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*A Danish Nationwide Study*

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ORIGINAL RESEARCH

# Time Trends in Simple Congenital Heart Disease Over 39 Years: A Danish Nationwide Study

Mohamad El-Chouli , MD; Grímur Høgnason Mohr, MD; Casper N. Bang, MD PhD; Morten Malmberg , MD; Ole Ahlehoff, MD PhD; Christian Torp-Pedersen , MD DMSci; Thomas A. Gerds, Dr.rer.nat.; Lars Idorn, MD PhD; Jakob Raunsø, MD PhD; Gunnar Gislason , MD, PhD

**BACKGROUND:** We describe calendar time trends of patients with simple congenital heart disease.

**METHODS AND RESULTS:** Using the nationwide Danish registries, we identified individuals diagnosed with isolated ventricular septal defect, atrial septal defect, patent ductus arteriosus, or pulmonary stenosis during 1977 to 2015, who were alive at 5 years of age. We reported incidence per 1 000 000 person-years with 95% CIs, 1-year invasive cardiac procedure probability and age at time of diagnosis stratified by diagnosis age (children  $\leq 18$  years, adults  $>18$  years), and 1-year all-cause mortality stratified by diagnosis age groups (5–30, 30–60, 60+ years). We identified 15 900 individuals with simple congenital heart disease (ventricular septal defect, 35.2%; atrial septal defect, 35.0%; patent ductus arteriosus, 25.2%; pulmonary stenosis, 4.6%), of which 75.7% were children. From 1977 to 1986 and 2007 to 2015, the incidence rates increased for atrial septal defect in adults (8.8 [95% CI, 7.1–10.5] to 31.8 [95% CI, 29.2–34.5]) and in children (26.6 [95% CI, 20.9–32.3] to 150.8 [95% CI, 126.5–175.0]). An increase was only observed in children for ventricular septal defect (72.1 [95% CI, 60.3–83.9] to 115.4 [95% CI, 109.1–121.6]), patent ductus arteriosus (49.2 [95% CI, 39.8–58.5] to 102.2 [95% CI, 86.7–117.6]) and pulmonary stenosis (5.7 [95% CI, 3.0–8.3] to 21.5 [95% CI, 17.2–25.7]) while the incidence rates remained unchanged for adults. From 1977–1986 to 2007–2015, 1-year mortality decreased for all age groups ( $>60$  years, 30.1%–9.6%; 30–60 years, 9.5%–1.0%; 5–30 years, 1.9%–0.0%), and 1-year procedure probability decreased for children (13.8%–6.6%) but increased for adults (13.3%–29.6%) were observed.

**CONCLUSIONS:** Increasing incidence and treatment and decreasing mortality among individuals with simple congenital heart disease point toward an aging and growing population. Broader screening methods for asymptomatic congenital heart disease are needed to initiate timely treatment and follow-up.

**Key Words:** cardiovascular intervention ■ congenital heart disease ■ mortality ■ temporal trends

Congenital heart disease (CHD) is the most frequent major birth defect, accounting for nearly one third of all major congenital defects.<sup>1</sup> International guidelines categorize CHD as simple, moderate, or severe.<sup>2,3</sup> In most cases, moderate to severe CHD is cared for by specialists, whereas simple CHD is not. Because of improved diagnostic tools and treatment during the past decades,<sup>4</sup> most children with CHD reach adulthood, and the prevalence of CHD among

adults has been estimated to have surpassed that of children.<sup>5</sup> With an increasing number of individuals with CHD, studies are necessary to evaluate the potential burden on hospitals and society.

Previous studies have investigated the trends in the prognosis of simple CHD but were either limited to subgroups of simple CHD<sup>4,6,7</sup> based on an older cohorts before the time of echocardiography,<sup>8</sup> did not include calendar year trends on risk of mortality,<sup>6,8,9</sup>

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## CLINICAL PERSPECTIVE

### What Is New?

- The past 39 years have seen trends of increasing incidence rates and decreasing mortality for patients with simple congenital heart disease (CHD), and these trends are temporally related to improved diagnostic measures and treatment options.
- Particularly over the past decade, there has been a marked increase in detection of simple CHD, especially for the CHDs that were previously not readily clinically detectable.

### What Are the Clinical Implications?

- The increasing elder population with simple CHD and growing body of evidence of increased morbidity among these individuals suggest a significant potential burden on our health systems.
- Broader screening for CHD could help early identification of patients with asymptomatic CHD, enabling initiation of timely treatment and close follow-up.

## Nonstandard Abbreviations and Acronyms

<b>IR</b>	incidence rate
<b>PS</b>	(congenital) pulmonary stenosis

or did not include absolute risks but hazard ratio over time, making interpreting the results more difficult.<sup>6</sup>

In the present study, we therefore examined the calendar time trends of incidence, age at diagnosis, mortality risk, and invasive procedure probability in a contemporary cohort consisting of all simple CHDs.

## METHODS

Data used for this study contain sensitive information and because of Danish data regulations cannot be shared with any third party.

### Data Source

All Danish residents are issued a unique and permanent civil registration number at either birth or immigration. All data from the Danish national registries are linked to the individuals via the civil registration number, allowing for cross-referencing of the national registries at the individual level. Information regarding sex, date of birth, vital status, and emigration was obtained from the Danish Civil Registration

System Registry.<sup>10</sup> The registries are made available via Statistics Denmark.

Data concerning hospital discharge diagnoses, outpatient clinic visits, and surgery (including transcatheter procedures) are recorded in the National Patient Registry, which has been validated previously.<sup>11</sup> Diagnoses were coded according to *International Classification of Disease, Eighth Revision (ICD-8)* from 1977 until the end of 1993, and thereafter according to *International Classification of Disease, Tenth Revision (ICD-10)*. Surgeries and procedures switched to a more comprehensive classification system in 1996.

### Study Population

The study population comprised all patients diagnosed with simple CHD between January 1, 1977, and December 31, 2015. In this study, simple CHD was defined as isolated diagnosis of ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), or congenital pulmonary stenosis (PS), which is in line with international guidelines.<sup>2,3</sup> Patients who did not survive the first 5 years of life were excluded, which was inspired by a method used previously.<sup>8</sup> Individuals diagnosed with multiple simple CHDs, other types of CHD, Eisenmenger syndrome, or pulmonary hypertension or who had invasive treatment for another type of simple CHD than diagnosed at any point in life were excluded. We used conditioning on the future to reduce the classification error attributable to unregistered moderate or severe CHD.

Diagnosis codes and procedure codes used to define the study population are listed in Table S1.

### Follow-up and Outcome

The index date was defined as the date of simple CHD diagnosis. If a patient was diagnosed with a CHD and had preceding CHD-related invasive treatment, then the index date was moved to time of the invasive treatment. Outcomes were all-cause mortality within 1 year after the index date or cardiac invasive procedure (surgery and transcatheter procedures, but treatment of ischemic heart disease was not included) within 1 year after the index date.

### Statistical Analysis

Patient characteristics at index date are reported as count (%) for categorical variables and as median with interquartile range, using the 25th and 75th quartile, for continuous variables. We calculated the incidence rate (IR) of diagnosis with simple CHD according to age and calendar year. Reported were IRs per 1 000 000 person-years with 95% CIs separately for patients diagnosed

above and below 18 years of age. Probability of all-cause mortality was calculated using the Kaplan-Meier estimator and the probability of cardiac invasive procedure in the presence of competing risks of death with the Aalen-Johansen estimator. Reported were the 1-year mortality and the 1-year probability of cardiac invasive procedure, respectively, in subgroups defined by age at index date and calendar year. Kernel smoothing was used when reporting probabilities. We reported the proportion of ASD diagnoses preceded by ischemic stroke within 1 year.

All analyses were performed using the statistical software R.<sup>12</sup>

**Ethics**

Retrospective registry-based studies using anonymized data do not need ethical approval in Denmark. The Danish Data Protection Agency has approved the project (approval number P-2019-348).

**RESULTS**

We identified a total of 15 900 patients diagnosed with simple CHD (VSD, 5589 [35.2%]; ASD, 5563 [35.0%]; PDA, 4010 [25.2%]; PS, 738 [4.6%]) between January 1, 1977, and December 31, 2015 (Table 1). A total of 12 081 individuals (76.0%) were diagnosed before 18 years of age (Table 1). Numbers of individuals excluded in each step are listed in Figure 1 and Table S2. The sex-specific analyses are shown in Figures S1 to S6 and show similar trends to the overall results.

**Incidence Rate and Age at Time of Diagnosis**

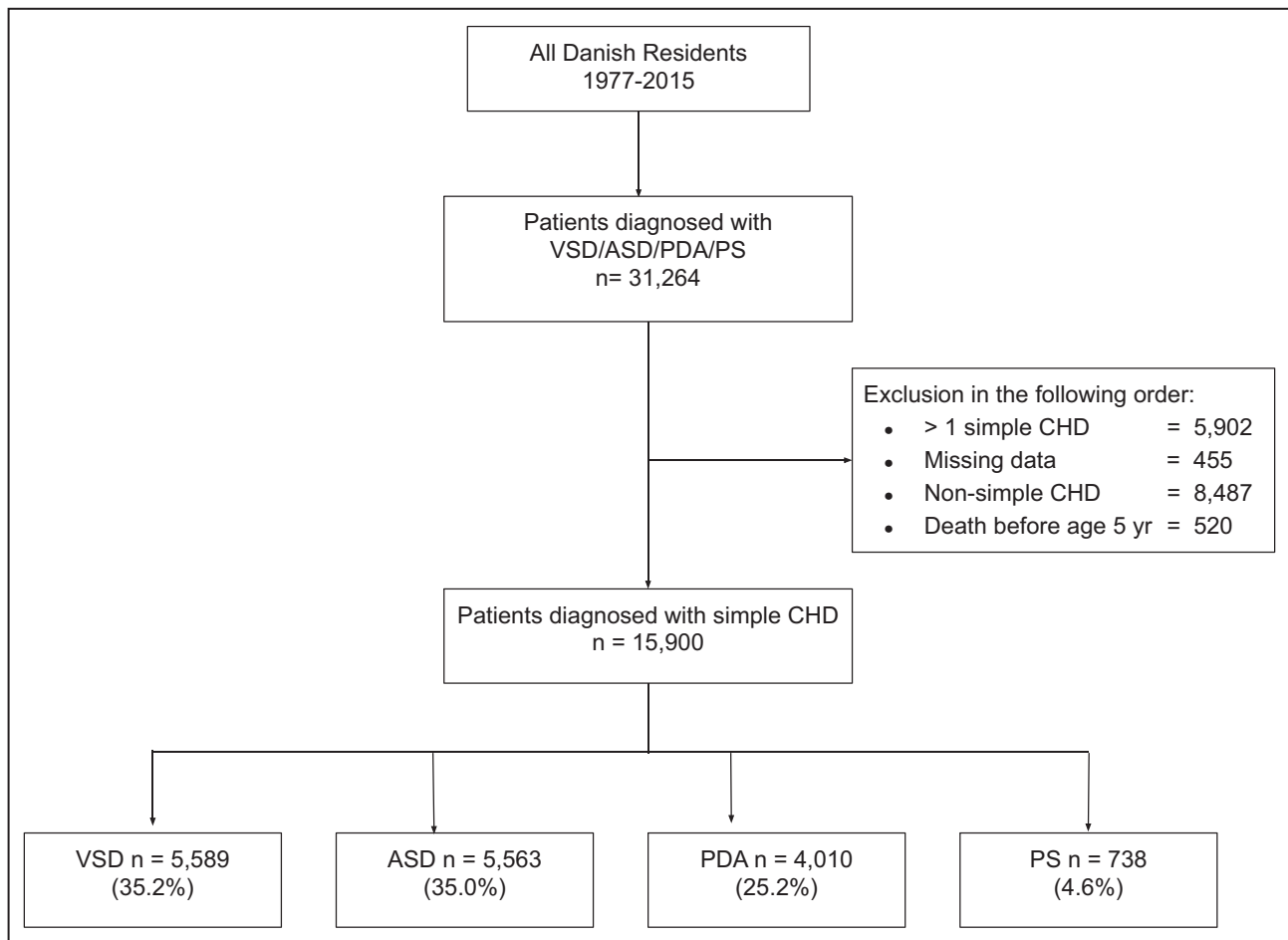
Overall, the IR of simple CHD has increased during the past 40 years (Table 2, Figure 2A). ASD and VSD were the overall most prevalent defects through the study period, followed by PDA (Table 1, Table S3). Among those diagnosed as children (before 18 years of age), the largest increase in IR throughout the study period was observed for ASD, in which the increase in IR was somewhat consistent between the early 1990s until the end of the study (Figure 2A). The second largest increase among children was observed in VSD, notably during the 1990s. Among those diagnosed as adults (≥18 years of age), the largest increase in IR was observed in ASD between 1997 and 2015, while the IRs of VSD, PDA, and PS remained relatively unchanged (Figure 3A). Since 2001, an increasing proportion of individuals diagnosed with ASD had a stroke diagnosis within 1 year

**Table 1. Baseline Characteristics of the Study Population, Stratified by Age at Time of Diagnosis**

Age, y	0-5	6-17	18-29	30-49	50-69	70≥	Total
Patients, n	10 408	1641	785	1351	1222	493	15 900
Sex, male, n (%)	5182 (49.8)	805 (49.2)	258 (32.9)	540 (40.0)	618 (50.6)	189 (38.3)	7592 (47.7)
Median age at diagnosis (IQR)	0.1 (0.0-0.4)	9.2 (6.6-13.3)	23.4 (20.5-26.6)	40.1 (34.9-45.2)	59 (54.0-64.1)	75.7 (72.7-79.5)	0.5 (0.1-16.0)
Genetic syndrome, n (%)	2537 (24.4)	267 (16.3)	113 (14.4)	129 (9.5)	79 (6.5)	10 (2.0)	3135 (19.7)
Ventricular septal defect, n (%)	3792 (36.4)	686 (41.8)	313 (39.9)	346 (25.6)	297 (24.3)	155 (31.4)	5589 (35.2)
Atrial septal defect, n (%)	2667 (25.6)	579 (35.3)	364 (46.4)	862 (63.8)	801 (65.6)	290 (58.8)	5563 (35.0)
Patent ductus arteriosus, n (%)	3517 (33.8)	218 (13.3)	72 (9.2)	95 (7.0)	76 (6.2)	32 (6.5)	4010 (25.2)
Pulmonary stenosis, n (%)	432 (4.2)	158 (9.6)	36 (4.6)	48 (3.6)	48 (3.9)	16 (3.2)	738 (4.6)

IQR indicates interquartile range, using the 25th and 75th quartile.

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**Figure 1.** Flowchart depicting study design and exclusion criteria.

ASD indicates atrial septal defect; CHD, congenital heart disease; PDA, patent ductus arteriosus; PS, pulmonary stenosis; and VSD, ventricular septal defect.

before their simple CHD diagnosis (Figure S7), but similar trends were not observed for the other simple CHD diagnoses (data not shown).

Among children, age at time of diagnosis decreased for all 4 types of simple CHD during the study period (Figure 2B); however, age at diagnosis among adults remained consistent (Figure 3B).

## Mortality

The overall 1-year mortality risk for all simple CHD diagnoses decreased throughout the study period. The largest absolute reduction in mortality was seen for the 60+ years group from 1977 to 1986 (30.9%) to 2007 to 2015 (9.6%; Table 3, Figure 4). For all included age groups, the largest decrease in mortality risk was observed in the period 1988 to 2003 (Figure 4). Similar trends were seen when stratifying by type of simple CHD (Figure S8) and when stratifying between those who have not undergone cardiac invasive procedures (1-year mortality risk from diagnosis time) and those who have (1-year mortality risk from 30 days after

first invasive procedure; Figure S9). The number of events and at-risk population used in risk calculation are listed in Table S4.

## Invasive Procedures

The 1-year probability of cardiac invasive procedure for individuals diagnosed as children decreased between the time periods 1977 to 1984 and 2007 to 2015 from 13.8% to 6.6% (Figure 5, Table 3), but increased for individuals diagnosed as adults from 13.3% to 29.6% (Figure 5, Table 3). The 1-year probability of invasive procedure stratified by type of simple CHD are shown in Figures S10 to S11 and Table S5. The number of events and at-risk population used in risk calculation are listed in Table S4.

## DISCUSSION

This nationwide study is the first to report annual changes in mortality risk and probability of invasive procedures in a nationwide population diagnosed with

**Table 2. Incidence Rates of Simple CHD per 1 000 000 Person Years, Stratified by Age and Calendar Year at Time of Diagnosis**

	1977–1986 IR per 1 Million PYRs (95% CI)	1987–1996 IR per 1 Million PYRs (95% CI)	1997–2006 IR per 1 Million PYRs (95% CI)	2007–2015 IR per 1 Million PYRs (95% CI)
<b>Children</b>				
ASD	26.6 (20.9–32.3)	47.2 (29.3–65.1)	72.8 (60.2–85.3)	150.8 (126.5–175.0)
VSD	72.1 (60.3–83.9)	100.9 (76.3–125.6)	112.0 (105.9–118.0)	115.4 (109.1–121.6)
PDA	49.2 (39.8–58.5)	99.8 (88.3–111.4)	85.6 (77.6–93.5)	102.2 (86.7–117.6)
PS	5.7 (3.0–8.3)	10.2 (5.3–15.1)	16.1 (11.7–20.5)	21.5 (17.2–25.7)
<b>Adults</b>				
ASD	8.8 (7.1–10.5)	6.8 (5.0–8.5)	13.9 (9.1–18.7)	31.8 (29.2–34.5)
VSD	6.2 (4.9–7.5)	6.8 (4.5–9.2)	6.7 (5.2–8.2)	7.8 (6.2–9.3)
PDA	2.3 (1.4–3.3)	1.4 (1.0–1.8)	2.0 (0.5–3.6)	1.4 (1.0–1.8)
PS	1.5 (0.9–2.1)	0.8 (0.3–1.2)	0.7 (0.5–0.9)	0.9 (0.7–1.1)

Children=diagnosed <18 years of age; adults=diagnosed ≥18 years of age.

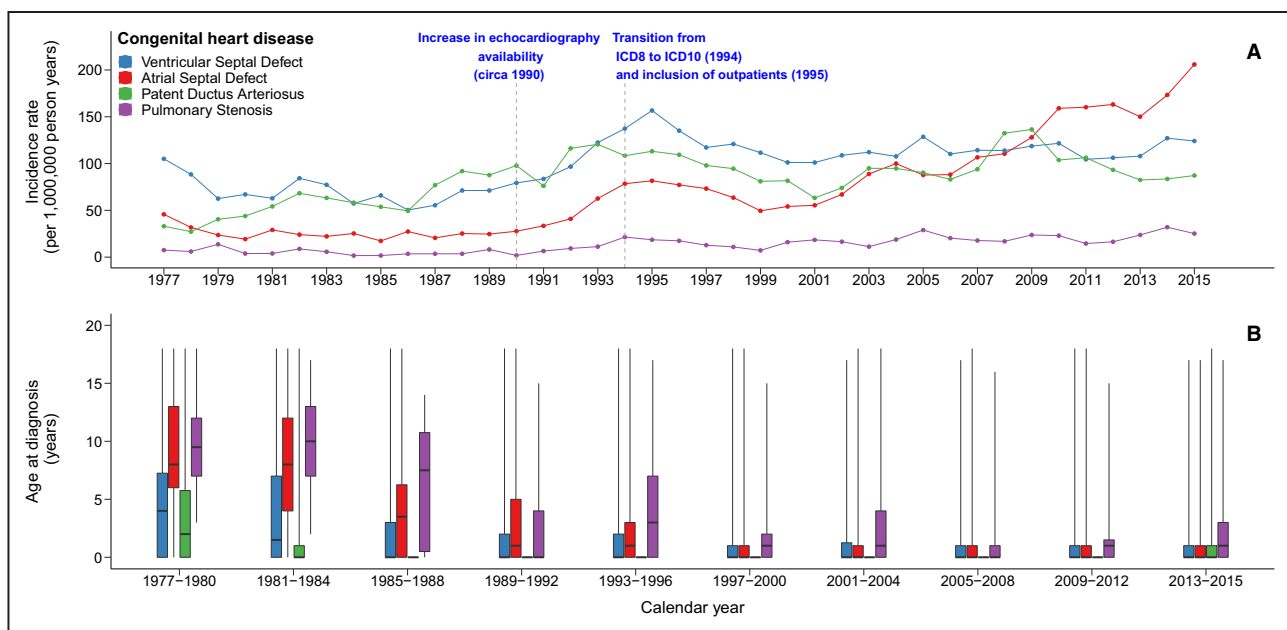
ASD indicates atrial septal defect; CHD, congenital heart disease, IR, incidence rate, PYRs, person-years, PDA, patent ductus arteriosus, PS, pulmonary stenosis; and VSD, ventricular septal defect.

simple CHD. We found an overall increase in incidence of simple CHD during the past 40 years, but a reduction of 1-year mortality among all ≥5 years of age. Furthermore, we observed an increased 1-year probability of invasive procedures among adults, driven mainly by increased probability of transcatheter procedures, but a decrease among children.

The observed increase in the incidence of all simple CHD in our study coincided with the widespread use of routine echocardiography in Denmark during the early 1990s.<sup>13,14</sup> Similarly, increased birth prevalence of ASD in the early 2000s has been observed

globally in a period that saw a higher usage of echocardiography as well as a general increase in hospital referrals.<sup>15</sup> Furthermore, general usage of cardiac computed tomography and, to a lesser degree, cardiac magnetic resonance imaging during the past 2 decades has increased for diagnostic and prognostic purposes.<sup>16</sup> Cardiac computed tomography and cardiac magnetic resonance imaging provide, in most cases, a superior noninvasive diagnostic and mapping capability compared with echocardiography, most notably in cases with involvement of the vascular system and are essential in prognostic

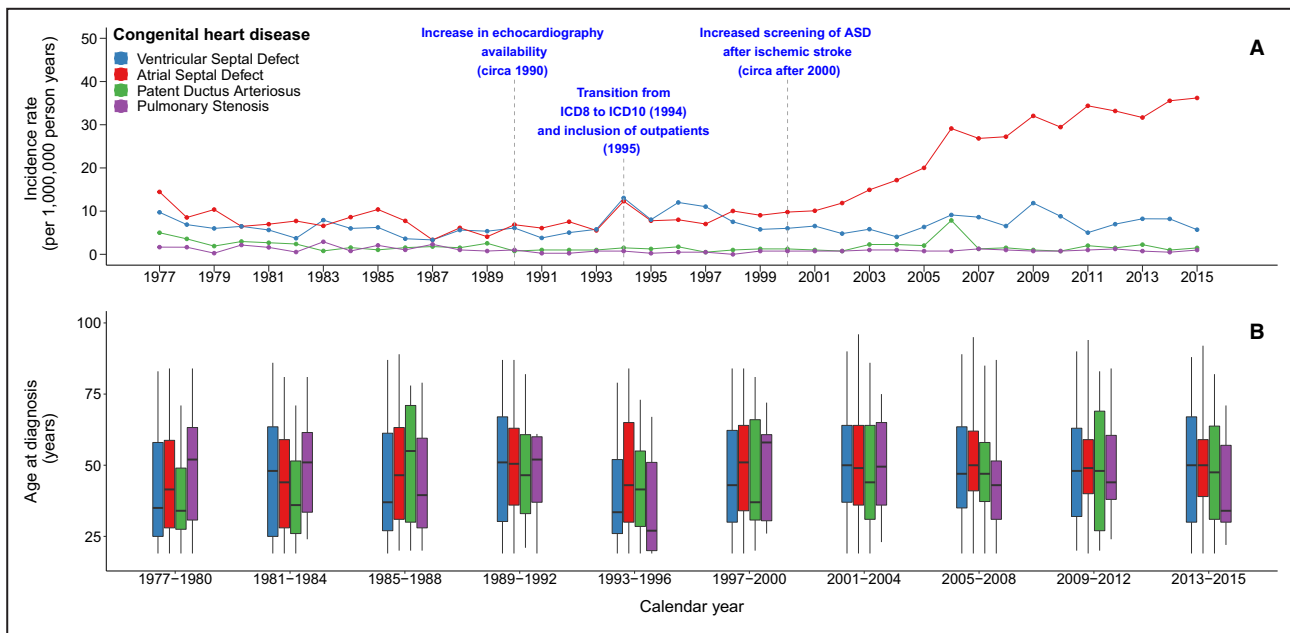
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**Figure 2. Incidence rate and age at time of diagnosis for individuals diagnosed before 18 years of age in Denmark between 1977 and 2015.**

(A) Crude incidence rate per 1 million-person years. (B) Distribution of age at time of diagnosis shown as boxplots.





**Figure 3.** Incidence rate and age at time of diagnosis for individuals diagnosed after 18 years of age in Denmark between 1977 and 2015. (A) Crude incidence rate per 1 million person-years. (B) Distribution of age at time of diagnosis shown as boxplots. ASD indicates atrial septal defect.

evaluation.<sup>3</sup> As such, it may be speculated that better detection of simple CHD is the primary reason for the increase in incidence, rather than an actual increase in frequency.<sup>17–19</sup> As an example, there was an increase in echocardiography screening of paradoxical embolism among stroke patients shortly after the year 2000.<sup>20</sup> This coincided with a higher proportion of ASD diagnoses but not other types of simple CHD, following a stroke diagnosis in adults in our study. In accordance with our study, an increase in device closures of ASD in Denmark has been reported,<sup>4</sup> as well as increased prevalence and rates of ischemic stroke among patients with ASD compared with the background population, regardless of closure status.<sup>6,7</sup> In the Danish registries, differentiating between ASD

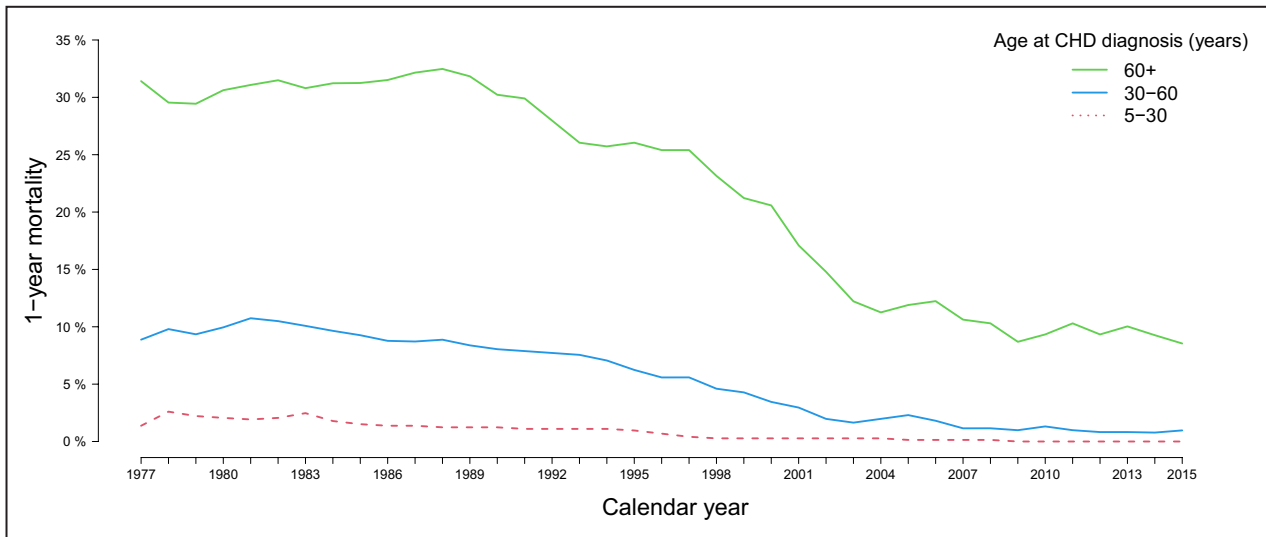
and patent foramen ovale using *ICD* diagnosis codes is difficult and unreliable; thus, an unknown part of the uptick in ASD incidence among adults might be attributable to patent foramen ovale. Unlike a small ASD, which is often subclinical, VSD and PDA have a more prominent murmur and, depending on the size of the defect, might be more symptomatic and readily clinically detectable leading to earlier diagnosis.<sup>8,21–24</sup> Thus, the general increase in hospital referral may be the explanation for why the ASD incidence has been steadily increasing even long after the introduction of echocardiography.

A recent meta-analysis showed a global increase in birth prevalence of “mild” CHD between 1970 and 2017, where the prevalence of VSD remained higher than ASD

**Table 3.** 1-Year Risk of Mortality and 1-Year Probability of Cardiac Invasive Procedure After Diagnosis in the Study Population of Simple CHD, Stratified by Age and Calendar Year at Time of Diagnosis

Age group	Calendar year of diagnosis			
	1977–1986	1987–1996	1997–2006	2007–2015
1-y mortality (%) (95% CI)				
5–30 y	1.9 (1.7–2.2)	1.1 (1.0–1.2)	0.3 (0.2–0.3)	0.0 (0.0–0.1)
30–60 y	9.5 (9.0–10.0)	7.6 (6.9–8.3)	3.1 (2.1–4.1)	1.0 (0.9–1.1)
60+ y	30.1 (30.3–31.5)	28.3 (26.3–30.3)	17.2 (13.4–20.9)	9.6 (9.0–10.2)
1-y procedure probability (%) (95% CI)				
Children	13.8 (12.6–15.0)	10.7 (9.3–12.1)	6.0 (5.1–7.0)	6.6 (6.0–7.2)
Adults	13.3 (11.1–15.5)	21.8 (20.4–23.2)	21.1 (20.2–22.0)	29.6 (26.2–32.9)

Children=diagnosed <18 years of age; adults=diagnosed ≥18 years of age. CHD indicates congenital heart disease.

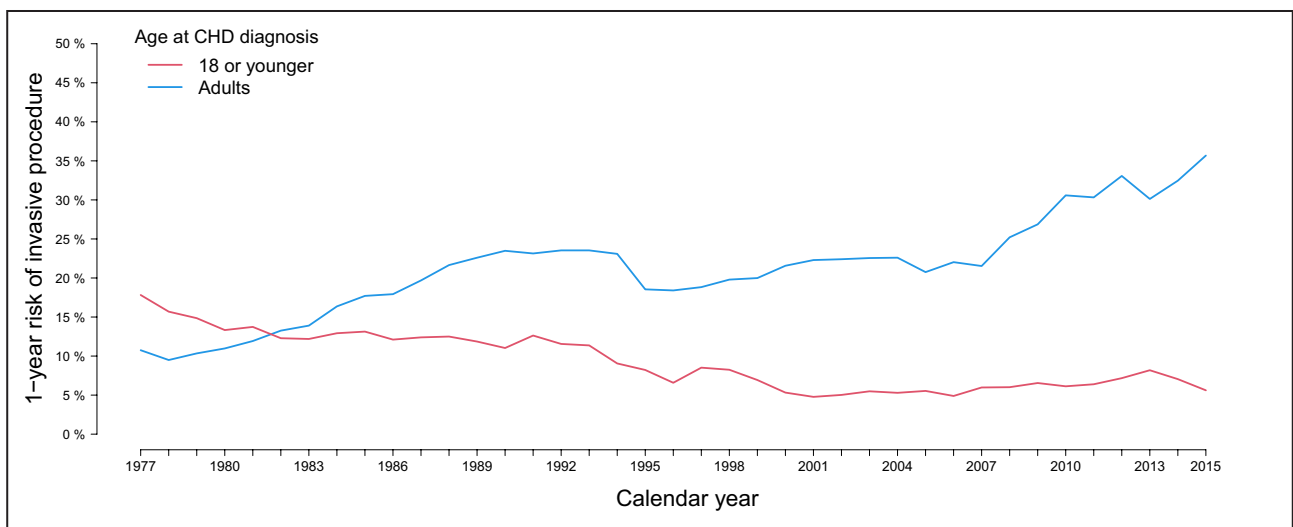


**Figure 4. All-cause mortality risk within 1 year after time of diagnosis, stratified by age at time of diagnosis.** CHD indicates congenital heart disease.

throughout the study.<sup>15</sup> Most of the studied papers, unlike our study, included only children up to 1 year of age and did not exclude those who died at a young age, both of which would affect the prevalence of ASD more negatively than VSD.<sup>22</sup> They also found a lower prevalence of PDA than would be expected from our study, possibly because of our study not excluding potential preterm PDA. Among adults, some cohort studies found that ASD, similarly to our observations, was the most frequently diagnosed CHD among adults between 1991 and 2014,<sup>25,26</sup> while another cohort study found VSD to be the most frequent CHD.<sup>27</sup> The discrepancy might be partly attributable to exclusion of those who

died during the first 5 years of age in our study. VSD has a higher early-life mortality and is detected clinically more readily than ASD, and as such this would affect the prevalence of VSD more negatively than ASD.

We found a lower incidence of PS than that of some studies<sup>14,28-30</sup> but not all.<sup>31,32</sup> This difference may be attributable to the studies classifying multiple concomitant CHDs as simple,<sup>14,28,30</sup> or they were conducted before echocardiography was widespread.<sup>29</sup> Correspondingly, most of the individuals with PS we identified from the National Danish Patient Registry also had other CHDs and were therefore not considered to have simple CHD in the present study.



**Figure 5. Probability of surgery within 1 year after time of diagnosis, stratified by age at time of diagnosis.** CHD indicates congenital heart disease.

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## Invasive Procedures

The general decrease in 1-year probability of invasive procedures among children in our study can partly be explained by the increased use of echocardiography and thereby increased detection of subclinical cases without need of invasive treatment.<sup>21</sup> Similarly, a previous study found via the Danish nationwide registries showed an overall decrease in the proportion of patients undergoing invasive treatment between 1977–1989 and 2003–2015 in all severities of CHD.<sup>4</sup>

The increased probability of invasive procedures among adults in our study may be explained by the general increase in incidence of simple ASD among adults and wider availability of ASD device closure,<sup>4</sup> which has become the treatment of choice for larger secundum ASDs suitable for device closure and in patients experiencing stroke with patent foramen ovale/ASD.<sup>2</sup> Concordantly, we found a general decrease in probability of surgery and increase in transcatheter procedures between 1996 and 2015. Previous studies from Europe and North America found that ASD was the most common CHD among adults who required surgery.<sup>33,34</sup> In both studies, a total number of patients with ASD, including those not requiring surgery, was not provided, making probability calculation impossible.<sup>33,34</sup>

## Mortality

The observed decrease in 1-year all-cause mortality risk after diagnosis of simple CHD in all included age groups in this study was most marked during 1988 to 2003. Increased life expectancy was observed generally among all individuals living in Denmark, including individuals with CHD.<sup>35,36</sup> Among individuals  $\geq 60$  years of age, we have observed a substantial drop in mortality during the study period. This drop appeared to coincide with the advent of interventional procedures in the late 1980s and early 1990s, hence minimizing the need for surgery, as well as the use of devices and improvements in pharmacological treatment of heart failure.<sup>37,38</sup>

Similar to our findings, Scandinavian studies have observed a temporal trend of improving survival among individuals with all severities of CHD, including simple, who have undergone surgical or catheter interventions between 1977 to 2015<sup>4</sup> or 1971 to 2011.<sup>39</sup> The study also found the biggest overall improvement in survival simple VSD, increasing from 84% to 98% during the past 4 decades.<sup>4</sup> Likewise, a multicenter registry-based study between 1979 and 2005 found a decline in the age-adjusted yearly mortality among ASD, VSD, and PDA, primarily in VSD, but without discerning between simple and nonsimple.<sup>40</sup>

## Strengths and Limitations

The main strengths of this study are the large sample size, long-term study period, minimal loss to follow-up,

and low risk of selection bias attributable to the nationwide registry and the tax-supported health care for all Danish citizens. The discharge codes for all types of CHD in the registry have been validated previously and were found to have a positive predictive value of 98.4% (*ICD-10*)<sup>11</sup> and 88.2% (*ICD-8*)<sup>11</sup> and a sensitivity of 89.9% for *ICD-8* and *ICD-10* codes combined. Although some of the studies validating the discharge diagnoses included only discharges from university hospitals, we included all Danish hospitals.<sup>11</sup>

A limitation of our study concerns the *ICD-10* system used in Denmark not discerning between simple and severe CHD. Information on subtype of simple CHD or size of shunt are not available in the registries, which raises the risk of misclassification. Previous registry-based studies use a hierarchical approach without requiring a simple CHD to be isolated to reduce misclassification.<sup>4,9,39,41</sup> In the present study, we have chosen to require a simple CHD to be isolated in accordance with American Heart Association guidelines,<sup>3</sup> and we have included only individuals who have survived the first 5 years as inspired by a previous study on simple CHD by Videbæk et al.<sup>8</sup> Unlike Videbæk et al, who included 15-year survivors, we opted to include 5-year survivors since most patients with clinically significant disease receive intervention earlier in life. Including only 5-year survivors excludes over 500 patients (Table 1). Comparatively, including only 15-year survivors excludes only 34 additional patients and has no impact on our results (data not shown).

Another limitation concerns individuals with multiple CHDs with different diagnosis dates, leading to a subgroup of patients with multiple CHDs whose size is unknown because of limited follow-up and truncation by death. To reduce this registration problem, we excluded patients if they received a second CHD diagnosis later.

A third limitation is that the transition from *ICD-8* to *ICD-10* codes in 1994 may have influenced our results to some degree since the *ICD-8* did not include a specific diagnosis code for pulmonary stenosis,<sup>11</sup> and the inclusion of outpatients since 1995 may have resulted in a sudden increase in our incidence results.

## CONCLUSIONS

The past 4 decades have seen considerable improvements in diagnostic and treatment options for CHD. These changes are reflected in increasing incidence rates, usage of cardiac procedures, and a temporally accompanying significant decrease in mortality in all age groups for simple CHD and point toward a steadily growing and aging population. However, there is still an undiagnosed portion of people with simple CHD as evident by the still increasing incidence rates in all

age groups. Broader screening for CHD could help to identify asymptomatic CHD and enable timely treatment and follow-up.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplementary Material

Tables S1–S5

Figures S1–S11

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# **SUPPLEMENTAL MATERIAL**

**Table S1.** Diagnosis and procedures codes used in this study.

	<b>ICD-8</b>	<b>ICD-10</b>
<b>Ventricular septal defect</b>	74639	Q210
<b>Atrial septal defect</b>	74640, 74649	Q211
<b>Patent ductus arteriosus</b>	74709	Q250
<b>Pulmonary stenosis</b>	74739, 74663	Q221
	<b>1977-1995</b>	<b>Since 1996</b>
<b>Cardiac surgery or procedure</b>	30200 – 32900	KFA-KFM, KFP, KPD, KFQ

ICD = International Statistical Classification of Diseases and Related Health Problems

**Table S2.** Exclusion of individuals in the order it was performed. Please note, in the first two columns are listed number of simple CHDs and not individuals. As such, one person can contribute to more than one simple CHD count.

Congenital defect	Exclusion criteria:				
	Relevant CHD identified, n	>1 simple CHD, n (individuals remaining)	Missing data, n (individuals remaining)	Non-simple CHD, n (individuals remaining)	Death <5 years, n (individuals remaining)
<b>ASD</b>	13,264	4,437 (8,827)	101 (8,726)	3,082 (5,644)	81 (5,563)
<b>VSD</b>	12,964	3,844 (9,120)	184 (8,936)	3,238 (5,698)	109 (5,589)
<b>PDA</b>	8,297	2,555 (5,742)	141 (5,601)	1,278 (4,323)	313 (4,010)
<b>PS</b>	3,149	1,476 (1,673)	29 (1,644)	889 (755)	17 (738)

CHD = Congenital heart defect, VSD = Ventricular septal defect, ASD = Atrial septal defect, PDA = Patent ductus arteriosus, PS = Pulmonary stenosis



**Table S3.** Number of individuals diagnosed with simple CHD in Denmark 1977-2015 and number of people at-risk, stratified by age and calendar year at time of diagnosis.

	<b>1977-1986</b> n events, (PYRS at-risk)	<b>1987-1996</b> n events, (PYRS at-risk)	<b>1997-2006</b> n events, (PYRS at-risk)	<b>2007-2015,</b> n events, (PYRS at-risk)
<b>Children</b>				
ASD	334 (12,470,590)	511 (10,864,333)	833 (11,398,398)	1,566 (10,424,670)
VSD	906 (12,470,590)	1,093 (10,864,333)	1,276 (11,398,398)	1,202 (10,424,670)
PDA	608 (12,470,590)	1,083 (10,864,333)	975 (11,398,398)	1,068 (10,424,670)
PS	72 (12,470,590)	110 (10,864,333)	185 (11,398,398)	223 (10,424,670)
<b>Adults</b>				
ASD	328 (37,433,997)	268 (39,535,800)	551 (39,675,882)	1,144 (35,915,300)
VSD	232 (37,433,997)	270 (39,535,800)	266 (39,675,882)	279 (35,915,300)
PDA	87 (37,433,997)	56 (39,535,800)	80 (39,675,882)	51 (35,915,300)
PS	55 (37,433,997)	31 (39,535,800)	28 (39,675,882)	33 (35,915,300)

Children = Diagnosed age <18 years, Adults = Diagnosed age ≥18 years.

CHD = Congenital heart disease, PYRS = person years, VSD = Ventricular septal defect, ASD = Atrial septal defect, PDA = Patent ductus arteriosus, PS = Pulmonary stenosis.

**Table S4.** Number of events and at-risk population used for calculating mortality risk and invasive procedure probability in the study population of simple CHD in Denmark 1977-2015, stratified by age and calendar year at time of diagnosis.

Please note: At-risk population for mortality does not include children age 0-5 years but they are included in procedure probability.

	<b>1977-1986 event, n (at-risk)</b>	<b>1987-1996 event, n (at-risk)</b>	<b>1997-2006 event, n (at-risk)</b>	<b>2007-2015 event, n (at-risk)</b>
<b>Mortality:</b>				
5-30 years	19 (993)	6 (493)	<5 (413)	<5 (527)
30-60 years	27 (319)	26 (294)	9 (492)	10 (924)
60+ years	50 (168)	61 (184)	37 (292)	39 (393)
<b>Procedure:</b>				
Children	259 (1,914)	286 (2,794)	248 (3,266)	375 (4,569)
Adults	114 (745)	193 (658)	335 (942)	757 (1,757)

Children = Diagnosed age <18 years, Adults = Diagnosed age ≥18 years.

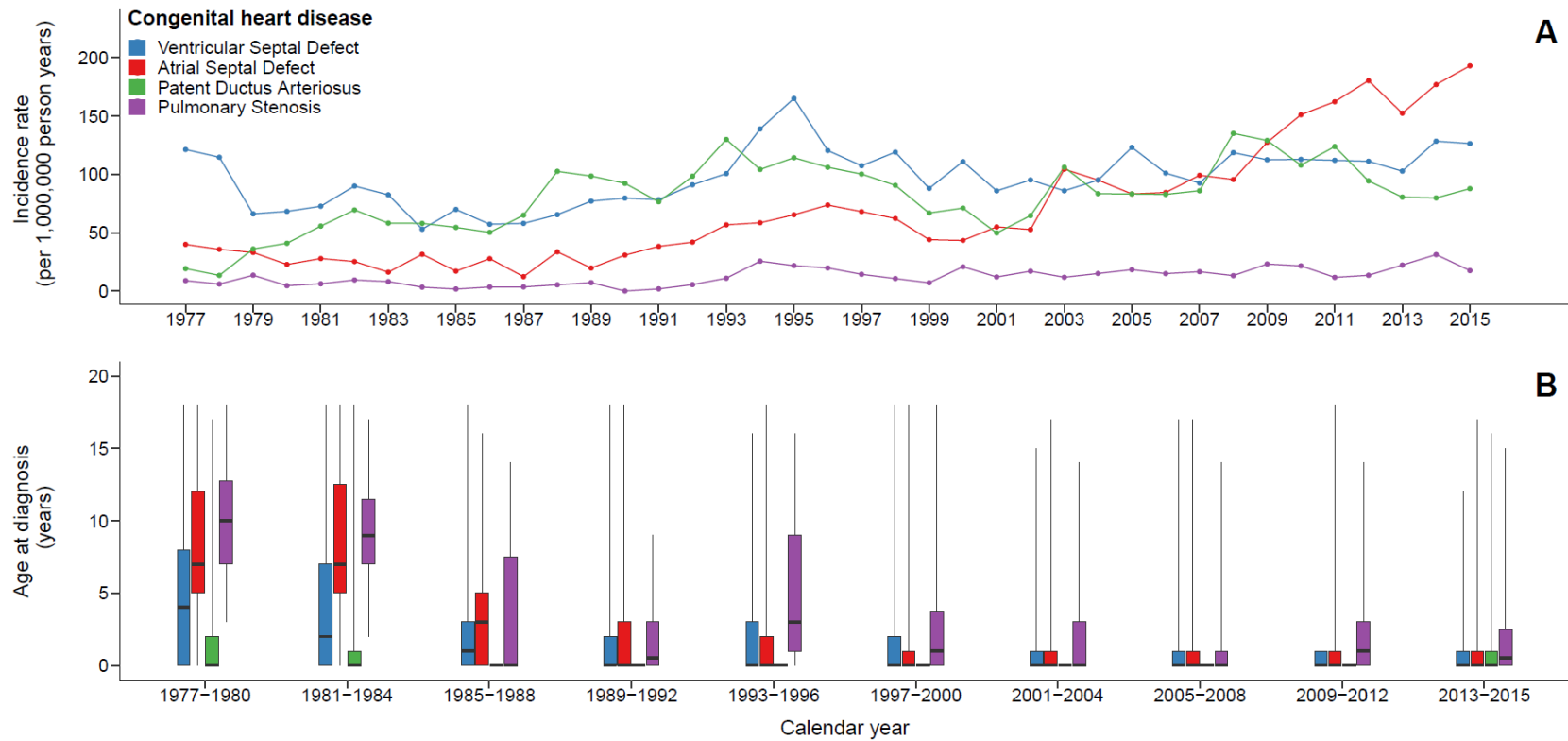
CHD = Congenital heart disease

**Table S5.** Number of procedures performed within 1 year after diagnosis time, stratified by calendar time groups, age at time of diagnosis and by diagnosis.

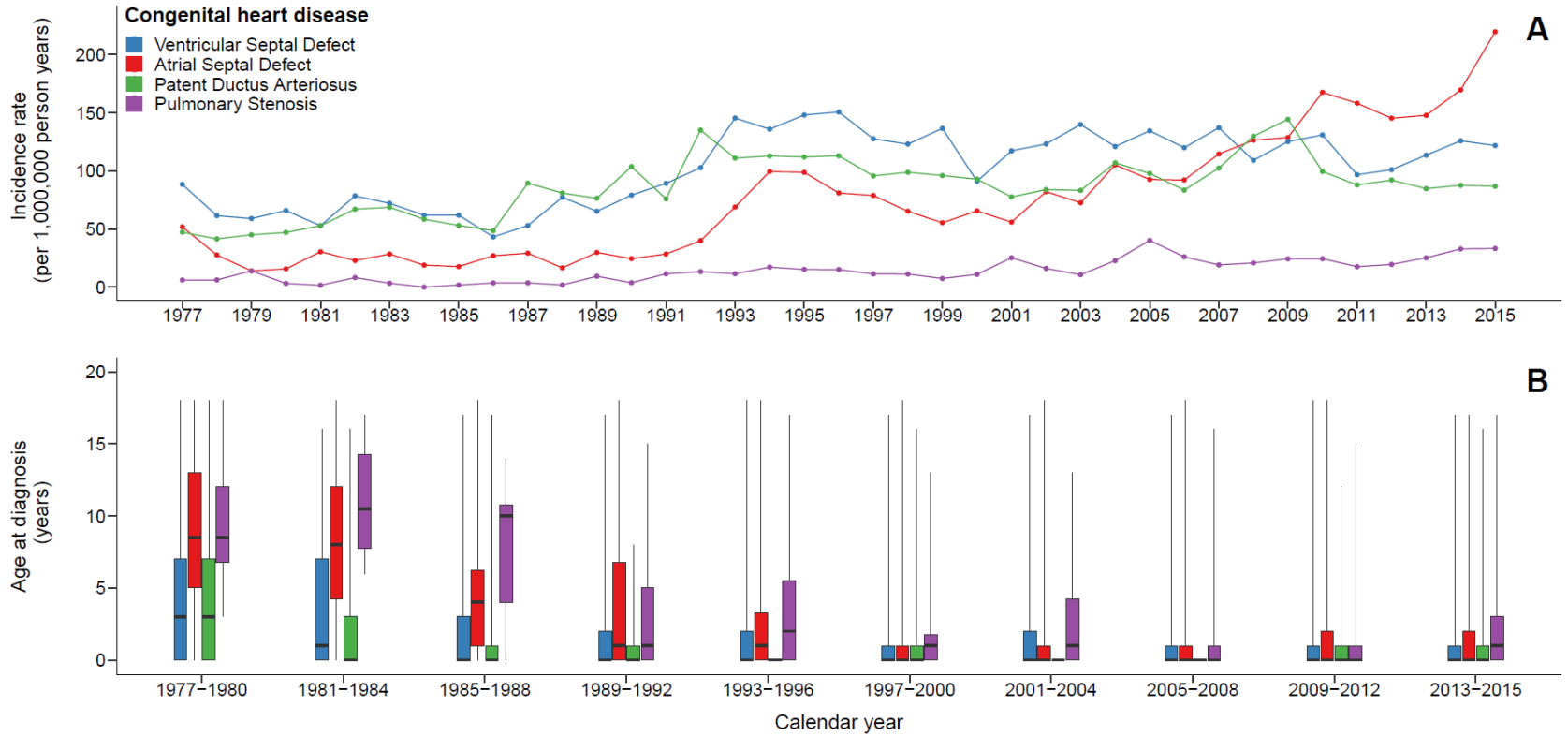
	<b>1977-1986 event, n (at-risk)</b>	<b>1987-1996 event, n (at-risk)</b>	<b>1997-2006 event, n (at-risk)</b>	<b>2007-2015 event, n (at-risk)</b>
<b>ASD</b>				
<b>Children</b>	75 (331)	76 (509)	43 (832)	90 (1,563)
<b>Adults</b>	80 (342)	113 (281)	247 (556)	584 (1,149)
<b>VSD</b>				
<b>Children</b>	27 (906)	41 (1,092)	60 (1,276)	84 (1,202)
<b>Adults</b>	25 (256)	61 (289)	63 (277)	50 (291)
<b>PDA</b>				
<b>Children</b>	153 (608)	167 (1,083)	137 (974)	143 (1,069)
<b>Adults</b>	5 (<100)	16 (<100)	20 (<100)	21 (<100)
<b>PS</b>				
<b>Children</b>	<5 (<100)	<5 (110)	8 (186)	17 (223)
<b>Adults</b>	<5 (<100)	<5 (<100)	5 (<100)	<5 (<100)

CHD = Congenital heart defect, VSD = Ventricular septal defect, ASD = Atrial septal defect, PDA = Patent ductus arteriosus, PS = Pulmonary stenosis

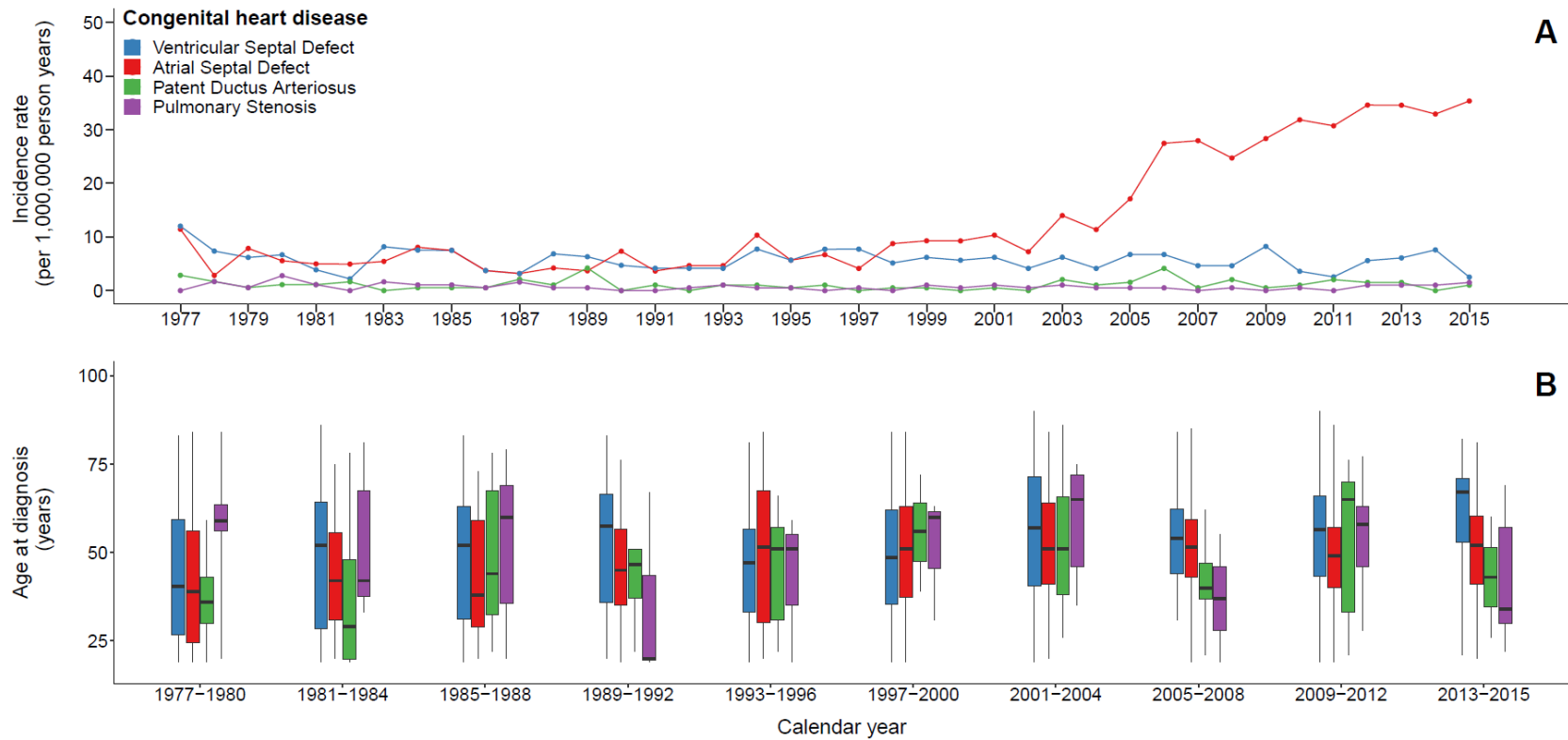
**Figure S1.** Males: incidence rate and age at time of diagnosis for individuals diagnosed before the age of 18 years in Denmark between 1977-2015. A: Crude incidence rate per 1 million-person years. B: Distribution of age at time of diagnosis shown as boxplots.



**Figure S2.** Females: incidence rate and age at time of diagnosis for individuals diagnosed before the age of 18 years in Denmark between 1977-2015. A: Crude incidence rate per 1 million-person years. B: Distribution of age at time of diagnosis shown as boxplots.

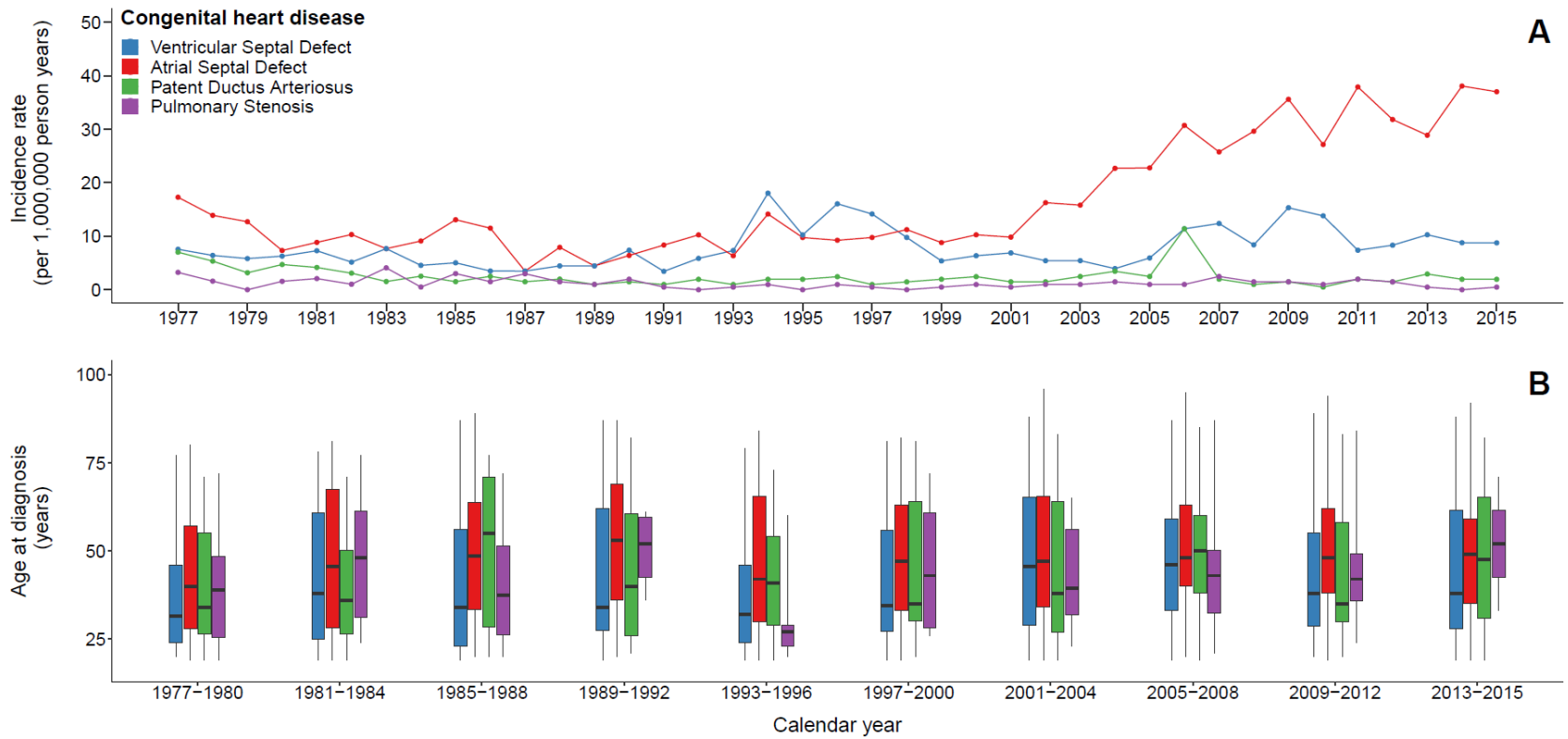


**Figure S3.** Males: Incidence rate and age at time of diagnosis for individuals diagnosed after the age of 18 years in Denmark between 1977-2015. A: Crude incidence rate per 1 million-person years. B: Distribution of age at time of diagnosis shown as boxplots.

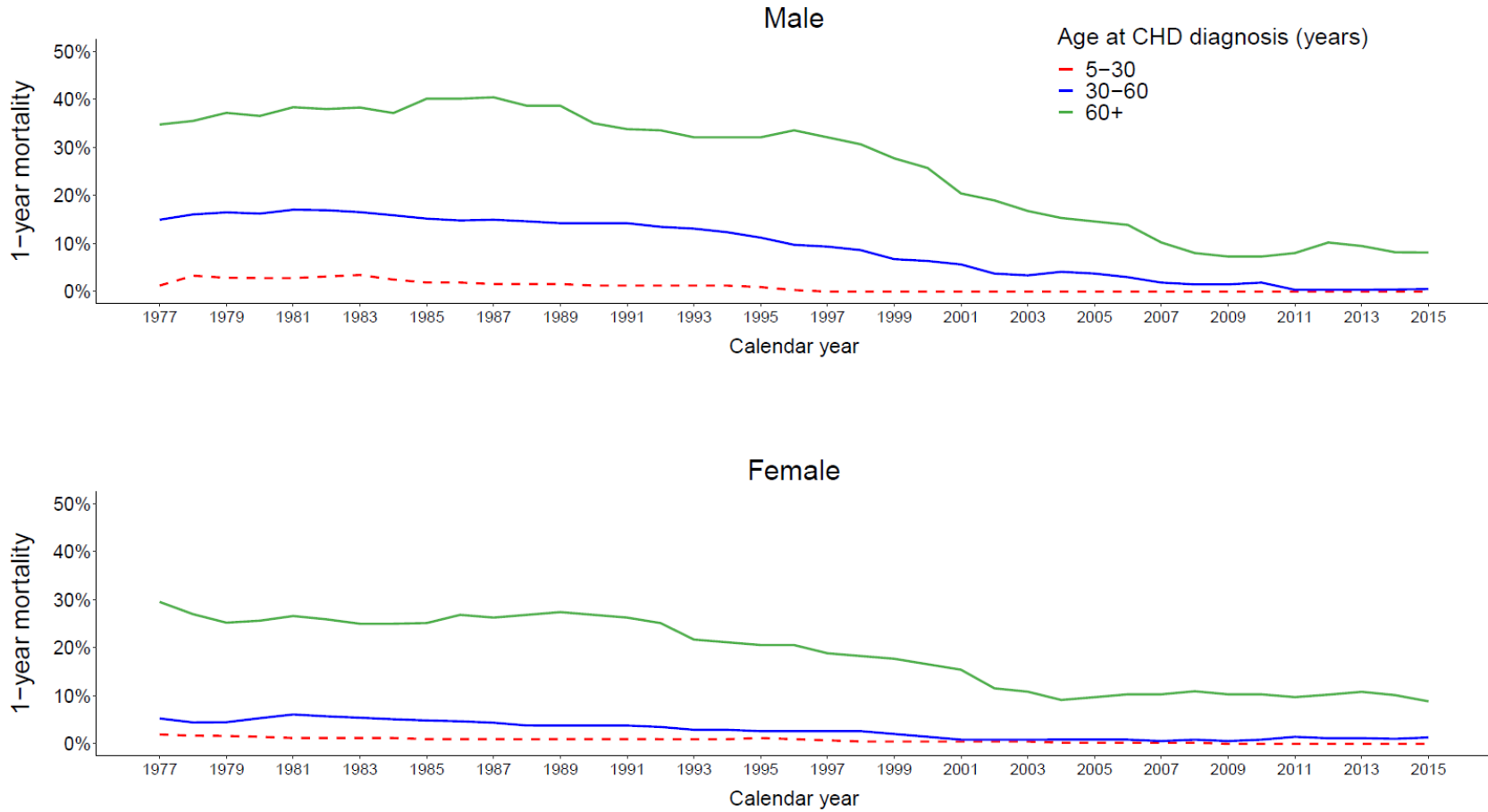




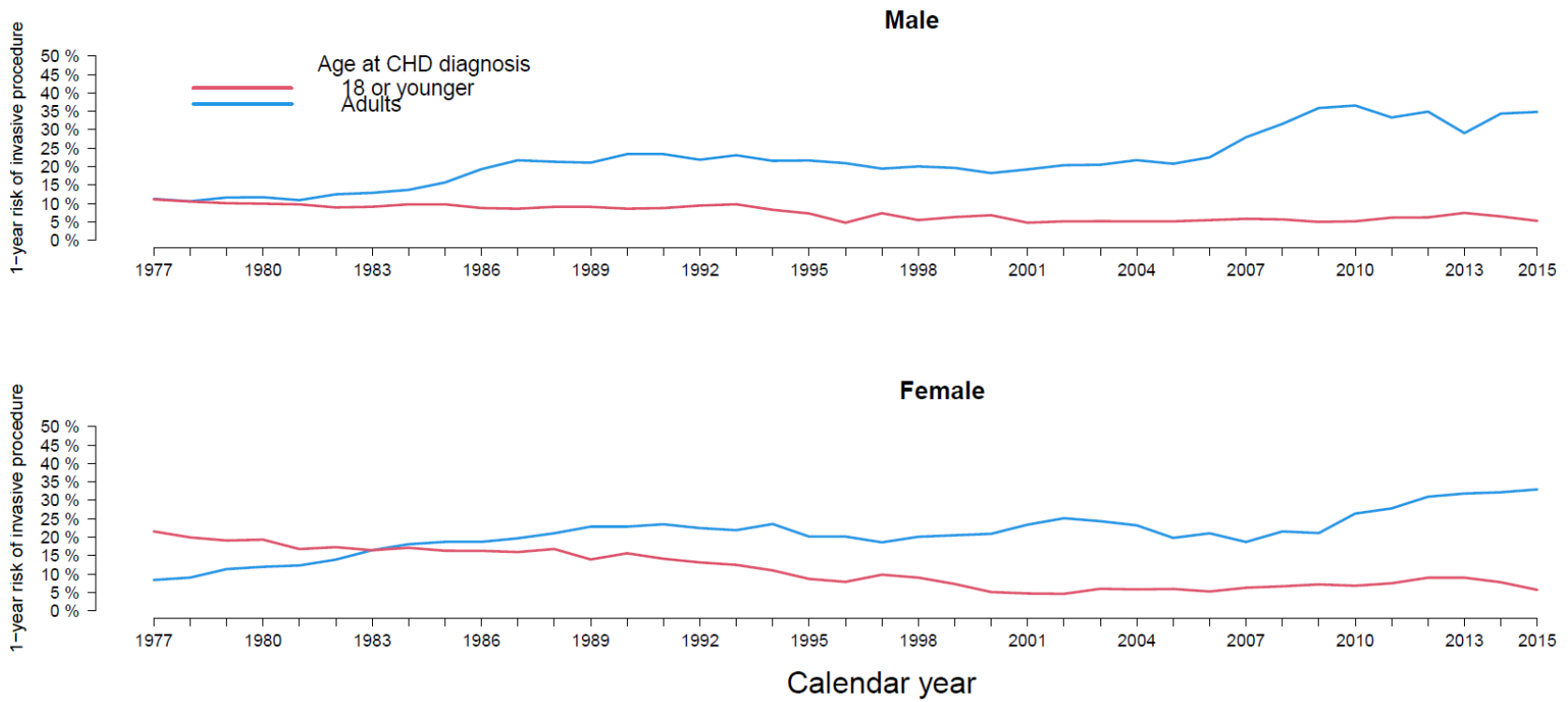
**Figure S4.** Females: Incidence rate and age at time of diagnosis for individuals diagnosed after the age of 18 years in Denmark between 1977-2015. A: Crude incidence rate per 1 million-person years. B: Distribution of age at time of diagnosis shown as boxplots.



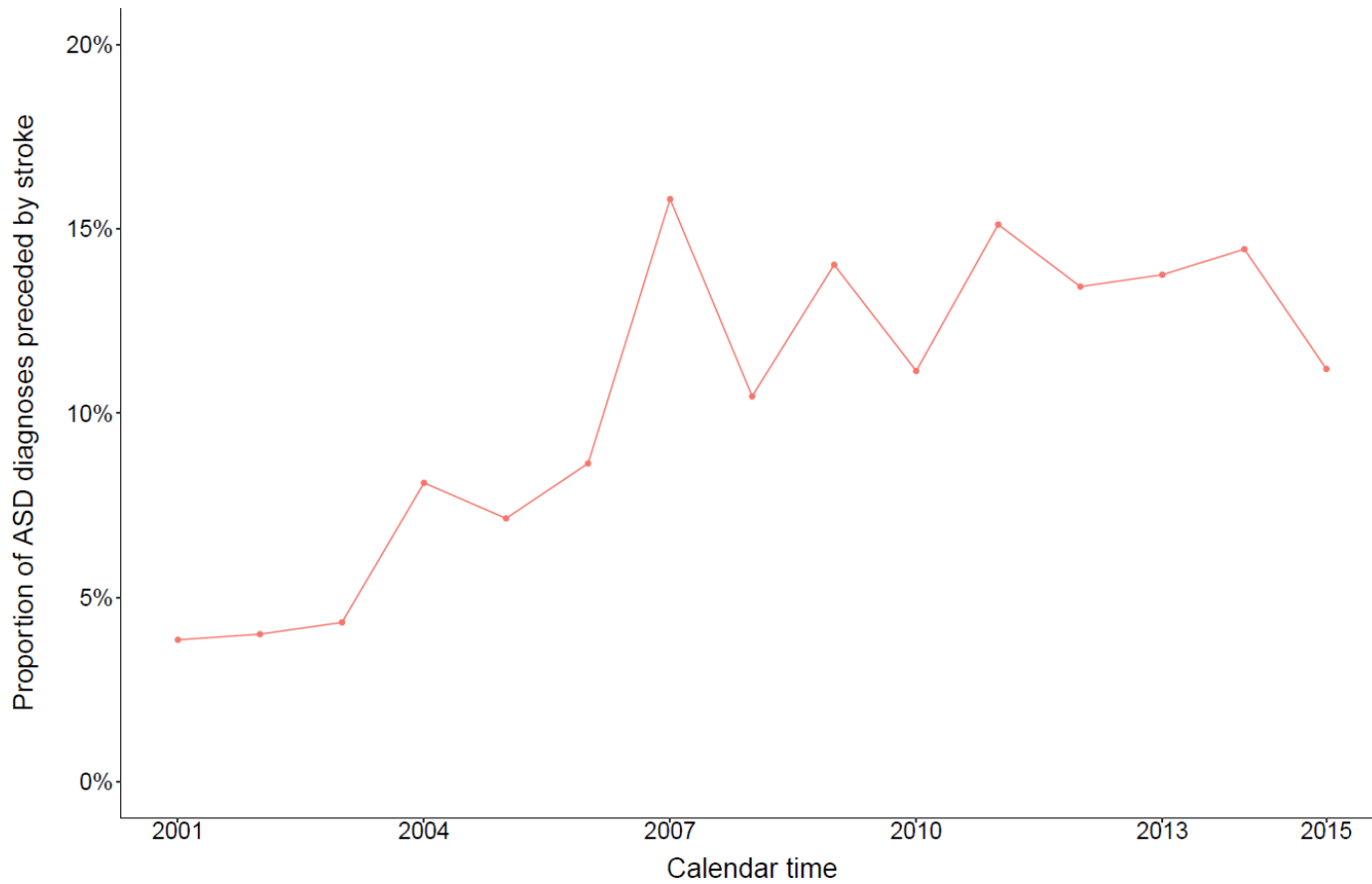
**Figure S5.** All-cause mortality risk within 1 year after time of diagnosis, stratified by age at time of diagnosis (in-plot) and by sex (between plots).



**Figure S6.** Probability of cardiac invasive procedure within 1 year after time of diagnosis stratified by age (in-plot) and sex (between plots).

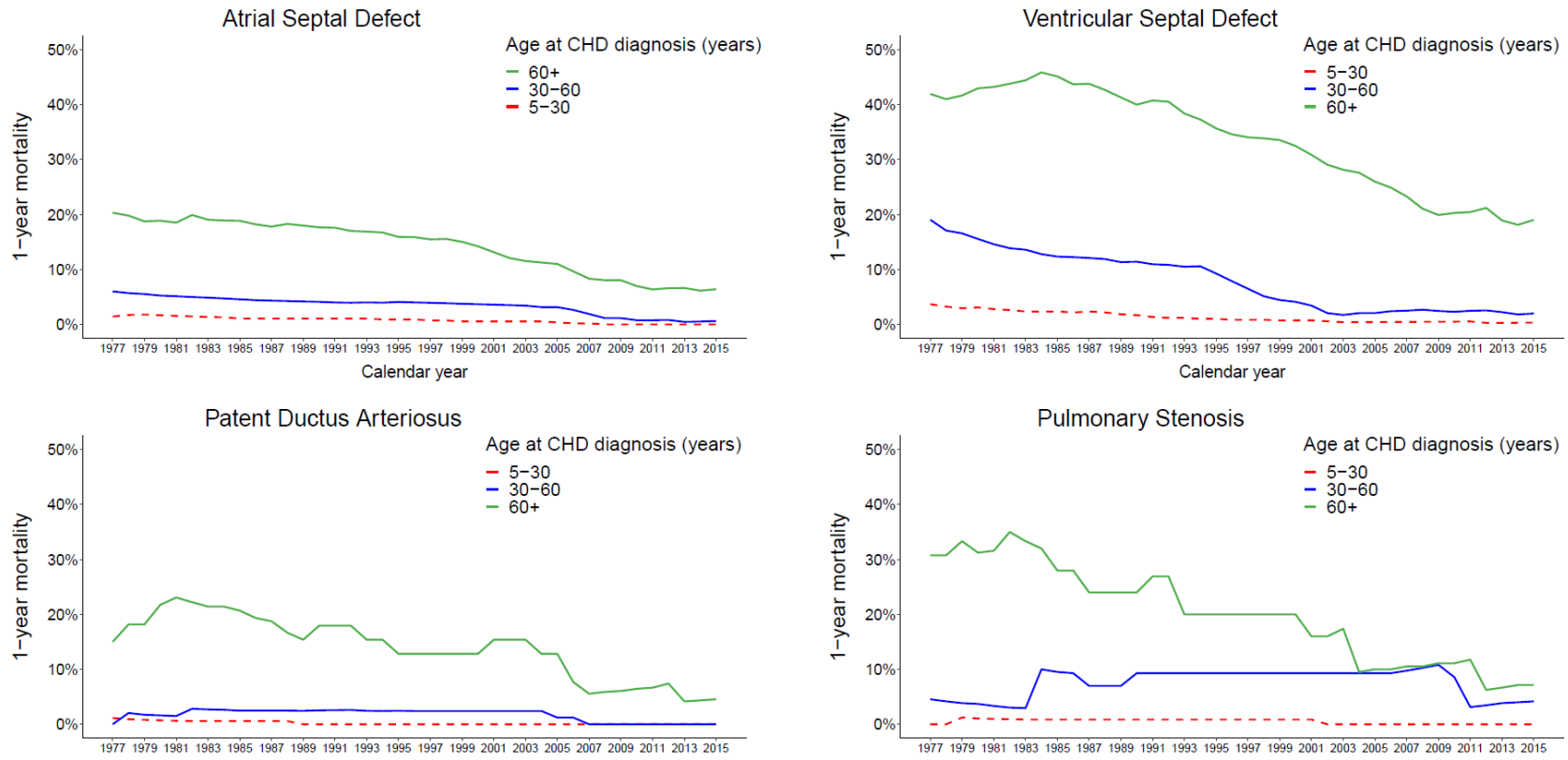


**Figure S7.** Proportion of simple atrial defects diagnoses who received stroke diagnosis within 1 year before ASD diagnosis between 2001-2015.



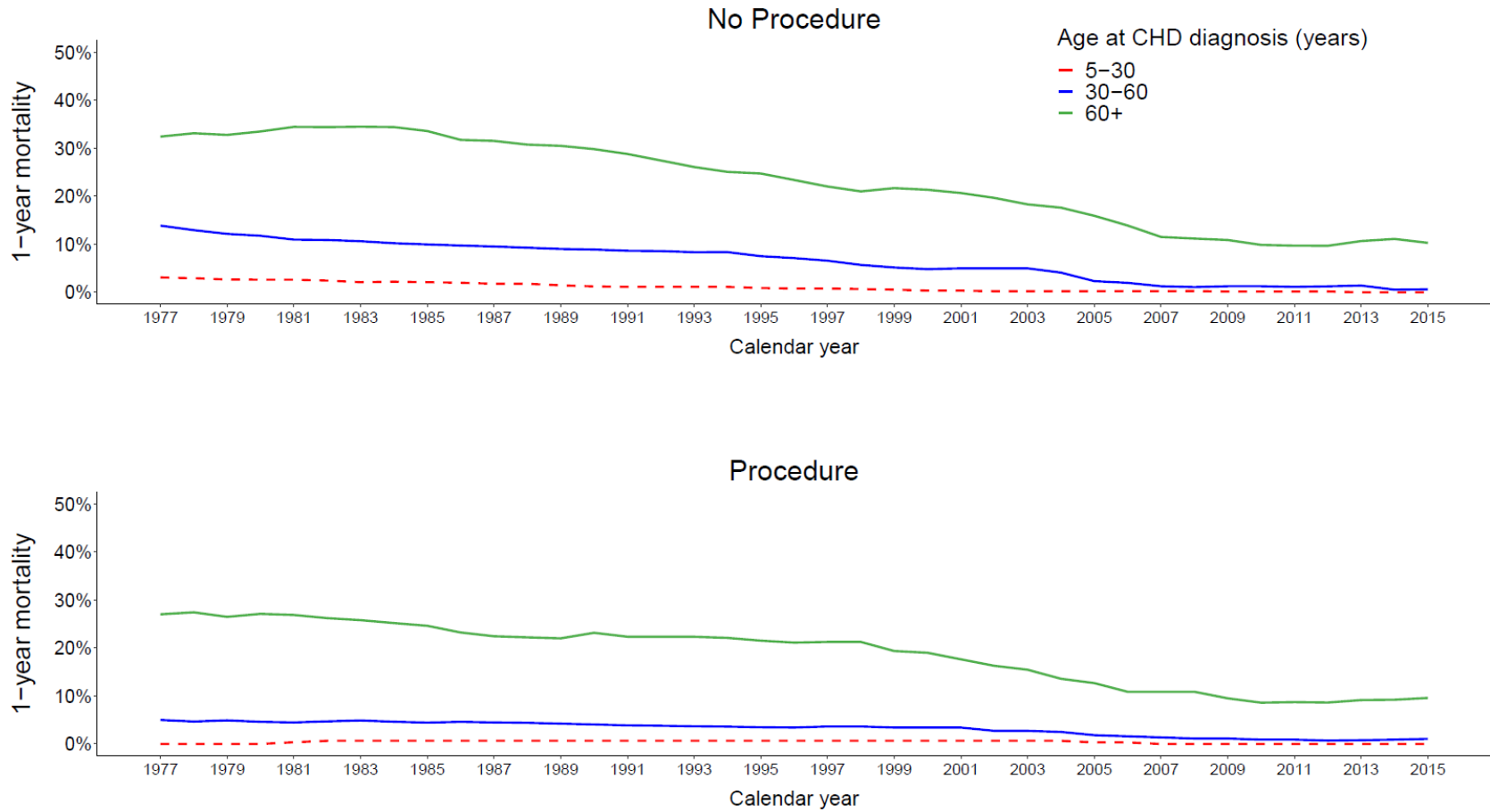
ASD = Atrial septal defect

**Figure S8.** All-cause mortality risk within 1 year after time of diagnosis, stratified by age at time of diagnosis (in-plot) and by diagnosis (between plots).



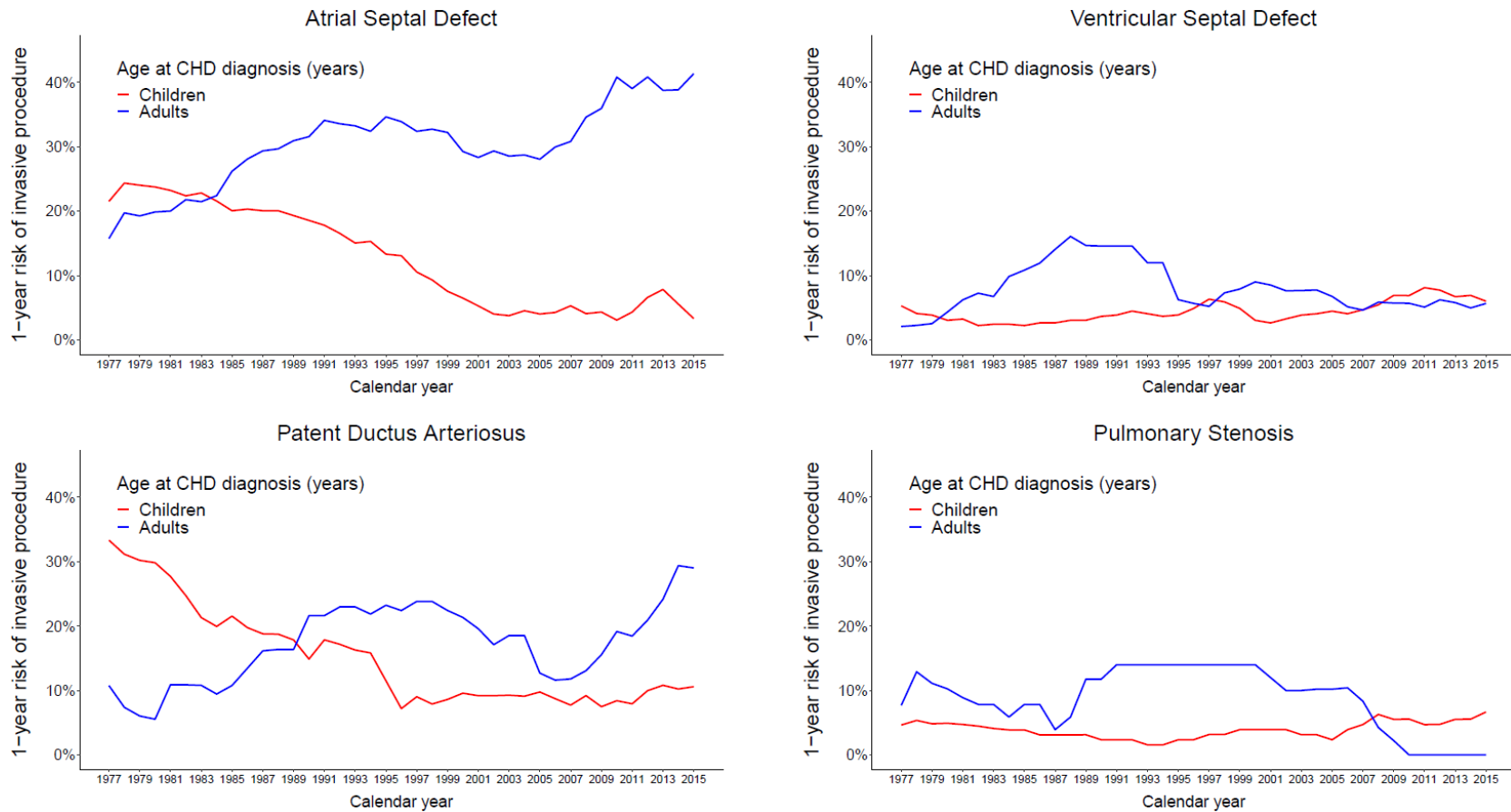
CHD = Congenital heart defect

**Figure S9.** All-cause mortality risk within 1 year after time of diagnosis, stratified by whether cardiac procedure was performed (between plots) and by age at time of diagnosis (in-plot).





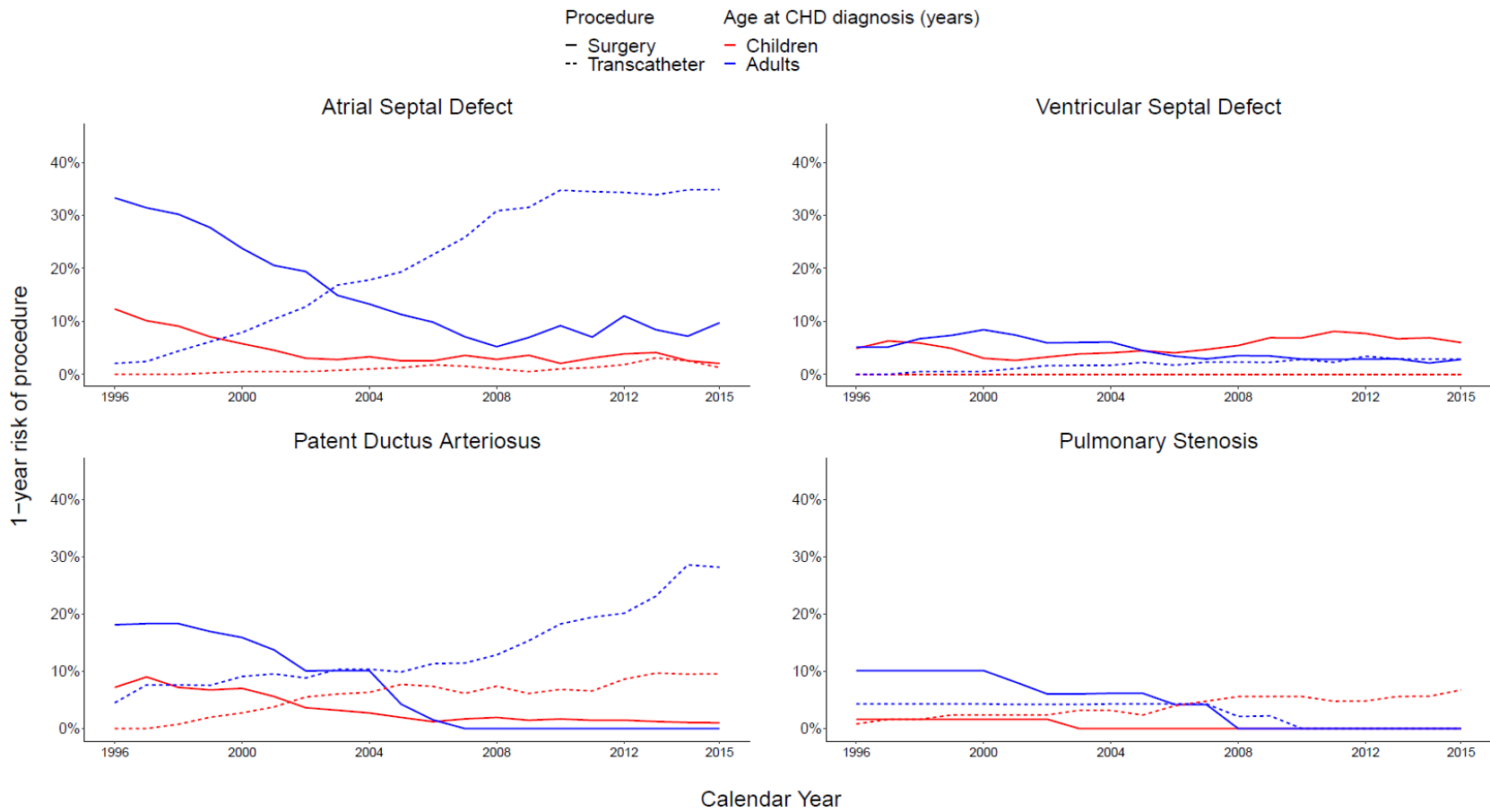
**Figure S10.** Probability of cardiac invasive procedure within 1 year after time of diagnosis stratified by age (in-plot) and by diagnosis (between plots).



Children = 18 years or younger, adults = Over 18 years

CHD = Congenital heart defect

**Figure S11.** Probability of cardiac invasive procedure within 1 year after time of diagnosis stratified by age (in-plot), diagnosis (between plots) and type of procedure (dotted vs solid lines).



Children = 18 years or younger, adults = Over 18 years

CHD = Congenital heart defect