, in which a two-fold increase was observed from 1990 (*n* = 283,060) to 2017 (*n* = 570,825). The second largest increase was in the 20–49 years age group, which had a 1.45-fold increase.

Different patterns regarding the changes in prevalence by age groups were observed between countries with high and low sociodemographic index (**Fig. 3**). In regions with high sociodemographic index, the CHD prevalence in all patient groups aged <19 years decreased between 1990 and 2017, whereas the CHD prevalence of the older age groups (20–49 years and 50+ years) increased over this observation period. In regions with low sociodemographic index, an increase in CHD prevalence was observed across all age groups, with older age group (50+ years) showing the greatest increase. Of note, a significant increase in CHD prevalence in adults were observed across all regions regardless of sociodemographic index, which reflects the overall prolonged survival of the CHD population.

Although all population data sources are subject to ascertainment bias, important differences prevail between sources, and caution should be exercised when directly comparing results from studies that use varying methodology. As such, prevalence measurements that are obtained, for example, from the Québec CHD database, which are not modelled, but are based on empirical observations with longitudinal population cohorts followed-up for up to 35 years cannot be directly compared to modeled estimates or point measurements of prevalence in different years.

To summarize, measurable changes in the prevalence of CHD have occurred as a result of evolving trends in incidence and survival of CHD over time. The best proxy for the incidence of CHD is birth prevalence. Changes in birth prevalence over time and by region are, at least in part, attributable to ascertainment with variations in the availability of diagnostic tools. Critical appraisal of prevalence analyses from different data sources should be applied when comparing results from different data sources. Demographic shifts associated with age-specific population numbers will continue to reflect the underlying age distribution of regional populations where prevalence rates are measured. Despite regional variations, CHD survival has improved globally, as exemplified by the increasing age of CHD populations. Approaches to define, manage and improve CHD outcomes across the lifespan are increasingly important in keeping with the longitudinal perspectives that survival now permits. The questions remain: what disease burden is governing outcomes in CHD populations, what outcomes matter, how should they be measured and can they be changed?

[H1] Changing outcomes in CHD populations

With prolonged survival in patients with CHD, mortality has shifted from a bimodal distribution of death to a distribution skewed towards older age, resembling that of the normal population[1]. Therefore, as the CHD population ages, the observed median age of patients with CHD is expected to continue to increase. This gradual rise in the number of adult patients with CHD has important

public health implications, as these patients have a high morbidity and mortality burden, as well as high rates of hospitalization, which all necessitate extensive health-care resources.

H2 Acquired Cardiovascular disease (CVD)

Patients with CHD have a multitude of cardiac complications including arrhythmia, endocarditis, pulmonary hypertension and heart failure. In a 2005 population-based study that included a total of 38,428 adults with CHD, the prevalence of atrial arrhythmias was 15%, and the cumulative risk of developing atrial arrhythmia over 20 years was 7% in patients aged 20 years and 38% in patients aged 50 years[42]. The cumulative risk was high among patients with severe CHD who survived beyond 18 years: half of these patients developed arrhythmia by the age of 65 years[42]. A study of 26,420 adult patients (aged 18–64 years) with CHD from the Quebec CHD database reported a 2.96% prevalence of pulmonary arterial hypertension[43]. The prevalence of pulmonary arterial hypertension increases with age, from 2.5% in those aged <30 years to 25% in those aged 65 and over[44]. A population-based study from East Asia used data from a national insurance research database to assess the incidence of major adverse cardiovascular events (MACE), including acute coronary syndrome, heart failure, malignant dysrhythmia, stroke, death, etc., in 3,267 adult patients with CHD identified between 2000 and 2003 with a median follow-up of 11 years. The crude incidence of MACE was 18.2 cases per 1000 person–years in patients with CHD, which was 3.6 times higher than in patients without CHD[45].

Acquired CVD is also significant and include coronary artery disease (CAD), systemic hypertension, and stroke[46] The rate of CAD among adult patients with CHD is higher than in the general population[47]. Among 26,420 adult patients with CHD (aged 18–64 years) from the Quebec CHD database, the prevalence of CAD was 17.93%[43]. An analysis of data from the Dutch CONCOR registry, which included a total of 11,723 adult patients with CHD with a median age of

33 years, reported an increased relative risk of CAD, associated with female sex, younger age and more severe CHD lesion, with the general population as the reference group.[46]. The relative risk of CAD in patients aged 20 years was 12.0 (95% CI 2.5–56.3) in women and 4.6 (95% CI 1.7–12.1) in men. Furthermore, the relative risk associated with mild, moderate and severe CHD was 1.3 (95% CI 0.9–1.9), 1.6 (95% CI 1.0–2.5) and 2.9 (95% CI 1.3–6.9), respectively[46].

A centre-based retrospective analysis of elderly patients (aged ≥60 years) with CHD in Poland reported a high burden of cardiovascular risk factors[48]. Among the 322 patients hospitalized in an ACHD center from 2013 to 2020, the prevalence of arterial hypertension was 60.56%[48]. A high prevalence of hypertension among adult patients with CHD has also been observed in a comprehensive CHD centre in North Carolina, USA, where nearly 1 out of 2 patients with severe CHD had hypertension. The prevalence of hypertension was even higher among patients with non-severe and valve lesions (63.9% and 74.7%, respectively)[49].

Stroke is another important cause of morbidity and mortality among patients with CHD. In a retrospective study of 29,638 patients from Quebec (aged 18–64 years) with 23 years of follow-up (1998–2010), the cumulative risk of ischaemic stroke was 6.1% (95% CI 5.0–7.0%) in women and 7.7% (95% CI 6.4–8.8%) in men, whereas the cumulative risk of haemorrhagic stroke was 0.8% (95% CI 0.4–1.2%) in women and 1.3% (95% CI 0.8–1.8%) in men[50]. When compared with rates reported in the general Quebec population, the age–sex standardized incidence of ischaemic stroke was 9–12 times greater in the patients aged <55 years and 2–4 times greater in the patients aged 55–64 years. In addition, the rates of haemorrhagic stroke were 5–6 times greater in patients aged <55 years and 2–3 greater in patients aged 55–64 years compared with the general population[50].

[H2] Systemic complications.

Systemic complications of CHD include neurocognitive disorder, liver disease, kidney dysfunction, diabetes mellitus and cancer. Nearly 1 out of 10 adult patients with CHD (aged 18–64 years) from the Quebec CHD database were diagnosed with diabetes (prevalence of 9.65%)[43]. Among the patients with severe CHD lesions, the prevalence of diabetes and chronic kidney disease was 22.9% and 35.7%, respectively. The prevalence of these conditions was even higher in patients with non-severe lesions and valve lesions[49]. The retrospective study in Poland mentioned above also reported a high prevalence of diabetes (21.43% of their cohort of elderly patients with CHD (aged ≥60 years) hospitalized in an ACHD centre[48].

Patients with CHD are also at increased risk of neurocognitive injury owing to surgery, including cardiopulmonary bypass. An impairment in psychomotor and mental development has been observed in infants undergoing neonatal cardiac surgery for CHD that are related to post-operative factors[51]. According to data from the Quebec CHD database, the cumulative risk of neurocognitive disorder reached 37% at 10 years after a shunt closure surgery in patients who underwent the surgery at a very young age (aged ≤0.4 years). For patients who underwent the surgery at a later age (aged 0.4–2.5 years or ≥2.5 years), the cumulative risks were lower (25% and 15%, respectively), but still substantial[52].

An increased incidence of cancer has also been reported in CHD patient population that might be associated with genetic syndromes or increased exposure to low-dose ionizing radiation. In an analysis of 24,833 adult patients with CHD patients aged 18–64 years from 1995 to 2009, the cumulative incidence of cancer was 15.3% (95% CI 14.2–16.5)[53].

[H2] Mental health and quality of life. Mental health and quality of life are becoming increasingly important in the context of CHD as substantial comorbidity in patients increases the uncertainty of

life expectancy. Traumatic experiences during childhood shape the lived experiences of children with CHD and their families[54-56]. Up to 52% of patients with CHD develop post-traumatic stress disorder, with variability in rates depending on measures and geographical location[57-63]. However, the prevalence of post-traumatic stress disorder is consistently reported to be higher in patients with CHD than in those without CHD[58,63]. Systematic reviews of qualitative research have demonstrated that disrupted normality, powerlessness, and enduring medical ordeals and transitions, are core features of patients' lived experiences[54,56]. Despite these experiences, a substantial proportion of patients are able to harness 'positive remodelling' to build resilience[54]. Reported experience of such positive remodeling included but were not limited to demarcating disease from life, determination to survive, taking limitation in strides, embracing the positives, finding personal enrichment, and replying on social or spiritual support from families, friends, and religion[54]. When compared to age-matched and sex-matched healthy individuals, adolescents with CHD showed a higher sense of coherence (indicative of greater resilience) as well as better perceived health[64]. Furthermore, in a large international study that included 4,028 patients with CHD from 15 countries, sense of coherence correlated significantly with quality of life, explaining 17.2% of its variance[64,65]. As a result of positive remodelling, patients with CHD generally have a good overall quality of life[66]. A systematic review and meta-analysis that included 18 studies with a total of 1,786 patients concluded that the overall quality of life in adolescents and young adults with CHD was not lower than in healthy controls[67]. Another meta-analysis pooled findings from 33 studies that evaluated quality of life using Short Form-36[68]. Patients with moderate or complex CHD had worse physical functioning and general health perception compared to healthy individuals[68].

[H2] Societal costs of shifting demographics

In addition to the individual cost of CHD, the disease is also associated with substantial societal cost. Health-care utilization is expected to reflect the substantial burden of illness described above. A systemic review of 21 studies showed that in patients with moderate or severe heart defects, hospitalization rates have increased by 3–7% per year in the past two decades[69]. An even greater increase in hospitalization rates (8–13% per year) was observed in patients with mild heart defects, which was mainly explained by the increased availability of percutaneous treatment options[69]. The overall relative risk of hospitalization was 2–3 times higher in patients with CHD compared to the general population[69]. In patients with complex heart defects, this relative risk increases by 8-fold[70]. Furthermore, the rate of cardiac outpatient visits was 2.24 times higher than in the general population[69]. The number of outpatient visits to general practitioners and other medical specialists are also generally higher than those to cardiologists[71], which reflects the substantial burden of extra-cardiac diseases.

The societal cost of CHD has also expressed in the form of absence from work or school and work disability. One study in the USA showed that 27% of 1,416 children with CHD were absent from school for ≥11 days in the past year, which was almost double the rate of absenteeism in children without CHD (15%)[72]. A Belgian study found that absence from work or school occurred in 69% of 255 young adults (age range: 24 – 28) with CHD, with illness identity (engulfment) being a significant contributor to both all-cause absence and absence for CHD reasons[73]. Absenteeism also extends to disabilities and the inability to work. In a US cohort of 1,478 adults with CHD, 40% were found to have at least one disability, the most prevalent of which were cognitive (29%) and independent living (22%)[74]. Among the patients with disabilities, 45% received disability benefits (18% of the total cohort)[74]. Furthermore, a study that assessed data from 4,028 adults with CHD from 15 countries reported that only 8% of adults with CHD received disability benefits, ranging from 0% in India to 17% in Norway[75].

The health-care cost of ACHD is increasing alongside the increase in the median age of the CHD population, especially in developed countries. Data from the USA and Canada consistently show substantial increases in health-care costs for ACHD over a 10-year observation period[76,77]. The increases are more pronounced in older patients[77] and in adult patients with complex lesions[76].

To summarize, data from high-income jurisdictions that are reported using standard statistical outcome models in applied epidemiology have demonstrated that as patients with CHD age, disease burden shifts away from the heart and towards acquired cardiovascular disease and systemic complications measured throughout the lifespan. The effect of CHD on quality of life starts in infancy and although positive remodelling and resilience protect patients against poor quality of life, the societal costs of the disease are high, not just in terms of health-care utilization but also with regards to disability that can impair the patient's contribution to society. Therefore, as we shift our focus from lifespan to health-span and disease trajectories to health trajectories, we need to determine how outcomes should be measured and integrated across the lifespan.

[H1] Population-based deep learning tools

Artificial intelligence-informed methods and digital tools have the potential to improve research efficiency and the care of patients with CHD. Artificial intelligence-based applications have been incorporated in several aspects of CHD care, including prenatal and postnatal CHD screening, and cardiovascular image processing and interpretation.

With prolonged long-term survival in patients with CHD, a trajectory-based concept is required to fully capture the effect of various interdependent components of health on an individual's life over time[38,78]. This trajectory-based concept emphasizes the importance of long-term outcomes rather than only focusing on the short-term, cardiovascular-related complications, and highlights the important notion that patients status over the lifespan oscillates between episodes

of health and disease[79]. Lifespan trajectories of patients with CHD are thus determined by a multitude of factors, including underlying genetic and epigenetic factors, socioeconomic status and lifestyle factors, previous medical interventions and disease complications, as well the phenotypic expression of the underlying conditions. With increasing patient age, these factors increasingly interact in an unpredictable fashion, thus augmenting phenotypic heterogeneity even between patients with similar diagnoses[80]. Capturing the longitudinal nature of the CHD trajectory requires a multipronged approach that includes deep learning models. For example, the neural Hawkes process not only consider the effect of past events on future complications, but also use a recurrent neural network to predict the underlying probability function of the events[81,82]. Recurrent neural networks are a promising option to capture information from longitudinal medical data. A study has used this approach to predict future heart failure events as well as heart failure trajectories using data from the Quebec CHD database[79]. While these technologies are still in their infancy with regards to applicability in medicine, they have the potential to improve risk stratification and guide medical treatment in patients with CHD. Future work should focus on refining these algorithms and broadening the underlying learning data set, as well as establishing the clinical utility of and superiority compared with conventional statistical models in CHD[83,84].

To enable risk stratification of long-term disease trajectories, complementary approaches are needed to incorporate biological and clinical data with deep learning algorithms. When combined with hypothesis-driven research and mechanistic-based disease models that can take into account treatment interventions over time, this approach can improve the diagnosis and management of individual patients with CHD over their lifespan, thus paving the way to personalized medicine[85]. We and others have demonstrated the feasibility of an automatic artificial intelligence-based risk stratification strategy for patients with CHD. Deep learning-based natural language processing algorithms that were trained with raw medical record data from >10,000 adult

patients with CHD successfully determined the underlying lesion complexity for each patient and predicted the need for closer medical attention to reduce the risk of death[86]. Similarly, another artificial intelligence-based algorithm for risk stratification that has been trained and externally validated on cardiac magnetic resonance imaging datasets have been used to estimate prognosis in patients with TOF[87]. To gain a better understanding of lifespan disease trajectories, long-term outcomes are becoming increasingly important to define, and novel risk stratification methods are needed to plan clinical trials that are relevant for the whole CHD population. Strategies to improve CHD outcomes are more important than ever.

[H1] Improving the quality of care

Despite major progress in reducing mortality in children with CHD, and the demonstration that ACHD specialized care reduces mortality, the same gains are not seen in adults as they are in children with CHD[88]. In large European CHD cohorts, survival remained constant in adults, despite major improvements seen in childhood cohorts from 1973 to 1993. [35,88]. Moreover, care gaps and breaches in the transition of care between paediatric and adult health-care systems need to be addressed to improve integrated care over the entire lifespan.

[H2] Training programmes and accreditation

In the early 2000s, small but highly dedicated groups of cardiologists led programmes that focused on the care of adult patients with CHD. The first consensus document that provided a roadmap to improve the quality of care for adult patients with CHD was published in 2001[89]. To improve the quality of care for adult patients with CHD, programmes specializing in ACHD should be established globally, including the development of a new clinical subspecialty, with specific training requirements to meet the demands of the changing epidemiology and demographics of

CHD populations. Guidelines by the ACC/AHA and the ESC have recommended integrated, multidisciplinary care for adult patients with CHD[78,90]. In Canada, Germany, UK and USA, as well as regions in Asia, the Middle East and South America, substantial changes have occurred over the past decade in the care delivery models for adult patients with CHD. Collaboration between emerging ACHD cardiologists and policymakers have led to the development of high-level training for ACHD certification. In 2015, the American Board of Internal Medicine and the American Board of Pediatrics collaborated to develop the first ACHD board certification[91]. Since its approval and inception, >450 cardiologists are now ACHD-board certified in the USA, many with a lifelong experience in caring for both paediatric and adult patients that are now 'grand-fathered' into recognition of their expertise. Furthermore, in Germany, a tiered approach to ACHD care has been developed, with a certification process for cardiologists specializing in ACHD[92]. A total of approximately 350 cardiologists, including paediatric cardiologists, have been accredited as ACHD specialists[93]. These programs provide examples of approaches that can be adapted for the development of clinical and research training certification of ACHD cardiologists, elsewhere in the world..

The development of ACHD centers of excellence in the past 25 years has become one of the most important measures to support the delivery of high quality care for adult patients with CHD. The Canadian Adult Congenital Heart Disease Network (CACHNET) was established in 1991 and provided one of the first regionalized care models for adult patients with CHD, which involved dedicated care providers in the fields of surgery, imaging, electrophysiology, interventional cardiology and nursing. At present, there are 16 CACHNET centers in Canada for a population of 38 million individuals[94]. In the USA, the Adult Congenital Heart Association (ACHA) has a clinic directory to assist adult patients with CHD in finding care. With ACHD board certification, the ACHA has established ACHD programme accreditation with a defined set of requirements[95]. At

present, only 47 ACHA-accredited programmes have been established in the USA for a population of 329 million individuals. Germany has adopted a regionalized approach that includes 20 national ACHD centres for a population of 83 million individuals[92,93]. All of these care models are built on similar platforms; they are all team-based, multidisciplinary, highly specialized and meet a set of criteria that have been shown to improve outcomes for adult patients with CHD[96-98].

[H2] Limitations in access to care

Despite the improvements in the care models established in the past decades, as mentioned above, access to high quality of care for CHD remains a global challenge. Limiting factors that prevent access to care vary depending on the geographical region and resources. At one extreme, despite being a highly developed, resource-rich country, in the USA, many patients do not have access to high quality care for ACHD, limited by low availability and distance to an ACHD care centre, as well as divergent health insurance policies between different states (**FIG. 4**)[99]. Figure 4 shows the gradient of deficit in ACHD centers per state in the USA based on the published recommendation of one ACHD centre needed to serve a population of 2 million individuals[100]. This analysis was not intended to examine access to but to examine resources in terms of the number of specialized centres available to the population. Access to care is a reflection of the actual utilization of the resources that are, at least in part, related to their geographical location in rural or urban settings. At the other extreme, in the poorest countries around the world, CHD accounts for a large proportion of cardiovascular death in those aged <30 years, where CHD is the leading cause of disability-adjusted life–years related to cardiovascular disease. Variations in levels of expertise among medical specialists, as well as low funding for health-care systems, limit the diagnosis and treatment of CHD[101]. Technology-supported care has the potential to connect people with CHD to care centres through remote monitoring, telehealth and artificial intelligence-augmented disease

detection and surveillance, all of which can improve and expand the access to trained ACHD specialists[102-104].

[H2] Measuring CHD outcomes

To translate ACHD expertise and programme certification into measureable outcomes, high quality measures need to be developed. Quality measures should take into account a lifespan trajectory perspective, promoting decisions that will optimize outcomes over a lifetime, given that treatment decisions made in utero or during infancy can affect long-term outcomes[80]. The field of CHD will benefit from standardized core outcomes that are meaningful to both patients and the health-care system to improve delivery of quality care. Incorporation of outcome measures that are driven and reported by patients will facilitate the development of care models that can accommodate the needs of patients with CHD[105]. Such outcomes should be personalized, patient-centred and goal-oriented, embodying principles of shared decision-making between clinicians and patients. To that end, the International Consortium of Health Outcome Measurement (ICHOM) (www.ichom.org) established a set of patient-centred outcome measures including measures across the lifespan based on input from a multi-stakeholder panel that included parent and patient representation[105]. Incorporation of these measures into clinical practice and research will help to build the evidence needed to support quality care delivery and value-based health care. Other efforts to promote quality measurement and guideline adherence, such as the ACC's National Cardiovascular Disease Registry and the Adult Congenital and Pediatric Cardiology Quality Network will also support expansion of ACHD programmes to the rest of the world[106].

[H1] Conclusions

Measurable changes in the prevalence and age distribution of CHD in the past decades are the result of evolving trends in the incidence and survival rates of CHD over time. The rate of death from CHD has decreased globally in the past 50 years. However, as patients with CHD age, disease burden shifts away from the heart and towards acquired systemic complications, necessitating new strategies to improve the outcomes of patients with CHD throughout the lifespan. Deep learning methods applied to large data sources can facilitate the development of long-term trajectory prediction and risk stratification tools. The effect of CHD on quality of life starts during infancy. Furthermore, the societal costs of the disease are high, not just in terms of health-care utilization, but also with regards to disabilities that might reduce the potential for meaningful contribution to society. Important efforts have begun in high-income countries to improve the standard of specialized CHD centres, as well as in the development and incorporation of measures to assess the quality of care that can be measured across the lifespan.

Despite this tremendous progress, many knowledge gaps remain, and more evidence is needed to inform clinical decision-making. Additional research is needed to quantify life expectancy measures that are adjusted and unadjusted for disability and quality of life. So far, the early applications of deep learning in the diagnosis and management of CHD populations are promising. Future research will be needed to characterize new artificial intelligence applications to decrease diagnostic errors, optimize treatment protocols and predict optimal outcomes. Large multimodal data assessment methods that can incorporate and analyze complex data from multiple sources might contribute to improving ACHD care globally.

The rapid growth of the ACHD populations worldwide is outpacing the development of ACHD programmes and the training of certified specialists. Policymakers need to fast-track ACHD specialist training programmes and fund ACHD research. The use of technology to support ACHD care has enormous potential through the broad dissemination of knowledge and can facilitate the

expansion of access to care to benefit patients globally. If strategically deployed, such models of high quality care will enable the integration of services that are needed to manage CHD and related comorbidities for the duration of the patient's life.

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Key points:

- Measurable changes in the prevalence of congenital heart disease (CHD) population in the past X years are the result of evolving trends in birth prevalence and survival of patients over time.
- Changes in birth prevalence over time and by region are, at least in part, attributable to variations in the availability of diagnostic tools, and ascertainment.
- Despite regional variations, the survival rates of patients with CHD has improved globally, as evidenced by an increasing median age of CHD populations.
- With prolonged survival among patients with CHD, the disease burden is shifting away from the heart and towards acquired cardiovascular and systemic complications throughout the lifespan.
- Lifespan disease trajectories for CHD populations with a high disease burden measured over prolonged time windows is becoming increasingly important to define long-term outcomes that can be improved.
- Strategically deployed, high-quality care will facilitate the integration of services that are needed to manage CHD and related comorbidities for the duration of the patient's life.

Glossary terms: congenital heart disease, adult congenital heart disease, epidemiology, prevalence, mortality, lifespan disease trajectory, quality of care, artificial intelligence

Acknowledgments: none

Competing interests: none. Form attached.

Figures

Fig. 1 | **Understanding the building blocks of CHD epidemiology**. a | The schematic illustrates the bridging of congenital heart disease (CHD) epidemiology and clinical care, both of which determine demographics and the prevalence of lesions carried from birth. b | A conceptual model of the elements contributing to the observed changes in prevalence of adult CHD (ACHD) showing the interplay between incidence and mortality over time. We have observed in the past several decades a rise in prevalence of adults with CHD that has been directly influenced by the incidence and mortality of CHD. Prevalence is thus the product of incidence and survival rates, both of which vary substantially globally depending on access to diagnosis, advanced cardiac interventions and specialized follow-up. Adapted from ref #[2].

Fig. 2. The numbers and proportions of adults and children in Quebec, Canada, with all forms of diagnosed CHD over time in 2000, 2005, and 2010. Over the 10 years of observation, the prevalence of CHD in children remained relatively stable. In contrast, the prevalence in adults increased such by the year 2010 two thirds of the CHD population were adults.[38]

Fig. 3. The change in global prevalence of CHD for all age groups between 1990 and 2017 in countries in low and high SDI. a | Change in global prevalence of CHD for all regions worldwide. b | Change in global prevalence of CHD for regions with a high sociodemographic index (SDI). c | Change in global prevalence of CHD for regions with a low SDI.[37]

Fig. 4. Map of USA showing the gradient of deficit in ACHD centers per state, from the darkest red, representing a deficit of 6–17 centres, to green, showing no deficit with a minimum of 1 centre. The states that are textured with diagonal lines are considered in need of an ACHD center for reasons of access rather than a number needed to serve a population of 2 million.

Adapted from ref #[99] (Fernandes SM, Marelli A, Hile DM, Daniels CJ. Access and Delivery of Adult Congenital Heart Disease Care in the United States: Quality-Driven Team-Based Care. Cardiology Clinics. 2020 Aug;38(3):295-304. doi: 10.1016/j.ccl.2020.04.012. Epub 2020 Jun 7. PMID: 32622485.)

Table 1. Studies that reported registry data (before 2000) on the prevalence of CHD for a minimum of 5 years

Study (year)	Country or region	Observation period	Population size	N of patients with CHD	Prevalence (per 1000 population)	Average yearly increase in prevalence (per 1000 population)
Wilson, et al (1993)[7]	USA	1981	70,916	200	2.8	0.19
		1982	73,137	228	3.1	
		1983	73,501	224	3.0	
		1984	74,814	277	3.7	
		1985	77,825	299	3.8	
		1986	79,567	287	3.6	
		1987	82,679	313	3.8	
		1988	86,928	389	4.5	
Oyen et al, (2009)[8]	Denmark	1977–1979	180,155	1,292	7.2	0.24
		1980–1984	260,989	2,153	8.3	
		1985–1989	280,016	2,433	8.7	
		1990–1994	324,501	3,570	11.0	
		1995–1999	326,514	3,820	11.7	
Dadvand et al (2009)[4]	Northern England	1985–1989	192,243	1,231	6.4	0.34
		1990–1994	188,601	1,548	8.2	
		1995–1999	165,338	1,679	10.2	
Rodríguez, Dehli et al (2009)[5]	Spain	1990	7,722	38	4.9	0.63
		1991	7,693	30	3.9	
		1992	7,474	37	5.0	
		1993	7,012	42	6.0	
		1994	6,626	38	5.7	
		1995	6,553	50	7.6	
		1996	6,507	53	8.1	
		1997	6,473	55	8.50	
		1998	6,321	61	9.70	
		1999	6,516	69	10.6	
Riehle-Colarusso et al (2015)[6]	USA	1982–1987	172,087	538	3.1	0.13
		1988–1994	254,638	903	3.5	
		1995–2000	247,686	1,178	4.8	
		2001–2004	190,048	1,125	5.9	

CHD, congenital heart disease

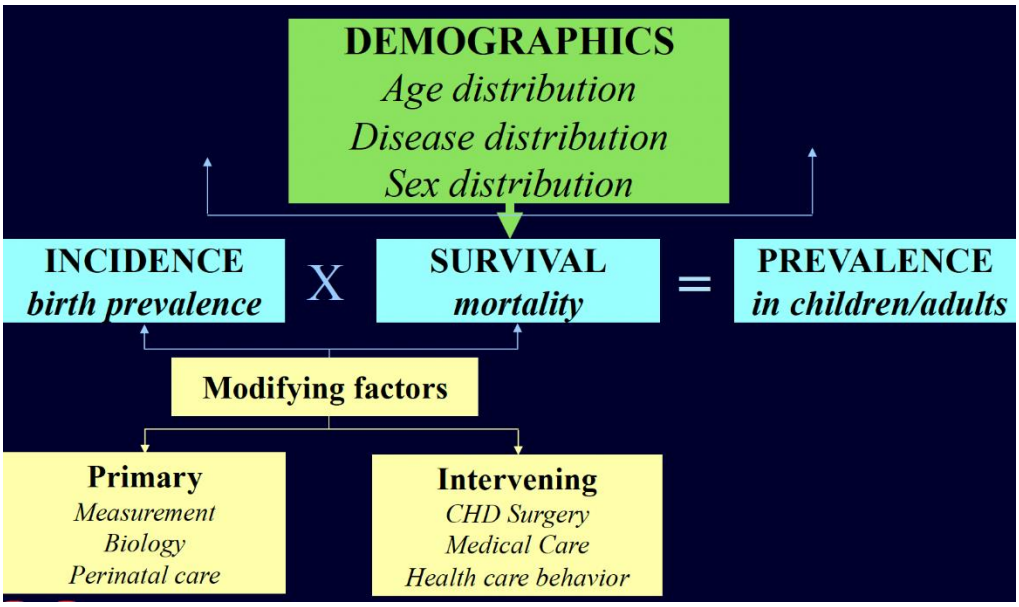
Table 2. Studies that reported registry data (since 2000) on the prevalence of CHD for a minimum of 5 years

Study (year)	Country	Observation period	Population size	N of patients with CHD	Prevalence (per 1000)
Rodríguez Dehli et al (2009)[5]	Spain	2000	6,718	44	6.6
		2001	6,833	72	10.5
		2002	6,711	56	8.3
		2003	7,088	65	9.12
		2004	7,205	68	9.4
Malcic et al (2011)[10]	Croatia	2002	9,704	79	8.1
		2003	39,668	314	7.9
		2004	40,307	289	7.2
		2005	42,492	314	7.4
		2006	41,446	277	6.7
		2007	31,434	207	6.6
Liu et al (2013)[13]	Canada	2002	198,807	2,167	10.9
		2003	213,774	2,266	10.6
		2004	245,189	2,599	10.6
		2005	256,442	2,667	10.4
		2006	259,802	2,624	10.1
		2007	274,796	2,693	9.8
		2008	279,286	2,737	9.8
		2009	284,316	2,701	9.5
		2010	280,204	2,746	9.8
Yu et al (2015)[11]	China	2003-	35,575	16	0.45
		2004	36,894	13	0.3
		2005	36,423	14	0.4
		2006	35,196	30	0.9
		2007	38,122	38	1.0
		2008	46,348	36	0.8
		2009	49,712	60	1.2
		2010	59,251	124	2.1
		2011	61,158	87	1.4
		2012	69,063	154	2.2
Xie et al (2016)[12]	China	2005	38,121	86	2.3
		2006	41,559	124	3.0
		2007	69,436	151	2.2
		2008	78,376	215	2.7
		2009	86,929	298	3.4
		2010	98,624	520	5.3
		2011	107,500	813	7.6
		2012	125,583	840	6.7

		2013	135,645	804	5.9
		2014	143,640	1,063	7.4

CHD, congenital heart disease

Figure 1: Panels A and B:



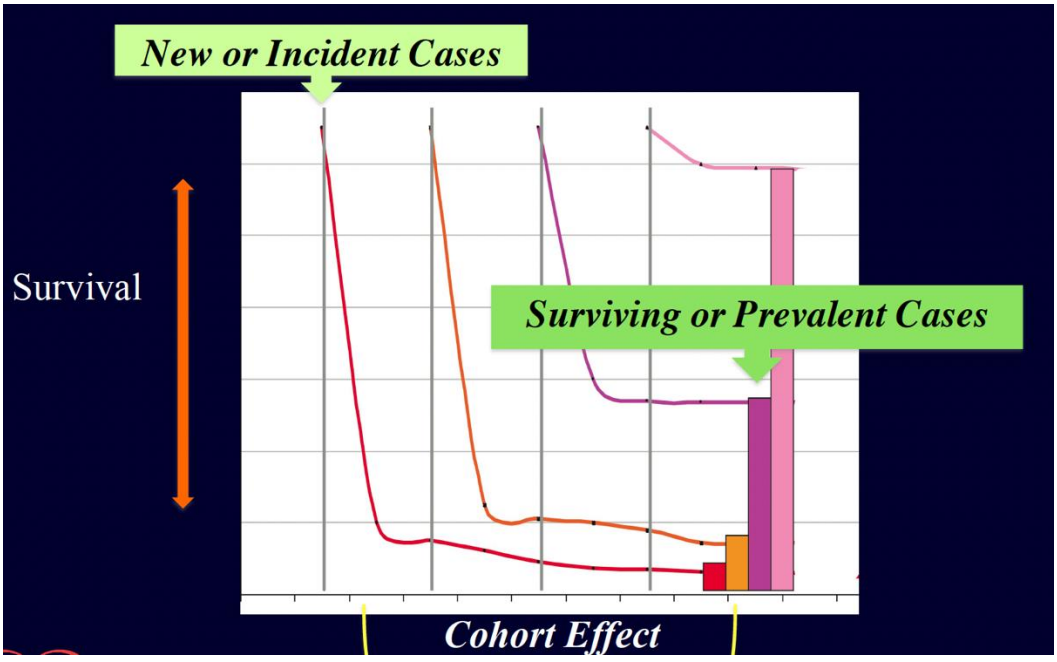


Figure 2:

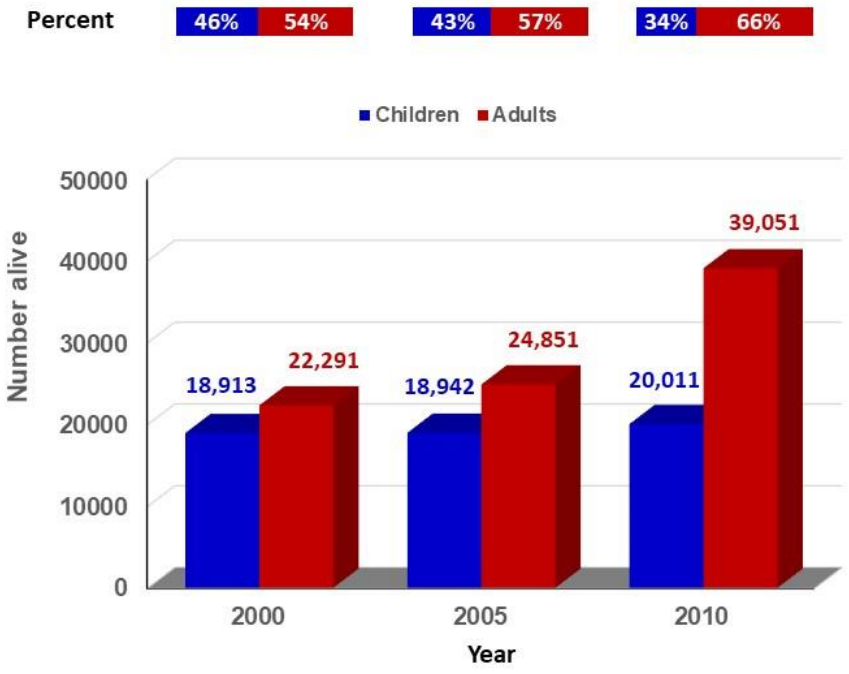
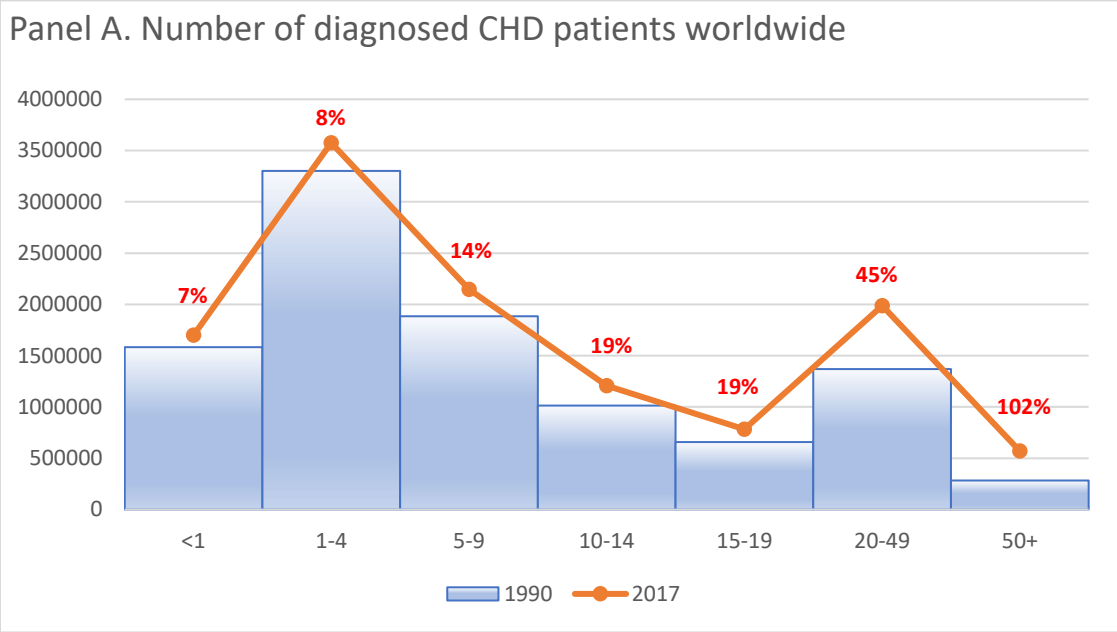
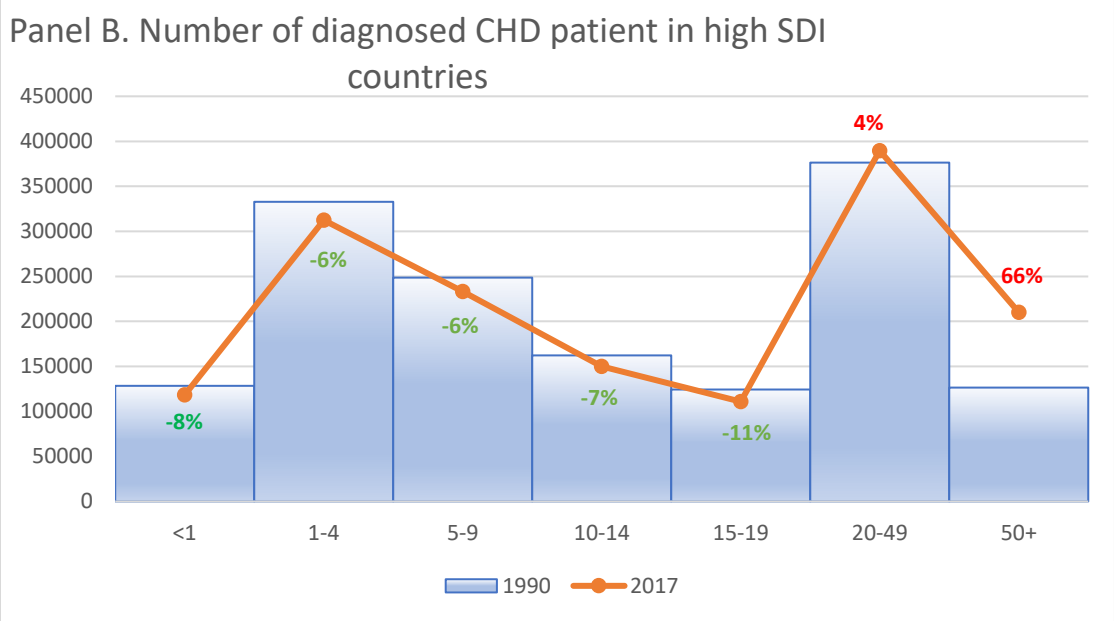

Percent
46%
54%
43%
57%
34%
66%
Children
Adults
Number alive
50000
40000
30000
20000
10000
0
18,913
22,291
18,942
24,851
20,011
39,051
2000
2005
2010
Year

Figure 3.


Panel A. Number of diagnosed CHD patients worldwide
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
8%
7%
14%
19%
19%
45%
102%
<1
1-4
5-9
10-14
15-19
20-49
50+
1990
2017


Panel B. Number of diagnosed CHD patient in high SDI countries
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-8%
-6%
-6%
-7%
-11%
4%
66%
<1
1-4
5-9
10-14
15-19
20-49
50+
1990
2017

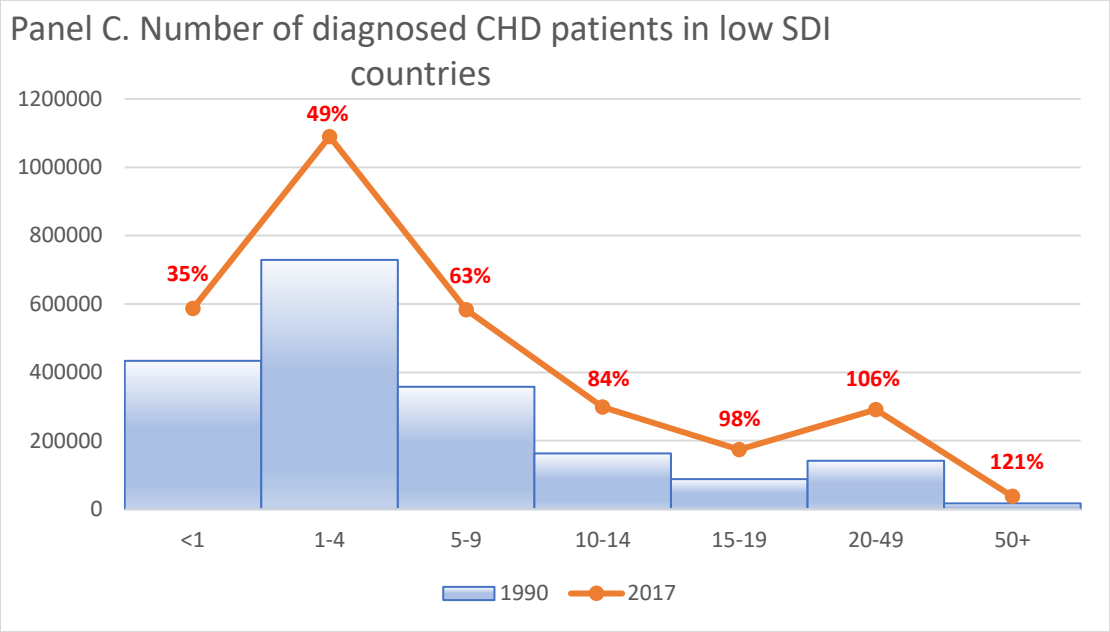
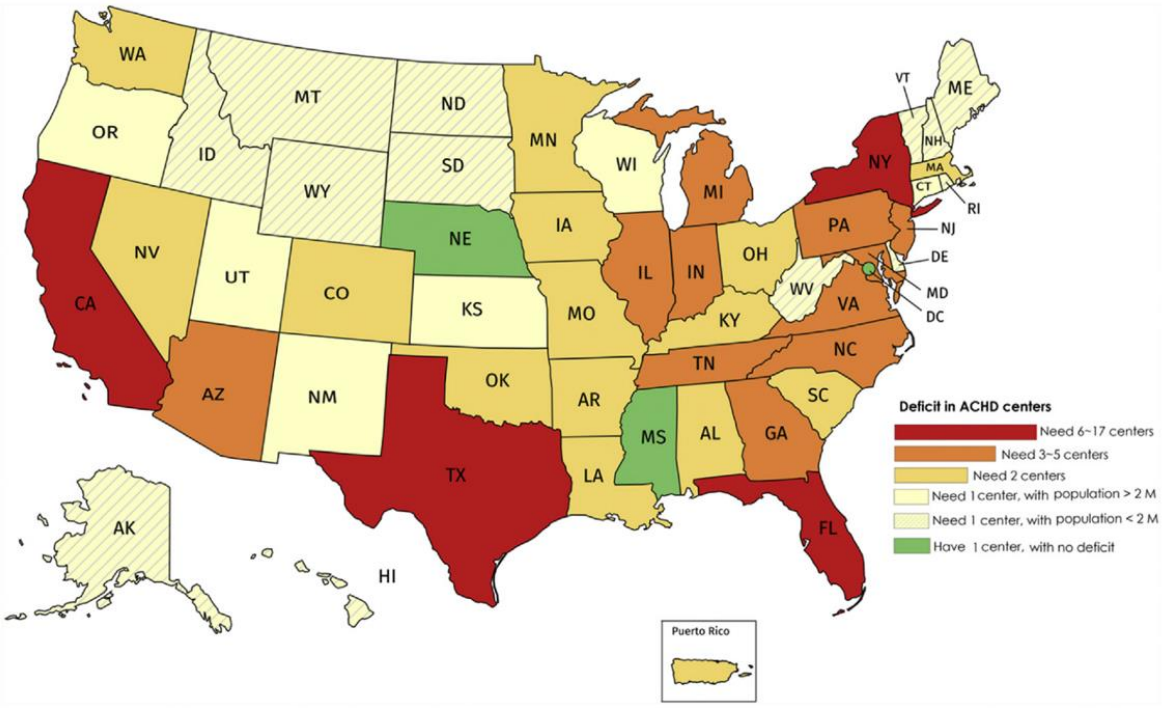

Panel C. Number of diagnosed CHD patients in low SDI countries
1200000
1000000
800000
600000
400000
200000
0
35%
49%
63%
84%
98%
106%
121%
<1
1-4
5-9
10-14
15-19
20-49
50+
1990
2017

Figure 4:


WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
VT
NH
ME
MA
CT
RI
NJ
DE
MD
DC
AK
HI
Puerto Rico
Deficit in ACHD centers
Need 6~17 centers
Need 3~5 centers
Need 2 centers
Need 1 center, with population > 2 M
Need 1 center, with population < 2 M
Have 1 center, with no deficit