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Young children with atrial septal defect

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“Do or do not, there is no try.” /Yoda

Contents

List of papers

This thesis is based on the following papers, which are referred to in the text by their roman numerals.

I. Tanghoj, G., Odermarsky, M., Naumburg, E. and Liuba, P.
Early complications after percutaneous closure of atrial septal defect in infants with procedural weight less than 15 kg
Pediatric Cardiology, Feb 2017

II. Tanghoj, G., Liuba, P., Sjoberg, G., Rydberg, A. and Naumburg, E.
Adverse events within 1 year after surgical and percutaneous closure of atrial septal defects in preterm children
Cardiology in the Young, May 2019

III. Tanghoj, G., Liuba, P., Sjoberg, G. and Naumburg, E.
Risk factors for adverse events within one year after atrial septal closure in children: a retrospective follow-up study
Cardiology in the Young, Jan 2020

IV. Tanghoj, G. Lindam, A., Liuba, P., Sjoberg, G. and Naumburg, E.
Incidence of atrial septal defect among preterm children and risk of atrial septal defects diagnosis
Congenital Heart Disease, Sept 2020

Abbreviations

ASD	Atrial septal defect
BPD	Bronchopulmonary dysplasia
CHD	Congenital heart defect
CI	Confidence interval
CPAP	Continuous positive airway pressure
IRDS	Infant respiratory distress syndrome
LV	Left ventricle/ventricular
MBR	Swedish Medical Birth Register
NICU	Neonatal intensive care unit
OR	Odds ratio
PDA	Persistent ductus arteriosus
PDC	Percutaneous device closure
PFO	Patent foramen ovale
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the new-born
RA	Right atrium/atrial
RV	Right ventricle/ventricular
SD	Standard deviation
SGA_w	Small for gestational age
SWEDCON	Swedish Registry of Congenital Heart Disease
TEE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
VLBW	Very low birthweight

Definitions

Term birth: Born after 37 completed gestational weeks.

Preterm birth: Born before 37 completed gestational weeks.

Late preterm: Born between 32 to < 37 gestational weeks.

Very preterm: Born between 28 to < 32 gestational weeks.

Extremely preterm: Born before 28 completed gestational weeks.

VLBW: Birthweight less than 1,500 g.

SGA_w: Born with weight less than -2 SD from expected normal weight based on gestational age.

ASD II: Secundum atrial septal defect. A defect within the fossa ovalis usually due to one or several defects within septum primum.

Qp:Qs: The ratio between pulmonary blood flow and systemic blood flow. Normal value 1:1.

Abstract

Background
Secundum atrial septal defect (ASD II), situated within the fossa ovalis, is the third most common congenital heart defect and even more common among preterm children. Spontaneous closure usually occurs during the first year of life. Most children with an ASD II remain asymptomatic during early childhood. Guidelines recommend ASD II closure in the presence of a significant left-to-right shunt. Percutaneous device closure, which is most commonly used, and surgery are both considered safe, with few major adverse events.

In Sweden, approximately 6% of all children are born preterm. The morbidity of preterm children includes increased risk of chronic pulmonary disease and altered cardiac morphology and function which remain into adulthood. Most studies on ASD II incidence and interventional and surgical risks following ASD II closure are based on otherwise healthy children. Preterm children are a special subset of patients with ASD II and the hypothesis in this thesis is that preterm birth may be associated with increased risks of ASD II diagnosis and adverse events following closure.

Aim
The overall aim of this thesis was to assess the incidence of ASD II, independent risk factors associated to ASD II diagnosis, and adverse events following ASD II interventional closure.

Methods
Paper I: A retrospective case-control study assessing associated risk factors for adverse events after percutaneous device closure among children with an interventional weight of less than 15 kg.
Paper II: A cohort study assessing a preterm and a term cohort and time to first adverse event within one month or one year after ASD II closure, as well as number of events.
Paper III: A retrospective case-control study assessing the association between major and minor adverse events after ASD II closure, and potential paediatric risk factors.
Paper IV: A national registry-based retrospective incidence and case-control study calculating the incidence of ASD II diagnosis among term and preterm children and assessing potential maternal, neonatal, and paediatric risk factors for ASD II.

Results
Paper I: No independent risk factor was associated with adverse events after percutaneous device closure. However, major adverse events occurred in 11 (10%) of the children weighing less than 15 kg, compared with six (4%) children weighing over 15 kg ($p = 0.04$).
Paper II: There was no difference between the preterm and term cohorts in time to first adverse event or in multiple adverse events within one month or within a year, neither in number of major events ($p = 0.69$) nor in number of minor events ($p = 0.84$). However, the preterm cohort was younger (2.1 versus 3.4 years, $p < 0.01$), lighter (11.6 versus 15.1 kg, $p < 0.01$), had a smaller ASD II size (12.0 versus 13.0 mm, $p< 0.01$), and a larger ASD II size to weight ratio (1.1 versus 0.8, $p < 0.01$) compared with the term cohort.
Paper III: ASD II with significant clinical symptoms was associated with both minor OR = 2.18, (CI 95% 1.05–8.06) and major OR = 2.80 (CI 95% 1.23–6.37) adverse events following closure.

Paper IV: The yearly overall incidence of ASD II was 150 per 100,000 live births. However, this incidence ranged from 449 to 1,737 per 100,000 live births, with higher incidence in preterm children. ASD II was associated with a presence of persistent ductus arteriosus; OR = 8.11 (CI 95% 2.80–16.69), female gender; OR = 1.39 (CI 95% 1.18–1.63), and being small for gestational age; OR = 1.86 (CI 95% 1.29–2.68). Being born preterm was also associated with ASD II diagnosis: born at 32–36 gestational weeks; OR = 3.21 (CI 95% 2.46–4.19), and born at < 32 gestational weeks; OR = 4.02 (CI 95% 2.80–7.12).

Conclusions

Preterm children have a high incidence of ASD II diagnosis, increasing with lower gestational age at birth, and is an independent risk factor for ASD II diagnosis. Few adverse events occurred among children following ASD II closure, and there were no neonatal or paediatric risk factors (including procedural body weight and gestational age) associated with adverse events. There was an association between clinical symptomatic ASD II and major adverse events. Despite younger procedural age, larger ASD II size to weight ratio and increased comorbidity, preterm children appeared to have similar risks of adverse events during the first year after ASD II closure when compared with term children.

Preterm children and children with symptomatic ASD II need careful management both prior to and after ASD II closure. A new, structured follow-up programme with assessment of indication and timing of treatment and closure should be considered for children born preterm.

Sammanfattning på svenska

Små barn med hål mellan förmaken, ASD II

Bakgrund

Av alla barn som föds i Sverige har ungefär 1 % ett medfött hjärtfel. Ett av de vanligaste medfödda hjärtfelen är förmaksseptumdefekt, där blod kan flöda från vänster till höger förmak genom ett hål i förmakens skiljevägg och sedan vidare ned till hjärtats högra kammare. Detta ökade flöde av blod kommer på sikt att skada hjärtats kammarmuskulatur. Under barnaåren har barnet oftast inga symptom vid förmaksseptumdefekt och vanligen behöver hålet inte åtgärdas förrän en tydlig hjärtmuskelpåverkan är synlig. Dagens riktlinjer rekommenderar en slutning vid tre till fyra års ålder. Såväl öppen kirurgisk som kateterledd slutning av förmaksseptumdefekt anses som säkra metoder även för små barn.

I Sverige föds ca 6 % av alla barn prematurt, det vill säga innan den 37:e gestationsveckan. Dessa barn har ofta flera medicinska problem, både i samband med födelsen och långt upp i åren. Lungmognaden sker sent under graviditeten och prematurt födda barn får ofta lungproblem till följd av en avbruten utveckling av lungorna samt ett förhöjt tryck i lungkretsloppet. Dessutom är deras hjärtmuskulatur strukturellt och funktionellt förändrad jämfört med de fullgångna barnens. Det är dubbelt så vanligt att prematura barn har ett medfött hjärtfel jämfört med fullgångna barn och de behöver oftare behandling av hjärtfelet.

Prematurt födda barn med förmaksseptumdefekt kan utveckla sjukdomar såväl i lungorna som i hjärtat och i större utsträckning än fullgångna barn. Vissa studier visar att en tidig behandling med slutning av en förmaksseptumdefekt kan vara gynnsam för prematura barn. Man kan nu genomföra en slutning av en förmaksseptumdefekt på allt yngre och lättare barn. Denna intervention anses vara en relativt enkel och säker åtgärd. Vidare är prematurt födda barn överrepresenterade bland barn som behöver behandling av en förmaksseptumdefekt.

Få studier har studerat sambandet mellan en behandling med slutning av en förmaksseptumdefekt och risk för komplikationer hos prematurt födda barn. Det saknas också aktuella incidensstudier av diagnosen förmaksseptumdefekt hos prematura barn.

Hypotesen i denna avhandling är att prematura barn har en ökad risk för komplikationer efter en behandlande åtgärd av förmaksseptumdefekten. Vidare, att små barn, lättare än 15 kg vid slutning, har en ökad risk för komplikationer efter åtgärd av förmaksseptumdefekten jämfört med tyngre barn. Slutligen att prematura barn har en ökad förekomst, incidens, av förmaksseptumdefekt.

Mål

Målet med denna avhandling var att kartlägga riskfaktorer för komplikationer efter åtgärd av förmaksseptumdefekt, samt att kartlägga riskfaktorer för och incidensen av förmaksseptumdefekt hos prematura och fullgångna barn.

Metoder

Denna avhandling består av fyra delarbeten och gemensamt för alla arbeten är att de är retrospektiva, det vill säga tillbakablickande.

Delarbete I: En fall-kontrollstudie som bedömde möjliga riskfaktorer för komplikationer till följd av kateterledd förmaksseptumdefektslutning hos barn. Fall definierades som barn med komplikationer och kontroller som barn utan komplikationer. Bland riskfaktorerna som analyserades var kroppsvikt under 15 kg vid slutningen, en stor förmaksseptumdefekt i förhållande till kroppsvikten eller kroppsytan, en annan hjärtsjukdom eller en kromosomdefekt.
Delarbete II: En kohortstudie som bedömde skillnader i förekomst och tid till en komplikation, inom en månad och inom ett år efter förmaksseptumdefektslutning (såväl kateterledd som kirurgisk), samt förekomsten av flera komplikationer. Två kohorter, prematurfödda barn och fullgångna barn, jämfördes.
Delarbete III: En fall-kontrollstudie som bedömde möjliga pediatriska riskfaktorer för komplikationer till följd av slutning av förmaksseptumdefekt (kateterledd eller kirurgisk). Fall definierades som barn med komplikationer och kontroller som barn utan komplikationer.
Delarbete IV: En nationell registerbaserad fall-kontrollstudie som bedömde möjliga pediatriska riskfaktorers betydelse för risken att diagnostiseras med en förmaksseptumdefekt. Studien beräknade också förekomsten, incidensen av diagnosen förmaksseptumdefekt för såväl fullgångna som prematurt födda barn.

Resultat
Delarbete I: Inga riskfaktorer kopplade till komplikationer efter kateterledd slutning av förmaksseptumdefekter kunde identifieras. Däremot var det statistiskt sett vanligare med allvarliga komplikationer hos barn lättare än 15 kg (10 stycken, 11 %) än hos tyngre barn (sex stycken, 4 %).
Delarbete II: Ingen skillnad i förekomst av komplikationer eller tiden till komplikationer kunde identifieras mellan den prematura och den fullgångna kohorten. Däremot var den prematura kohorten statistiskt yngre (2,1 jämfört med 3,4 år), lättare (11,6 jämfört med 15,1 kg), och hade en mindre förmaksseptumdefekt (12,0 jämfört med 13,0 mm) än kohorten av fullgångna barn.
Delarbete III: Den enda riskfaktorn som var associerad med komplikationer efter slutning av förmakseptumdefekten var att denna var symptomgivande och innebar en nästan dubbelt så stor risk att utveckla komplikationer efter slutningen.
Delarbete IV: Incidensen av förmaksseptumdefekter var 150 per 100 000 levandefödda barn och ännu vanligare hos prematurt födda barn (mellan 449 och 1 737 per 100 000 levandefödda barn, ökande vid högre grad av prematuritet). Prematuritet, undervikt vid födelsen, kvinnligt kön och öppetstående ductus arteriosus var alla associerade riskfaktorer för att diagnostiseras med förmaksseptumdefekt.

Slutsats
Prematurt födda barn har en ökad incidens av förmaksseptumdefekt och har även större risk att diagnostiseras med förmaksseptumdefekt. Varken prematuritet, vikt vid slutning eller annan samsjuklighet är riskfaktorer för komplikationer efter slutning av förmaksseptumdefekt. En symptomgivande förmaksseptumdefekt ökar risken att drabbas av komplikationer efter slutning hos barn. Prematurt födda barn tycks ha en risk jämförbar med den hos fullgångna barn, att drabbas av komplikationer efter slutning av förmaksseptum, även om de var både lättare och yngre vid slutningstillfället.

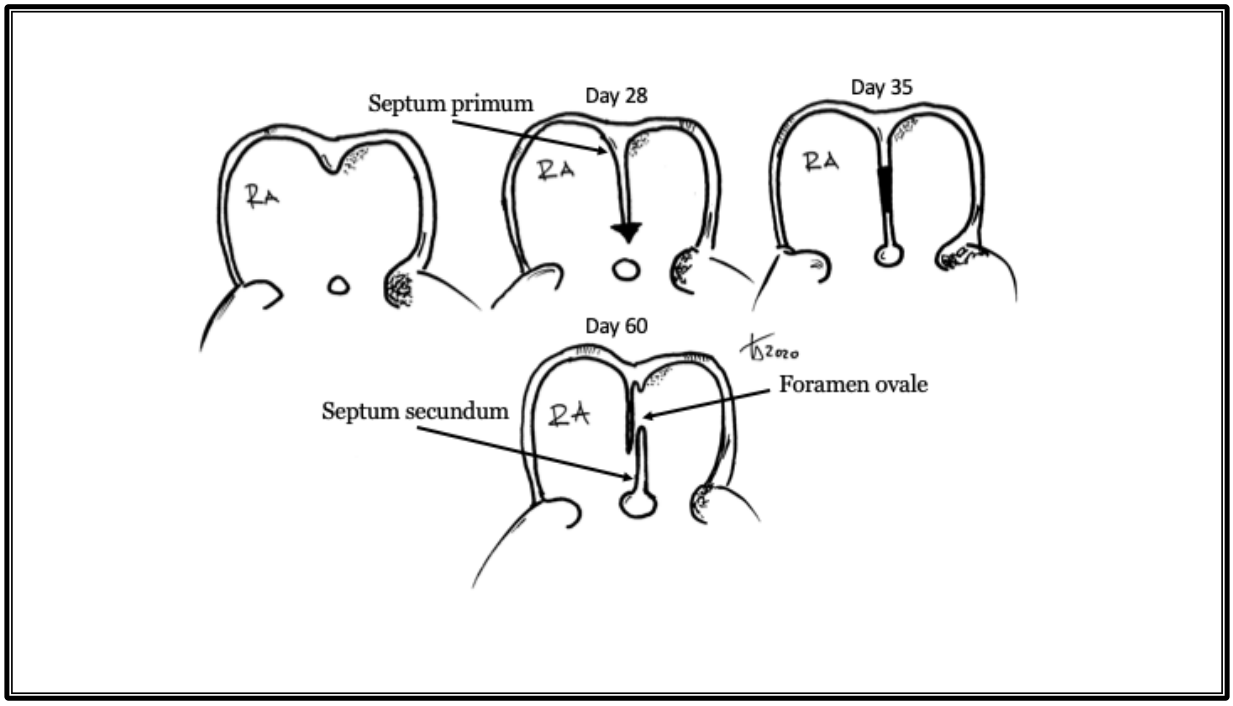
Sammanfattningsvis visar dessa studier att prematurt födda barn, med sin ökade förekomst av förmaksseptumdefekt, och barn med symptomgivande förmaksseptumdefekt måste följas noggrant, både inför och efter slutning av öppetstående förmaksseptum. Ett nytt nationellt uppföljningsprogram med tydliga riktlinjer, som beskriver när och hur en förmaksseptumdefekt skall slutas, bör skapas.

Introduction

Secundum atrial septal defect (ASD II) pathophysiology and natural history

The atrial septation starts at the fourth gestational week, with the formation of the myocardial primary septum. During the next following weeks the primary septum grows and fuses with superior endocardial cushion, close to the atrioventricular plane. The primary intra atria communication, "ostium primum" enables blood flow between the atriums. The posterior part of primary septum becomes muscularised and the upper part creates the "flap" in foramen ovale.
The secondary septa develop from the dorsal endothelial cushion, with a fold in the primary atrium, creating the upper rims of the foramen ovale (Figure 1) (1).

Figure 1. The embryonal septation of the heart chambers.



RA: Right atrium

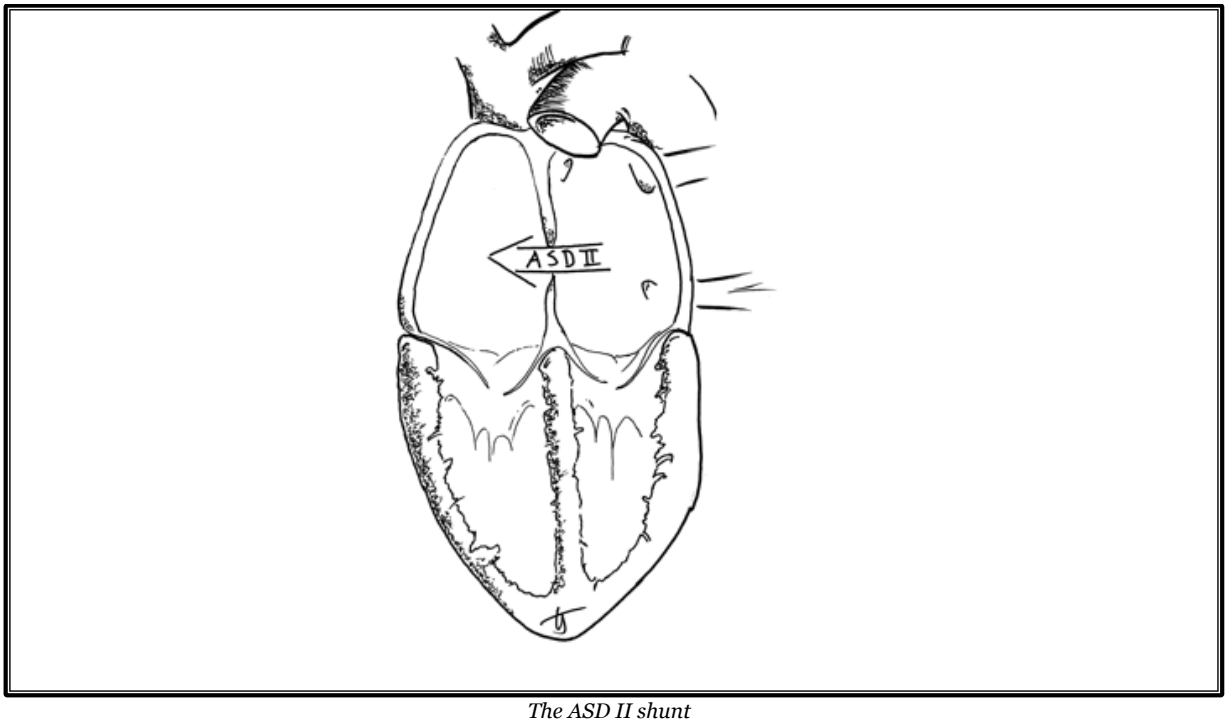
The foramen ovale is completed at the 12th gestational week and remains approximately constant relative to the size of the right atrium (RA) throughout the rapid growth during the remaining 20 weeks of human gestation (1, 2). However, the merging of the two atrial septa is not completed until after birth, when the left atrial diastolic pressure exceeds the RA diastolic pressure (3, 4). Only three quarters of all adult humans have a complete closure of the foramen ovale (5).

Atrial septal communications are classified into 1: primum atrial defects, located between the anterior-inferior margin of the fossa ovalis and the atrioventricular valves, 2; secundum atrial defect (ASD II) located in the fossa ovalis, and 3; sinus venosus defects between right pulmonary veins and the cardiac end of the superior vena cava or the posterior-inferior atrial wall (6, 7).

Transthoracic echocardiography (TTE) is the primary method to diagnose an ASD II (6). The identification of an inta atrial shunt within the fossa ovalis, may either be classified as an ASD II or a PFO (6). Anatomically, ASD II is located within the true septum with deficient or absent atrial walls, and the PFO is a tunnel-like slit between the free edges of the foramen ovale, with intact muscular rim (8). However, to distinguish between ASD II and PFO with TTE is difficult, and there is no general consensus in how to best differentiate between them. Both a defect size < 3 - 4 mm, and a present flap confirmed with high-gain echo have been suggested to confirm a PFO (7, 9, 10). The differentiation of PFO and ASD II is difficult in the neonatal period due to high pulmonary vascular resistance and pulmonary overload during normal transition from intra-uterine life (11). Preterm children with reduced pulmonary compliance, greater phasic respiratory intrathoracic changes, and higher LA and RA pressures, may have shunts correlated to respiratory cycle, preventing soldering of the two atrial septa (12, 13). PDA is common among preterm children, and creates an increased pulmonary blood flow potentially stretching the arterial wall dislocating the PFO "flap" (9, 14). Speculatively, these factors may displace a PFO to an ASD II, which would lead to overestimation of the incidence of ASD II diagnosis in preterm children.

The incidence of ASD II range from 50 to almost 100 per 100,000 livebirths (15, 16). The temporal trend of increasing incidence may partly be explained by the identification of small and asymptomatic ASD II, that previously would have been diagnosed later in life or closed spontaneously (17-19). ASD II are commonly found in association with a wide spectrum of CHD (20).

Figure 2. The ASD II shunt.



The ASD II shunt

ASD II induces an inter-atrial left-to-right shunt during late ventricular systole and early diastole which increases during the atrial contraction (Figure 2) (20). The shunt is related to the defect's size and right ventricular (RV) diastolic compliance (20). Larger ASD II creates a volume overload, and later a pressure overload, which causes a RV and RA enlargement,

impaired function and, eventually, an adverse inter-ventricular interaction causing decreased left ventricular (LV) diastolic filling (6, 20).

Additional myocardial cell hypertrophy, cellular injury and, potentially, myocardial fibrosis and apoptosis will occur over time in the RA and RV (21, 22). The increased pulmonary blood flow stimulates pulmonary vascular remodelling and, if left untreated, manifests as irreversible changes of the pulmonary arteries and pulmonary hypertension (PH), so-called Eisenmenger's syndrome or physiology, which is a fatal condition (23, 24).

The natural history of ASD II varies widely. Spontaneous closure occurs in 14–66% of children with small defects (≥3 mm – 6mm), and uncommonly for ASD II of > 10 mm in size (10, 17). The main predictors of spontaneous closure of ASD II are size and age at diagnosis, with higher spontaneous closure in small ASD II and age < 1 year at diagnosis (17). However, regardless of the initial ASD II size, an enlargement may occur over time, with potential outgrowth of the possibility to perform a percutaneous device closure (PDC) (10, 17). ASD II symptoms includes tachypnoea, reduced growth, slow weight gain, and/or recurrent respiratory infections (6). Children with an isolated ASD II generally remain asymptomatic during infancy, childhood, and adolescence (25, 26). About 1% of all children with moderate to large isolated ASD II experience symptoms as well as more severe conditions such as arrhythmias, PH, and congestive heart failure (27, 28).

ASD II indications for closure and state of the art

According to current guidelines, ASD II interventional closure is indicated in the presence of a significant left-to-right shunt (i.e., Qp:Qs > 1.5:1), which is defined as a right heart enlargement due to volume overload, regardless of clinical heart symptoms. Small ASD II with no sign of RV enlargement are not considered for closure unless the right-to-left shunt cause significant hypoxaemia and/ or paradoxal embolism (29-32). An ASD II may either be closed by PDC or with surgery, and is referred to ASD II closure in this thesis. PDC is the preferred method in the presence of suitable anatomical features and rims (31). The device is typically introduced through a sheath in the femoral vein and guided by a combination of fluoroscopy and echocardiography. Today a wide range of occluding devices and delivery systems are available, with resembling methods of placing and centering the device within the ASD II (6). PDC devices can be implanted successfully in children less than two years of age, although common practice suggests that asymptomatic ASD II preferably be closed at an age of three to five years with an interventional weight above 15 kg. These circumstances may offer technical advantages and simplify the procedure (6, 31). Accordingly, asymptomatic children are followed during infancy and early childhood, and elective ASD II closure is planned at the age of four years. The majority (78%) of children with a diagnosis of ASD II, don't need an ASD II closure before the age of two years while children with chronic lung disease or a chromosomal defect may need a ASD II closure at a much younger age (<1 year) (33-35).

PDC and surgery are both considered safe and a consensus decision on the preferred method is based upon dialogues between the paediatric cardiologist, the interventionist, and the paediatric heart surgeon. Typically, larger ASD II – usually defined as defects > 38 mm in diameter – and/or deficient rims other than antero-superior, so-called complex ASD II, are referred to surgery, or if surgery is needed for other congenital heart defects (CHD) (36-38).

ASD II can be closed if the pulmonary blood pressure is less than or equal to half of the systemic blood pressure and if the pulmonary vascular resistance is less than two thirds of the systemic vascular resistance (29). Children or adults who have developed Eisenmeger's physiology are never considered for ASD II closure, as the open ASD II can serve as a safety "pop-off" valve to RV dysfunction (30).

ASD II closure, risk assessment, and adverse events

The use of PDC has increased over the last decades and is now the preferred method, used in 85–90% of all ASD II closures, in both adults and children (37, 39).
This trend of increasing usage of PDC, compared with surgery, has also been seen among the youngest children (35). PDC has a higher success rate, lower incidence of adverse events, and a shorter hospital stay compared with surgery (40, 41). Although both PDC and surgery are considered safe, short- and long-term complications do occur (Table 1). The survival rate after ASD II surgery has increased over time, even with decreased age at time of the operation, with few early deaths and an excellent outcome over time (42, 43).

Meta-analyses on adverse events after PDC, including both children and adults, indicate that few major (1.0%) and minor (1.3%) adverse events occur (44). The categorisation of complications into either major or minor adverse events is clearly subjective and not based upon recognised definitions. Some authors present predefined classifications of types and severity of adverse events, while others use different classifications or do not describe their classifications at all (45, 46). At this time, no worldwide consensus is available on classification of adverse events following ASD II. Difficulties arise when comparing prevalence, morbidity and hierarchy of adverse events between studies (45, 47). Through the use of a predefined classification, also used by others, data in this thesis can be compared to those in previous studies (45).

In clinical practice, risk assessment scores may be used to determine the risk of an ASD II closure (46, 48, 49). CRISP is an assessment tool based on clinical parameters, the patient's clinical condition, body weight and surface area, associated pathology, and the presence of other CHD (49). CRISP has recently been validated with a good prognostic fit for adverse events (48). In Sweden, use of such scores is not mandatory, and only used in one of the three interventional centre, Gothenburg. The two centers providing patients for this thesis (Lund and Stockholm) did not use the risk assessment at the time of these studies.

Multicentre studies demonstrate an ASD II closure in-hospital mortality ranging from 0.000% to 0.015% for PDC and from 0.3% to 0.9% for surgery (39). Adverse events occur predominantly within the first 24 hours, but accurate estimations of device erosion – the most common major adverse event – are limited due to few longitudinal studies (39, 50). One study indicate that the majority of adverse events occurs within the first 30 days after ASD II closure (51). Serious adverse events following ASD II closure have most commonly been described to be device erosion, device embolization, pericardial tamponade and cerebrovascular events (44). Device erosion, is defined as an erosion of the device through the atrial wall into the aorta or pericardial space which may occur early or later after an ASD II closure (52). The frequencies of device erosion vary from 0.04% to 0.30% and fatal outcome is extremely rare (39, 52, 53). Device erosion and embolization have been associated with deficient or "floppy" rims, ASD II size, and interventionist experience (54, 55).

Arrhythmias have been associated with ASD II size, age, and the ratio between device size and ASD II size (54, 55). The overall risk of adverse events has a close association with the number of PDCs performed, favouring large centres with few interventionists (56).

ASD II surgery is associated with a higher risk of major and minor adverse events compared with PDC, partly because surgery is favoured over PDC in very young children and in complex ASD II (38, 57). Minor adverse events occur in approximately one quarter of all children following ASD II surgery, with infections and pericardial effusion being the most common (58). The overall proportion of adverse events in all types of surgical ASD II interventions varies between 4% and 16% (58, 59). A meta-analysis of 13 studies shows that adverse events following ASD II surgery occurred in 31% of all children and major adverse events in 7% (41). Mortality as well as morbidity after ASD II closure is associated surgeons experience (56).

ASD II closure in children and risk of adverse events by weight and age

The vast majority (93%) of PDC are performed in children weighing more than 15 kg (50). With the increasing use of PDC, there has been a trend toward treating lighter and younger children (50). Small atrial and/or vessel size are the major limitations for PDC (60, 61). In young children, less than three years of age, PDC is associated with fewer adverse events, shorter hospital stay, and minor scaring compared with intraoperative device closure (62). Descriptive studies analysing adverse events in children less than three years old have concluded that PDC is safe (61).

Even if the procedure is relative safe, adverse events do occur and especially in small children with severe comorbidity (45, 63-65). However, safety reports and small studies show diverging results, with an overall occurrence of adverse events ranging from 9% to 15% and major adverse event occurrence at about 5% (Table 1) (45, 63, 66-68). There is no consensus concerning the definition of significant adverse events in the literature, which may contribute to arbitrariness and disparities in the occurrence rates published (45).

The ASD II size to body surface area or size to weight ratio has been used to assess both the risk of adverse events and the success rate in small children. Cut-offs of 20 mm/m^2 or 1.2-1.5 mm/kg have been used (50, 67, 69). However, the lightest children often have additional associated severe symptoms as well as associated CHD and greater morbidity (47).
A vast majority (95%) of small children improve in symptoms and have a growth catch-up after ASD II closure (45, 63, 65). Reversed remodelling of the right heart myocardium to a normalisation of the RA and RV has been observed in some studies, but not in others (45, 61, 63). Early PDC, defined as less than two years of age at closure, and surgery have been described as beneficial to preterm children suffering from a combination of bronchopulmonary dysplasia (BPD), recurrent respiratory infections, PH, and failure to thrive, with clinical improvements and normalisation of TTE measurements during the follow-up period (33, 65, 70).

Today, early ASD II closure may be indicated in preterm children with chronic lung disease or chromosomal defects (33, 71). Additionally, PDC is indicated in small children with rapidly enlarging defects, to prevent an ASD II from developing beyond the possibility of PDC, and in

large defects with significant left-to-right shunt, as these defects seldom close spontaneously and may even enlarge (33, 71).

Table 1: Studies of ASD II closure in small children, reporting success rates and complications.

Met	*Intervention*	*Follow-up‡*	*Pop*	*Numbers*	*Outcome*	*Author*	*Year and journal*
Pro	PDC	12 m	≤ 10 kg	45	Success: 100% Comp: Major 6.9% Deaths: 0	Sharma, B.	2020 Ann.Ped Cars
Pro	1. PDC 2. Intraoperative DC (hybrid)	12 m	< 3 y age	1. 88 2. 98	1. Success: 97.7% Comp: 13.6%. Deaths: 0 2. Success: 98.0% Comp: 26.5%. Deaths: 0	Han, Y.	2020 J. Card Surg
Pro	PDC	1 m	≤ 10 kg	35	Success: 100% Comp: Major 2.8% Minor 5.7% Deaths: 0	Ghaderian, M.	2019 ARYA Ather
Pro	PDC	6 m	≤ 15 kg	case: 96 ctrl: 1,230	Success: 94.7% Comp: 5.2% vs 1.5%; p = 0.007; 3.1% vs 0.7%; p ≤ 0.007 Deaths: 0	Jalal, Z.	2018 JACC Cardi
Pro	PDC	12 m	D/W ≥ 1.5	40	Success: 97.5% Comp: Major 5% Minor 10% Deaths: 0	Houeijeh, A.	2018 Int J Card
Pro	PDC	12 m	< 3 y age	157	Success: 94.4% Comp: Major 0.6% Minor 8.2% Deaths: 0	Knop, M.T.	2018 Kard. Pol
Ret	PDC	4 m	< 10 kg	28	Success: 100% Comp: 3.5% Deaths: 0	Wyss, Y.	2016 J. Interv Card
Pro	PDC	12 m	≤ 10 kg	28	Success: 93.0% Comp: Minor 11.5% Deaths: 0	Knop, M.T.	2014 Cardiol J
Pro	PDC		< 17 kg	53	Success: 92.5% Comp: NR Deaths: NR	Petit, C.J.	2013 Pediat Cardiol
Ret	PDC	8 m	< 15 kg	128	Success: 98.0% Comp: Major 5.5% Minor 9.4% Deaths:0	Bartakin, S.	2012 JACC Cardi
Pro	PDC	20 m	< 1 y age	3	Success: 100% Comp: 0 Deaths: 0	Prada, F.	2009 Esp. Card
Ret	PDC		< 2 y age	71	Success: 95.8% Comp: 1.4% Deaths: 1 (sepsis)†	Fischer, G.	2009 Cath Cardiva Interv
Pro	PDC	6 m	< 15 kg	35	Success: 100% Comp: Major 2.8% Deaths: 0	Frassier, A.	2008 Cardiol Young
Pro	PDC		≤ 15 kg	52	Success: 94.0% Comp: Major 0ǂ Minor 15.4% Deaths: 0	Cardenass, L.	2007 Cath Cardiva Interv
Pro	PDC (11) Hybrid (3)	7 m	< 1 y age	15	Success: 92.7% Comp: Major 7.1% Minor 21.4% Deaths: 1 (PH crisis)†	Diab, K.A.	2007 J.Thor Cadi
Pro	Surgery	4 m	< 1 y age	24	Success: 100% Comp: NR Deaths: 1 (PH crisis)†	Lammers, A.	2005 J.Thor Cadi

† Uncertain relation to intervention, ‡ Shortest follow-up time, ǂ 2-device embolization reported as minor event.

Comp: complications, ctrl: controls, DC: device closure, D/W: device size to weight ratio (mm/kg), IND: individuals, INTERV: intervention type, m: months, MET: methods, NR: not reported PDC: percutaneous device closure, RET: retrospective, POP: population, PRO: prospective, y: years.

Preterm birth and CHD

Worldwide, approximately 11% or 15 million children are born preterm each year; in Sweden, the corresponding figures are approximately 6% or 6,500 children (72, 73). The World Health Organization defines preterm birth as a pregnancy ending before 37 completed gestational weeks, stratified as moderate or late preterm birth (32–37 completed weeks), very preterm birth (28–32 completed weeks), and extremely preterm birth (< 28 completed weeks) (74). The majority of preterm births, approximately 85%, occur between 32 and 36 completed gestational weeks (75). In Sweden, pregnancy length is estimated by routine ultrasound, usually during the 18th gestational week (76).

Globally, preterm birth and associated complications are the leading cause of death among children below the age of five years, accounting for 35% of all deaths in new-borns and 16% of all deaths in children younger than five years (77).

The morbidity burden for preterm children in the short term includes increased risk of several respiratory diseases (such as infant respiratory distress syndrome (IRDS) and BPD), necrotising enterocolitis, sepsis, neurological conditions (such as periventricular leukomalacia, seizures, intraventricular haemorrhage, cerebral palsy, and hypoxic ischemic encephalopathy), as well as feeding difficulties and visual and hearing problems (78-80). Even late preterm children have a higher risk of adverse outcomes compared with term children (81).

In the long-term perspective, there is an inverse association between gestational age and risk of neurodevelopmental impairment and cardiovascular, metabolic, and pulmonary conditions (82-85). Individuals born preterm exhibit increased resting systolic and diastolic systemic blood pressure in childhood and young adulthood (83, 86).

Children born with VLBW or preterm have a 2% incidence, compared with 0.8% in the general population, to be born with a CHD, with increased morbidity and a twofold risk of mortality before discharge compared with preterm children without CHD, suggested to be caused by congestive heart failure (87-90). Moreover, cardiac surgery is needed in approximately 12% of preterm children with CHD (88, 89).

The origin of the higher incidence of CHD in preterm children is uncertain and still a matter of speculation. Further, CHD have similar risk factors as preterm birth (91). Gestational age at birth, birthweight, and the presence of additional non-cardiac anomalies influence the overall mortality for all children with CHD (92).

Atrial shunts (ASD II and patent foramen ovale (PFO)) are present in 40% of children with VLBW and are five times more common in preterm children compared with term children (9). The majority of these atrial shunts are asymptomatic and resolve within two years of birth (9). In contrast, ASD II – the most prevalent CHD in preterm children at the NICU described in one study – is associated with an increased risk of necrotising enterocolitis, BPD with PH, and prolonged time to spontaneous closure, and early intervention ASD II closure, often before age of two, and increased mortality rate is reported (87, 93-99). However, causality is not possible to establish among these studies.

Children diagnosed with ASD II are more likely to be born preterm (20.3% to 29.3%) or with a lower birthweight, compared with non-CHD children (100, 101). Symptomatic preterm children may benefit from early ASD II closure, with improved clinical respiratory status, weight gain, fewer infections, and normalised RV size (33, 34, 70, 102-104). Early ASD closure, even before symptoms emerge, has been advocated by some authors (103).

The preterm child's circulation, pathophysiology and cardiac morphology

Preterm children have a biventricular systolic, and diastolic myocardial performance alteration present during the neonatal period (105). The functional and anatomical changes are explained by disorganised myofibrils, underdeveloped elastic tissue, and decreased cardiomyocyte cell division, demonstrated in animal studies. Elevated collagen deposit, larger cardiomyocytes, and altered maturation of the myocytes has been seen in animal studies (106). Human autopsy studies on preterm children born at a mean age of 27 gestational weeks, showed a cessation of cell proliferation (107). The proportion of proliferating cardiomyocytes declines from the 20'th gestational week, and at term fewer than 1% were proliferating. The preterm children had almost no proliferation after birth (107). Potentially, the cessation of proliferation after the 20'th week is associated with the need of cardiomyocyte maturation/differentiation, preparing the heart for increased postnatal functional demands (107). However, among preterm children the abrupt change in hemodynamic demands after preterm birth or the exposure to corticosteroids may induce cardiomyocyte cell maturation and discontinued cardiomyocyte proliferation (Table 2) (107). This alteration persists throughout the first years of life and into early adulthood, with a disproportionate increase in ventricular mass and a decrease in biventricular function (108-111). Even if this affects both chambers, the RV functional impairment is increased for a longer time than the LV alteration (108, 111).

Some studies, but not others, have reported that LV mass, end LV diastolic volume, and wall thickness are increased, in combination with shorter LV length and decreased LV stroke volume, during the first week after birth in preterm children compared with term children (108, 112, 113). These LV wall thickness alterations were independently correlated with low gestational age at birth, respiratory support > 48 h, and antenatal and postnatal treatment with glucocorticosteroids (112, 114). Diastolic and systolic cardiac functions improve during the neonatal period for preterm children, but a decreased LV myocardial performance is seen compared to that in term children. For extremely preterm children, this early improvement is less noticeable and a diastolic LV impairment and decreased LV mass is present throughout childhood (110, 115). Some LV alterations are associated with increased risk of mortality as well as impaired stress response during physical activity (Table 2) (114, 116).
However, a recent meta-analysis concluding these findings, and demonstrates reduced global LV systolic, and diastolic functions among preterm children during the neonatal period. Most prominent among children born prior to 32 gestational weeks. In conclusion, preterm children persistently developed smaller ventricular dimensions, lower LV diastolic function, and accelerated LV hypertrophy (105). Further, the analysis reveal smaller LV end- diastolic dimension, smaller LV end- diastolic volume indexed to body surface area, and shorter LV length in young adulthood among preterm born compared with term born individuals (105). This finding, may explain the reduced myocardial reserve under stress (105, 116)

Table 2: Cardiac morphological studies in preterm children

Modality	*Time*	*Pop*	*Number*	*Main measurements and findings*	*Author*	*Year and journal*
CMR	1: Adolescents 13 y μ 2: Adult 26.5 y μ	1. < 32 w 2. >36 w	Adolescent 40 Adult 70	Biventricular chamber size and mass↘ LVEDV Index (ml/m²)↘ SV index (ml/m²)↘ Biventricular longitudinal strain↗ RV circumferential strain↗	Goss K.N.	2020 JAMA Card
Echo and Neuro-hormonal	First 28 days	VLBW < 32 w	101	TDI (RV and LV diastolic functions) ↘ inversely correlated to NT pro BNP	Zafra-Rodriguez, P.	2019 Pediat Card
Echo	1: 32 PMA 2: 1 year corrected age	< 29 w	80 preterm 50 term	RV free wall longitudinal strain (1 month 1 year) ↘ RV systolic longitudinal strain rate (1 month 1 year) ↘	Erickson, C.T.	2019 Card Young
CMR	1: < 7 d 2: 37–42 w corrected age	< 37 w	34 (29) preterm 10 term	1. LV mass (g/kg)↗ LVEDV↗ RV mass (g/kg) **ns** RVEDV **ns** 2. LV mass (g/kg)↗ LVEDV↗ RV mass remodelling ↘	Cox, D.J.	2019 Pediatr Res
Stress Echo	18–40 years of age	Case: 32.8 w μ Ctrl: > 39.5 w μ	47 preterm 54 term	LV mass (g/kg)↗ Stress EF↘ COR (ml/min/m²)↘	Huckstep, O.J.	2018 J Am Coll Card
Echo	6 years of age	22–26 w ≥ 37 w	176 preterm 134 term	LVd length↘ AoV diameter↘ LV mass (g/kg)↘ LV longitudinal shortening (MAPSE)↘ LVd stiffness↗	Mohlkert, L.A.	2018J Am Heart Ass
Human heart tissue	Post-mortem	Case: < 36 Ctrl: ≥ 37	16 preterm 37 term	Proliferation↘	Bensley, J.G.	2018 Pediatr Res
Echo	< 2 w	28–32 w Case: IUGR Ctrl: AGA	20 preterm IUGR 20 preterm AGA	Septal hypertrophy↗ LV volume and wall dimensions↗ Diastolic function (TDI: E/E´↗) ↘	Sehgal, A.	2017 J Pediatr
Echo	prospective d 2 d 14 d 48	1. < 28 w 2. 28–31 w 3. 32–35 w	1. 8 2. 12 3. 13	Improvement over time in gr 2 and 3 TDI (S´A´E´)	Saleemi, M.S.	2017 Early Hum Dev
Register (cohort)	5–19 years of age	1. < 28 w 2. 28–31 w 3. 32–36 w 4. > 36 w	2,665,542	RR risk of HF 1. 13.0 (7.08–23.8) 2. 2.60 (1.33–5.09) 3. 1.54 (1.11–2.12) 4. ref	Carr, H.	2017 J Am Coll Card
Echo	1. foetal (intrauterine) 2. at birth 3. 3 months of age	preterm 37 w	Foetal 192 postnatal 255 (55 both)	LV volume (ml/m²)↘ LV mass (g/m²)↘ LV function (EF, SV)↘ RV volume (ml/m²)↘ (neo)RV mass (g)↗ 3. RV mass (g/m²)↗	Aye, C.Y.	2017 Pediatr Res
Echo	1. at birth 2. 3 months of age 3. 6 months of age	very preterm (26–30 w)	25 preterm 21 term	3. LV free wall strain ↘ LVd myocardial velocities ↘	Schubert, U.	2016 J Am Soc Echo
Echo	prospective 1. 1 d age 1. 3 d age 3. 32 w PMA age 4. 36 w PMA age	1. 23—28 w 2. >37 w	115 preterm 60 term	RV FAC improvement (2 times) ↗	Levy, P.T.	2015 J Am Soc Echo
CMR	< 1 d	Case: Preterm PDA Ctrl: Term/preterm no PDA	Case: 16 Ctrl: 29	LV output (ml/kg/min)↗ SV (ml/kg)↗ LVEDV(ml/kg)↗ LV mass (g/kg)↗	Broadhouse K.M.	2014 J Cardiovas Mag Res
CMR	Adults 25 y	1. < 36 w 2. > 37 w	102 preterm 132 term	RVEDV+RVESV (ml/m²)↘ RV EF↘ RV SV (ml/m²)↘	Lewandowski A.J.	2013 Circul
CMR	20-39 y age	1. 23–28 w 2. > 37 w	102 preterm 132 term	LVEDV + LVESV (ml/m²)↘ SV (ml/m²)↘LV longitudinal peak and systolic peak strain rate ↘ LV mass (g/ml)↗	Lewandowski A.J.	2013 Circul
Lamb	14 days after birth		7 preterm 8 term	Collagen deposit (LV+RV)↗ Cardiomyocyte volume (LV+RV)↗ Myocyte maturation↘	Bensley, J.G.	2010 Eur Hear J
Neuro-hormonal	1 y	1. < 37 2. > 37	12 preterm 6 term	TnI ↗	Quivers, E.S	1999 Clin Bioche

AGA: appropriate for gestational age, AoV: aortic valve, COR: cardiac output reserve, CMR: cardiovascular magnetic resonance, Ctrl: control, d: day, ECHO: echocardiography, EF: ejection fraction, FAC: fractional area change, HF: heart failure, IUGR: intrauterine growth retardation, LV: left ventricle, LVd: left ventricle diastolic, LVEDV: left ventricle end diastolic volume, LVESV: left ventricular end systolic volume, MAPSE: mitral annular plane systolic excursion, ns: no statistical significance, NT-Pro BNP: N-terminal pro-brain natriuretic peptide, PMA: Post-menstrual age, POP: population. RR: relative risk, RV: right ventricle, RVEDV: right ventricular end diastolic volume, RVESV: right ventricular end systolic volume, SV: stroke volume, TDI: tissue doppler imaging, TnI: troponin, VLBW: very low birthweight, w: weeks, y: years, μ: Population mean.

In preterm children with maladaptive RV performance, including reduction of RV systolic function, increased RV mass, and decreased ejection fraction, the changes are present immediately at birth and sustained over time (108, 111, 117). However, RV systolic function improves for preterm children during their first 3 months of life, possible even more than in term children (Table 2) (117, 118). However, a recent meta-analysis conclude this findings, and describes, decreased global RV systolic, and RV diastolic functions among preterm children compared with term children (105). The cause of RV alteration may, also in part, originate from the higher pulmonary vascular resistance with greater RV afterload, and the pulmonary bed stiffness confirmed increased RV afterload among preterm children (13). Indicating that preterm RV systolic deficits reflect the sensitivity of the thin-walled RV to loading conditions caused by pulmonary circumstances (13, 105, 119).

These preterm altered morphologies of RV and LV, with adverse impact on cardiac function, increase the risk of cardiovascular events, such as ischemic heart disease, by 50%, increase the risk of heart failure by four to 17 times (inversely correlated with gestational age), and mortality, and lead to impaired LV function during physical exercise in adults who were born preterm (105, 111, 113, 116, 119, 120). These cardiac alterations may induce vulnerability of secondary insults, potentially explaining the increased risk of heart failure and risk of ischemic heart disease.

The myocardium of the new-born is extremely sensitive to volume overload, more so in preterm infants, which will preserve the progressive RV dilatation and dysfunction (121). The neonatal period may be a key developmental window during which cardiac geometric and functional changes first emerge and non-appropriate biventricular increase in mass occurs (108). Speculatively, this window might be an ideal time period for pharmacological, and nutritional interventions enhancing myocardial development, and change the future risk of cardiovascular disease among adults born preterm (108).

Preterm children with bronchopulmonary dysplasia and pulmonary hypertension

PH is defined as a mean pulmonary artery pressure ≥ 25 mmHg at sea level in individuals > 3 months of age and is diagnosed by cardiac catheterisation (122). PH caused by a progressive structural pulmonary vascular change, predominantly in precapillary vessels, is called pulmonary arterial hypertension (PAH) (122).

According to WHO classification, neonatal PH is defined as either persistent pulmonary hypertension of the new-born (PPHN) (WHO group 1) or BPD-PH (WHO group 3). The underlying origins of PPHN and BPD-PH are diverse, with considerable overlaps between these two groups regarding cellular and clinical manifestation. PPHN is defined as failure to achieve and sustain the normal drop in PVR and increased pulmonary blood flow, which will result in a right-to-left shunt of deoxygenated blood and global hypoxia (122, 123).

PH is caused by pulmonary arterial impairments. The pulmonary arteries may be obstructed or have an altered arterial wall due to shunt lesions or high pressure on the left side of the heart. Any disease that primarily affects the air sacs and bronchi in the lungs may cause pulmonary arterial dysfunction. PH may also be caused by interrupted pulmonary arterial and capillary growth, as for preterm children, or be idiopathic (122).

Especially among very preterm children with PH it is more common have RV dysfunctions (23.9%), RV dilatation (52.1%) and RV hypertrophy (51.2%) compared with very preterm children without PH (97).

BPD, which is defined as a chronic lung disease in an infant born ≤ 32 weeks' gestation who requires ongoing oxygen therapy at 36 weeks adjusted age, is diagnosed in approximately 40% of all extremely preterm children (124, 125). BPD is characterised by multifactorial pathophysiology, associated with IRDS, mechanical ventilation, and oxygen therapy (124-126). Gestational age, reduced intrauterine growth, small for gestational age (SGA_w), and halted pulmonary capillary development are associated with less favourable outcomes in children with BPD (125, 127, 128). Postnatal factors, such as mechanical ventilation (barotrauma and volume trauma), infections, poor nutrition, and oxygen toxicity, may further compromise the immature lungs (125). Children with BPD have a high risk of developing PH, with more than five times increased mortality rates (125, 129, 130). The origin of BPD-associated PH can be speculated to be arrested pulmonary growth and reactive pulmonary vascular resistance, resulting in vascular remodelling and permanent increased vascular resistance (125).

ASD II with bronchopulmonary dysplasia and pulmonary hypertension

ASD II is associated with the development of PH, in preterm children with BPD (96). PH is present twice as often in preterm children with ASD II compared with preterm children without ASD II (26.3% vs 12.3%) (95). Very preterm children with ASD II carry a five-fold increased risk of long-lasting PH compared with preterm children without ASD II (94, 95, 97). ASD II is more common among preterm children with BPD and if severe PH is present, this increases mortality (94). Furthermore, ASD II may aggravate moderate and severe BPD (131). However, the causality between ASD II, BPD and PH is not proven by epidemiological methods, but an association has been proven by several authors.
The haemodynamically significant left-to-right shunt induces increased pulmonary circulation which in turn adds an extra stressor to the immature pulmonary vascular bed and increases vascular remodelling, fibrosis, and development of PH (132, 133). This can cause activation of endothelial cells and a cascade activation of growth factors, vasoconstrictors, and degeneration of the extracellular matrix, with a resulting reduction in the compliance of the pulmonary vessels (134, 135). Some children, both preterm and term, with isolated ASD II may develop severe PH in early infancy (28). PH is an indication for ASD II closure as well as a risk factor for ASD II closure before the age of two years (28, 31, 98).

Some authors have advocated early ASD II closure in children with BPD and PH, and have shown improved respiratory symptoms for 50–93% of the children with higher resolution rate for mild to moderate respiratory symptoms (33, 136). Clinical improvements have also been seen with less infections and weight gain among 50–63% of children with preterm birth and complex comorbidities (33, 136). In single-centre case reports and case series of children with ASD II and a combination of prematurity, BPD, and comorbidities, an ASD II closure improved respiratory outcomes, decreased the need for mechanical ventilation, and reduced use of diuretics (33, 65, 70, 104, 136). One study with few cases indicated reduced PA pressure after ASD II closure in children with severe comorbidities and preterm birth (136). Some authors have stated that the increased pulmonary blood flow and over-circulation

caused by an ASD II induces interstitial pulmonary oedema, endothelial injury, and negative vascular remodelling as well as impaired pulmonary function, leading to the conclusion that closure of small shunts may be beneficial (34, 103, 104).

Registries

The Swedish Registry of Congenital Heart Disease, SWEDCON
The Swedish Registry of Congenital Heart Disease (SWEDCON) is a national quality register, established in 2009, covers 84% of all hospitals, and consists of four parts: foetal cardiology, paediatric cardiology, GUCH (Grown-Up Congenital Heart Disease), and congenital heart surgery (137, 138). The parts share a common database, with information on each patient, including personal data, diagnosis, operations, and catheter interventions. The SWEDCON register makes it possible to follow patients with CHD throughout their entire life and collect and combine data from different parts of the register (137). SWEDCON covers 31 paediatric units collecting data on patients (0-18 years) with congenital heart diseases

Participation in SWEDCON is voluntary and the data is registered by either physicians, registered nurses, or specially trained secretaries at the time of the patient visit, or shortly thereafter (137). Children who have been examined and diagnosed with a cardiac disease are registered in SWEDCON. The prenatal screening programme for CHD with ultrasound at gestational week 18 contributes to the register, but many patients with CHD are still diagnosed after birth. ASD II is always diagnosed after birth as an open foramen ovale, which is always present and necessary for surviving intrauterine life, is not possible to distinguish from a foetal ASD II. After birth, a TTE may enable distinguishing between a PFO and ASD II, but there are diagnostic difficulties as previously described (4). The register has been validated against medical records with a concordance of diagnosis in at least 74% of all patients in all ages (139).

Swedish Medical Birth Register, MBR
The Swedish Medical Birth Register (MBR) register was established in 1973 and includes data on more than 99% of all births in Sweden. It is held by the National Board of Health and Welfare (140). MBR uses a standardised set for individual registration which starts at the first visit to the antenatal clinic and is completed when the mother and new-born infant are discharged from hospital. Information on maternal demographics, reproductive history, and smoking habits, as well as on pregnancy, delivery, and neonatal data is included in the registry for all births (140). The International Classification of Diseases 10th revision is used in MBR. The register is subject to annual quality control and validation (141).

Statistics Sweden, SCB
Statistics Sweden is responsible for developing, producing and disseminating official statistics. The Swedish National Statistics Database for live births, national and by region, was used to calculate preterm births per one hundred thousand live births per year between 2010 and 2015 (142).

Epidemiological methods

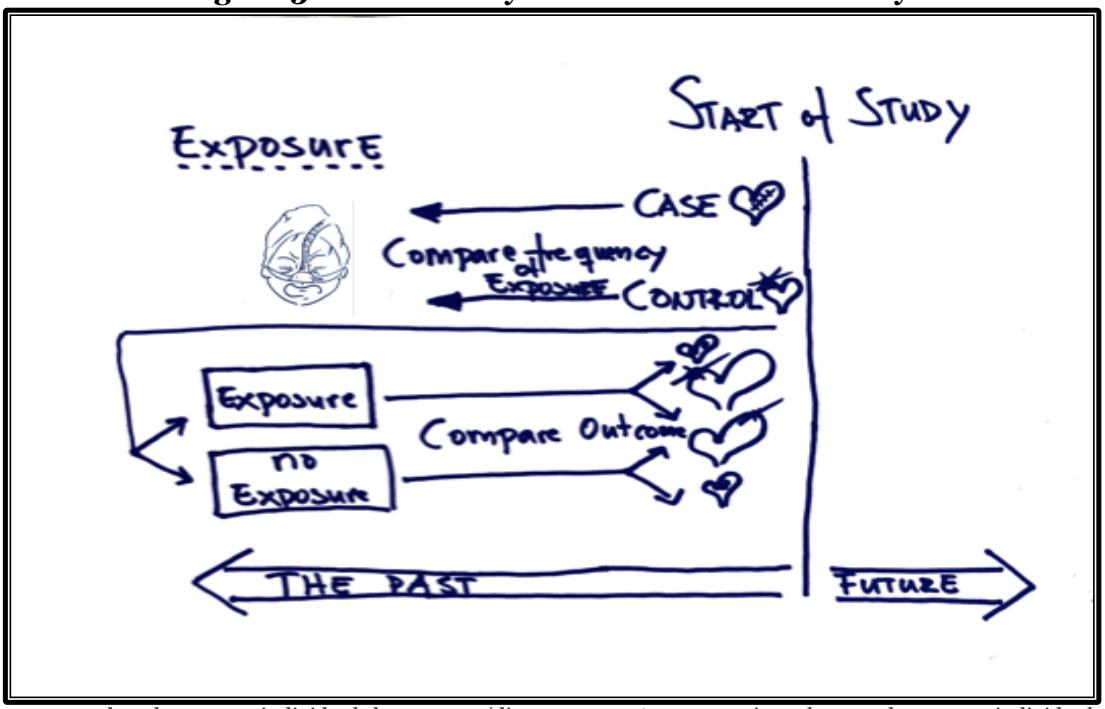
The epidemiological methodology involves assessment of associations between an exposure and an outcome, often a disease or an event, and comparison with unexposed or healthy

individuals. Depending on the type of exposure or disease, different epidemiological methods can be used. Selecting an appropriate method, variables, and outcomes is important, and the understanding of the disease, potential exposures or risk factors, and the theoretical linkage of variables to the outcome, is a key issue in epidemiological studies (143, 144).

In a cohort study, individuals subjected to a predefined exposure are compared with individuals without this exposure and the cohorts are followed over time until an outcome of interest occurs. This enables assessment of time causality with a potential strong scientific value (145, 146). Cohort studies may be conducted prospectively or retrospectively. The strengths of a well-conducted cohort study are that incidence rates (absolute risk, relative risk, attribute fraction) for a disease or event in the exposed group can be assessed and multiple outcomes can be studied from a single exposure. The disadvantages include requiring a large number of included patients and that cohort studies are often time-consuming and costly. Further, cohort studies are not optimal for rare outcomes or diseases with long latency (Figure 3).

Case-control studies are well suited to investigate rare outcomes or outcomes with a long latency period. A case is defined as an individual with a certain outcome, most often a disease or an adverse event, and controls are defined as individuals without this outcome, retrieved from the same population (Figure 3) (146). The associations between the outcome and the predefined exposures, regarded as potential risk factors, are assessed by comparing cases and controls. It is of utmost importance that the likelihood of exposure is the same for cases and controls (145, 146). It is also possible to assess confounding factors and adjust the odds for the association of a risk factor to a disease. The strengths of case-control studies are the possibility to include just a few study subjects and assess multiple exposures or risk factors, the often quick access to data, and the low costs (145, 146).

Figure 3. Cohort study versus case-control study.



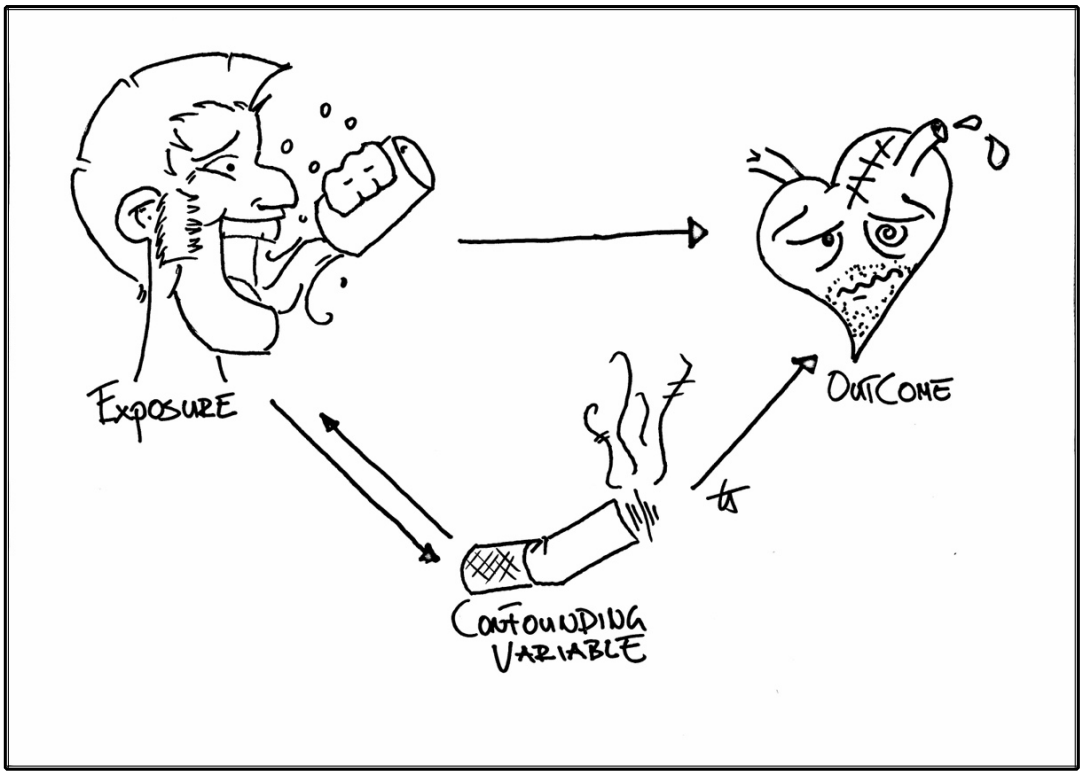
A case-control study assesses individuals by outcome/disease status. A retrospective cohort study assesses individuals by exposure status.

Confounding factors are associated with both the risk factor or the outcome, providing an alternative association between the exposure and outcome (Figure 4) (143). Such factors may have a causal linkage to the outcome or the exposure, or be a proxy measurement for some other, unknown pathway.

Logistic regression models assess the association of binary dependent variables (outcome) with independent variables (exposure). The key strength of logistic regression models is the possibility to adjust multiple independent variables to the outcome and the capacity to analyse both continuous and binary variables (143, 144). However, selecting the appropriate variables can be challenging. Including "as many factors as possible" decreases the power of the study. Further, a spurious significance to the outcome may be seen, as neither a theoretical nor a physiological basis of explanation is plausible, and risk conclusions may be erroneously stated (143, 144).

The means in a life table, or Kaplan-Meier curves, are used as an univariate method of comparing a cohort's time to an event and show the probability of an event at a certain time interval (147). The strengths of this method are the possibility of censoring reliability in small datasets and that no assumption of event distribution over time is needed. A key weakness is the univariate nature, which precludes other explanatory factors in the model (147).

Figure 4. Illustration of confounding factors and the exposure.



The exposure (alcohol), or risk factor, is associated with higher risk of acute myocardial infarction, but also with a higher prevalence of smoking (confounding factor). Smoking affects the risk of acute myocardial infarction, but also the risk of drinking alcohol.

Bias can be a generalised trend of skewness in the collected data, the data analyses, or the interpretation of results, which leads to systematic differences between the study conclusions and reality. In retrospective studies, the predominant biases are recall, selection, and attrition bias, when there is a systematic problem in remembering an exposure or outcome, or when study subjects differ from the population of interest, or when there is a systematic

loss to follow-up. The effect of bias will be an estimate either above or below the true value, depending on the direction of the systematic error. Risk of bias has to be carefully considered when designing and analysing epidemiological studies.

An epidemiological study may reflect the true effect of an exposure on the development of an outcome or disease, but the results may also have an alternative explanation. The effects of chance, bias, or confounding may produce spurious results leading to invalid conclusions. Further, epidemiological studies cannot be used to prove an origin or cause of a disease, but only demonstrate a link or association between an exposure and a disease.

Key factors in introduction

- *ASD II creates a left-to-right shunt, inducing RA and RV remodelling.*
- *Spontaneous ASD II closure is common, though delayed in preterm children.*
- *ASD II closure is indicated in the presence of a significant left-to-right shunt defined as a right heart enlargement, regardless of clinical heart symptoms.*
- *No guidelines on ASD II closure are available for preterm children.*
- *Both PDC and surgery are considered safe and complex ASD II is often referred to surgery.*
- *Classification of adverse events is subjective with no uniform definition currently available.*
- *Studies of PDC in small children show a wide range in frequency of adverse events.*
- *Preterm children have a higher incidence of CHD and atrial septal openings.*
- *Preterm children have an altered cardiac function and morphology.*
- *ASD II is a risk factor for development of PH in preterm children with BPD.*
- *Some authors advocate early ASD II closure in preterm children with BPD and PH.*

Rationale and hypothesis for the thesis

There is an ongoing discussion regarding favourable outcomes of ASD II closure in small children. Some studies indicate that preterm children are overrepresented among children with ASD II and ASD II closure. Few studies have assessed the incidence and risk factors of ASD II diagnosis in the new era of increased neonatal survival rates. The altered cardiac morphology and function and the influence of ASD II on pulmonary morbidity and vascular growth may foreshadow a new group of cardiac patients. Preterm children may be a subset of patients with unknown risk factors for ASD II and risk of adverse outcomes following ASD II closure. Traditional indications for closure of ASD II based on otherwise healthy children may not be appropriate.

The author hypothesises that preterm children have a higher incidence of ASD II compared with term children and that preterm birth is an independent risk factor for ASD II diagnosis. Furthermore, preterm and small children may have an increased risk of post-interventional adverse events.

Aim of the thesis

The overall aim of this thesis was to determine factors related to ASD II incidence and independent risk factors for diagnosis, morbidity, and mortality after ASD II closure in small and preterm children.

Specific aims for each paper:

Paper I
The aim was to assess the risks of major and minor adverse events following percutaneous transcatheter device closure of ASD II in children with procedural weight of less than 15 kg compared with heavier children. Other potential risk factors, such as cardiac and other comorbidities, including preterm birth, were also taken into account.

Paper II
The aim was to assess time to adverse events within one month and between one month and one year after surgery or PDC closure of ASD II in preterm children compared with term children, and to assess recurring adverse events comparing the two cohorts.

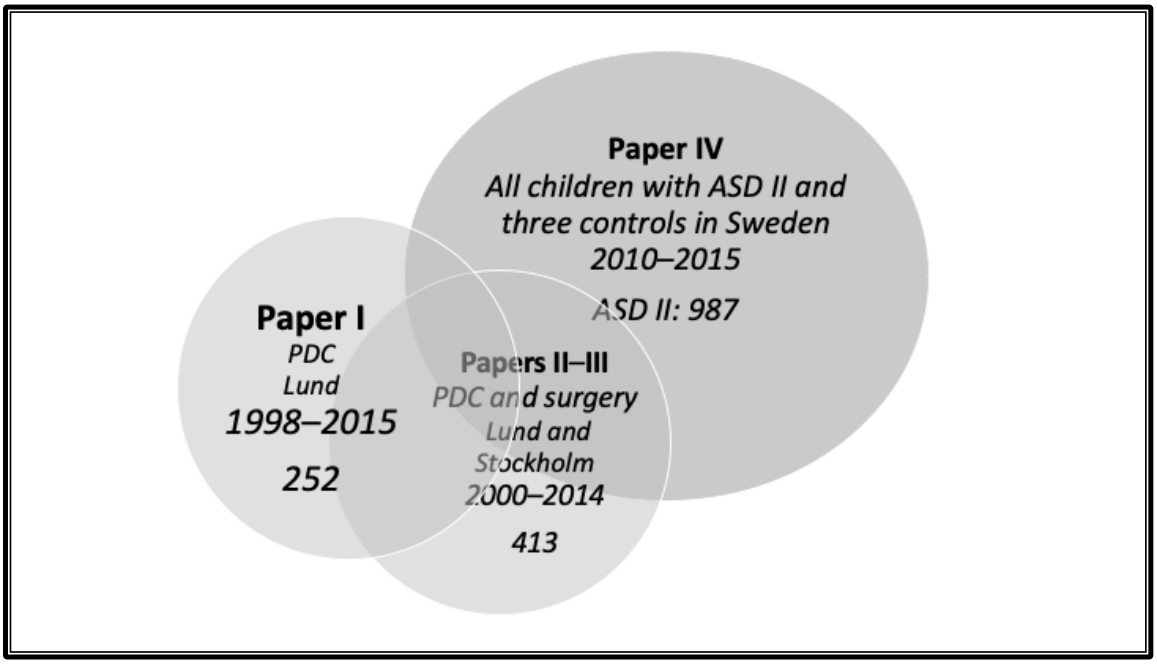
Paper III
The aim was to assess potential neonatal and clinical risk factors associated with major and minor adverse events within one year after ASD II closure.

Paper IV
The aim was to calculate the incidence of ASD II in Sweden, for all children and for children born at different gestational weeks, and to assess maternal, perinatal, and paediatric factors associated with the diagnosis of ASD II in preterm and term children.

Materials and methods

The first three studies (I–III) were case-control or cohort studies based on information retrieved from medical records and register data (Figure 5) (Tables 3–4). Paper IV was a retrospective national register-based case-control and incidence study (Table 4).

Figure 5. Study populations of the thesis.



ASD II: secundum atrial septal defect, PDC: percutaneous device closure.

In Papers II–IV, data retrieval was performed by the National Board of Health and Welfare and data were anonymised before referral to the research group.

In Papers II–III, SWEDCON was used to retrieve information on adverse events, complementary to information from medical records, and demographic data (Table 3).

Table 3. Variables and sources of information.

Variables	*I*	*Paper II–III*	*IV*	*Medical Records*	*SWEDCON*	*Echo*	*MBR*
ASD II diagnosis			✓		✓		
Date of ASD II diagnosis			✓		✓		
Adverse events	✓	✓		✓	✓		
Date of adverse event		✓		✓	✓		
Weight at closure	✓	✓		✓	✓		
Date of closure	✓	✓		✓	✓		
BSA	✓			✓			
ASD size (TEE/TTE)	✓	✓		✓		✓	
Gestational age	✓	✓	✓	✓			✓
Device type	✓			✓			
*Comorbidities **	✓	✓	✓	✓	✓		
Type of closure (PDC/surgery)		✓		✓	✓		
Indication for closure		✓		✓			
Pulmonary disease (IRDS/BPD)		✓	✓	✓			✓
Neonatal respiratory ventilation		✓		✓			✓
Neonatal CPAP		✓		✓			✓
Neonatal sepsis		✓		✓			✓
Pulmonary hypertension		✓		✓			✓
Symptomatic ASD		✓		✓	✓		
Maternal smoking at first visit			✓				✓
Maternal snuff use at first visit			✓				✓
Maternal weight			✓				✓
Maternal chronic renal disease			✓				✓
Maternal diabetes mellitus			✓				✓
Maternal epilepsy			✓				✓
Maternal chronic high BP			✓				✓
Birthweight			✓				✓
Small for gestational age			✓				✓
Large for gestational age			✓				✓
Very low birthweight			✓				✓
Non-specific infection			✓				✓
Persistent ductus arteriosus			✓				✓

** Other congenital heart defects, chromosomal, genetic and other.*

ASD: atrial septal defect, BP: blood pressure, BPD: bronchopulmonary dysplasia, BSA: body surface, CPAP: continuous positive airway pressure, Echo: echocardiography, IRDS: infant respiratory distress syndrome, MBR: the Swedish national birth register, PDC: percutaneous device closure, TEE: transoesophageal echocardiography, TTE: transthoracic echocardiography.

Table 4. Overview of study design and retrieved data.

Paper	*I*	*II*	*III*	*IV*
Design/method	Retrospective Case-control	Retrospective Cohort	Retrospective Case-control	Incidence and Retrospective Case-control
Data collection	Medical records, national registers and echo data	Medical records and national registers	Medical records, national register and echo data	National register data
Study population	PDC in Lund (n = 252) Cases: Adverse events (major/minor) Control: Non-adverse events Subgroup: ≤ 15 kg (n = 112) > 15 kg (n = 140)	PDC or surgery in Lund and Stockholm Cohorts: Preterm: (n = 93) Term: (n = 320)	PDC or surgery in Lund and Stockholm Case: Adverse events (n = 45 major/87 minor) Control: Non-adverse events (n = 264)	Cases: ASD II (n = 978) Control: Non-ASD II (n = 8,866)
Main statistical methods	Conditional logistic regression	-Kaplan-Meier survival curves -Gary-Anderson's method -zero-inflated Poisson distribution	Conditional logistic regression	-Incidence calculation -Conditional logistic regression

Echo = echocardiographic, n = number of included individuals

Statistical methods

Demographic data for all studies were analysed using Student's t-test (unpaired two-sided) for parametrically distributed variables and the Mann-Whitney U test for non-parametric distributed variables with a p value of < 0.01. Pearson's χ^2 test was used for categorical data and the Kruska-Wallis test was used for multiple categorical groups with non-parametric distributions, with a $p < 0.05$ considered to be significant. Data were analysed and presented according to fit. All data are presented as mean (SD), median (range), or percentage (n), depending on the type and distribution of the data.

Continuous data were primarily tested for normality using the Shapiro-Wilk test.

Study design and materials, Paper I

Materials

All children under the age of 18 years who underwent PDC between 1998 and 2015 at the Skåne University Hospital in Lund, Sweden, were included in the study. Demographic data, including body weight at ASD II closure, and information on adverse events and potential risk factors were retrieved from medical records, SWEDCON, and MBR (Tables 3–5). Information on ASD size was assessed manually from digitally saved transoesophageal echocardiography (TEE) and TTE examinations.

Table 5. Classification of adverse events Paper I (45).

Major adverse events	Minor adverse events
• Death	• Deployment malfunction
• Cardiac or respiratory arrest	• Suspected infection
• Stroke	• Bleeding not requiring transfusion
• Device erosion	• Significant access site haematoma
• Device embolization	• Prolonged transient limb paraesthesia
• Permanent limb injury	• Transient hypoxia during procedure
• Need for emergent surgical procedure	• Trivial pericardial/pleural effusion
• Events or intraprocedural arrhythmias requiring treatment	• Transient arrhythmias not requiring therapy (AV block, nodal rhythm, bradycardia)
• Bleeding requiring transfusion	
• Significant pericardial/pleural effusion requiring treatment	
• Arrhythmias requiring treatment (persistent therapy-requiring arrhythmias)	
• New valvular insufficiency/pulmonary vein obstruction	
• Pulmonary hypertension crisis	
• Discharge later than 24 hours post closure	

Design
This was a retrospective case-control study defining cases as children with adverse events and controls as children without adverse events. Body weight ≤ 15 kg was assessed as a risk factor for adverse events and adjustments were made for other potential risk factors.

Echocardiography
The largest diameter of each ASD II was measured on saved transthoracic echocardiography / transoesophageal echocardiography (TTE)/(TEE) images and expressed in millimetres. All measurements were made by two investigators with an intra-observer and inter-observer variability of 3.0% and 2.7%, respectively.

All post-procedural complications were recorded within 72 hours after PDC and classified into minor or major adverse events in accordance with the definition used by Bartakian et al. (Table 5) (45).

Specific analyses
Conditional logistic regression was performed to evaluate the association between major or minor adverse events for children of a procedure weight ≤ 15 kg compared with children weighing > 15 kg and adjusted for potential risk factors, significant in the univariate regression model (Table 6).

Maximum-likelihood estimates of the odds ratios (ORs) and 95% confidence intervals (CIs) were obtained, taking potential confounding factors into account.

Table 6. Potential risk factors and confounding factors by paper.

Variables	*Paper I*	*Paper III*	*Paper IV*
Weight ≤ 15 kg	✓		
BSA	✓		
ASD size	✓		
Device Size	✓		
Genetic comorbidities	✓	✓	✓
Other comorbidities	✓		
Additional congenital heart defects	✓	✓	✓
Preterm	✓	✓	✓
Late preterm		✓	✓
Very preterm		✓	✓
Extremely preterm		✓	✓
IRDS		✓	
BPD		✓	
Neonatal respiratory ventilation		✓	
Neonatal CPAP		✓	
Neonatal sepsis		✓	
Pulmonary hypertension		✓	
Symptomatic ASD		✓	
Sex			✓
Persistent ductus arteriosus			✓
Morbus down			✓
Calculated and grouped risk factors			
ASD/BSA	✓		
ASD/Weight > 1.2	✓		
Pulmonary diseases and general ventilatory support (Pulmonary Disease + IRDS + BPD + Neonatal respiratory ventilation + Neonatal CPAP)		✓	
Late preterm (32 to < 37 weeks)		✓	✓
Less than 32 weeks		✓	✓
Maternal smoking at first visit			✓
Underweight[§]			✓
Normal weight[§]			✓
Pre-Obesity[§]			✓
Obesity[§]			✓
Small for gestational age			✓

ASD: atrial septal defect, BPD: bronchopulmonary dysplasia, BSA: body surface, CPAP: continuous positive airway pressure, underweight, IRDS: infant respiratory distress syndrome,
BMI < 18.5 kg/m², normal weight: BMI 18.5–24.9 kg/m², pre-obesity: BMI 25.0–29.9 kg/m², obesity: BMI ≥ 30 kg/m².
§ Measured at the first antenatal clinic visit.

Study design and materials, Papers II–III

Materials for Studies II–III
All children born in Sweden and under the age of 18 years who were treated with ASD II closure (open heart surgery or PDC) between January 2000 and December 2014 at the Skåne University Hospital in Lund, Sweden, or at the Karolinska University Hospital in Stockholm, Sweden, were included in the study. Children born abroad were excluded.

Preterm birth was defined as birth at less than 37 completed gestational weeks, with further stratification to moderate to late preterm (32 to< 37 weeks), very preterm (28 to < 32 weeks), or extremely preterm (< 28 weeks). Information on ASD II size was measured and retrieved from digitally stored TTE or TEE examinations.

Table 7. Classification of adverse events in Papers II and III.

Adverse Event	*PDC*	*Surgery*
Major event		
Death	✓	✓
Cardiac/respiratory arrest	✓	✓
Stroke	✓	✓
Device erosion	✓	
Device embolization	✓	
Re-catheterisation due to device removal	✓	
Need for emergent surgical procedure	✓	✓
Persistent arrhythmias or intraprocedural arrhythmias requiring treatment	✓	✓
Significant pericardial/pleural effusion Requiring treatment	✓	✓
New valvular insufficiency/ pulmonary vein obstruction	✓	
Bleeding requiring transfusion	✓	✓
Pulmonary hypertension crisis	✓	✓
Permanent limb injury	✓	
Cardiac perforation/effusion	✓	✓
Endocarditis	✓	✓
Reoperation		✓
Pulmonary Oedema		✓
Minor event		
Deployment malfunction	✓	
Suspected infection	✓	✓
Bleeding not requiring transfusion	✓	✓
Significant access site hematoma	✓	
Prolonged transient limb paraesthesia	✓	
Transient hypoxia during procedure	✓	✓
Trivial pericardial/pleural effusion	✓	✓
Pulmonary hypertension drugs after discharge	✓	✓
Post pericardiotomy syndrome		✓
Surgical wound events/Infections		✓
Arrhythmias not requiring treatment (AV block, nodal rhythm, bradycardia)	✓	✓

PDC: Percutaneous Device Closure

Design of Study II
This was a retrospective cohort study. The two cohorts were stratified based on gestational age at birth: a preterm cohort with children born prior to 37 completed gestational weeks and a term cohort with children born after 37 completed gestational weeks.

All post-procedural adverse events occurring within short-term follow-up, ≤ 30 days, and long-term follow-up, 30 to 365 days, were recorded and classified into minor and major adverse events based on the definition used by Bartakian et al. for PDC (Table 7) and for surgery by other authors (40, 41, 45, 58). Time to first adverse event was retrieved from medical records (Table 3).

Design of Study III
This was a retrospective case-control study. Cases were defined as children with one or multiple adverse events, stratified as minor or major adverse events based on the definition used by Bartakian et al. (Table 7) and for surgery by other authors (40, 41, 45, 58). Controls were children without adverse events following an ASD II closure. Potential confounding factors were taken into account (Table 6).

The risk factor "symptomatic ASD" was used when stated in the medical record as a condition related to heart failure and in accordance with the International Classification of Disease (ICD 10 I50.0–9) and/or if the child was treated with diuretic drugs (148). The risk factor "PH" was used when TTE findings indicated a systolic RV pressure ≥ 25 mmHg, by measures of a tricuspid regurgitant velocity of > 2.6 m/s and calculated using the Bernoulli equation, or an invasive catheter measurement of a mean pulmonary artery pressure of ≥ 25 mmHg pulmonary, or a pulmonary vascular resistance of ≥ 3 WU x m^2, all prior to the ASD II closure (122).

Specific analyses Study II
Complications following ASD II intervention were analysed with the means in a life table, (Kaplan-Meier curve), comparing the cohort of preterm children with term children and time to first adverse event. The starting point was date of ASD II closure. Analyses were made for short-term and long-term follow up separately, using log rank with $p < 0.05$ as significant. Separate life table analyses were performed for minor or major adverse events:

1. Time to first event for short-term and long-term follow up for all (PDC and surgical) ASD II closures comparing the cohorts (preterm and term children).
2. Time to first event for short-term and long-term follow up for PDC and surgical closures separately comparing the cohorts (preterm and term children).

Recurring adverse events were analysed using a generalised model with zero-inflated Poisson distribution, and survival curves with Gary-Anderson's method in all ASD closures.

Specific analyses Study III
Conditional logistic regression was performed to study the associations between potential risk factors and major as well as minor adverse events following ASD II closure, in accordance with the definition used by Bartakian et al. and for surgery by other authors (Table 7) (40, 41, 45, 58). In this regression model, children with other CHD or chromosomal defects were excluded and susceptibility factors with potential synergistic neonatal or clinical

effect were stratified and arranged into groups based on affinity. Factors included in the adjusted model were preterm children >32 to < 37 gestational weeks, preterm children < 32 gestational weeks, pulmonary disease and general ventilatory support, neonatal sepsis, PH, and symptomatic ASD II (Table 6).

Study design and materials, Paper IV

Materials
A national registry-based retrospective incidence study and a national case-control study using SWEDCON, MBR, and Statistics Sweden (SCB) was conducted.

Cases in the case-control study were defined as children with ASD II (EPCC 05.04.02) diagnosis, and retrieved from the SWEDCON register, while controls were defined as children without diagnosis of ASD II, and not registered in the SWEDCON register, controls were retrieved from MBR. Three controls were matched to each case by birth hospital and month and year of birth. Demographic data, potential risk factors, and gestational age were retrieved from MBR (Table 3 and 6). Date of ASD II diagnosis for cases was retrieved from SWEDCON (Tables 3 and 6).

Preterm children and term children were stratified in accordance with the World Health Organization's definition. The corrected (adjusted) age of preterm children was calculated by subtracting the number of weeks of the child's birth prior to 40 weeks, and registered as the chronological age.

Maternal weight status was classified in accordance with the World Health Organization's definition as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), pre-obesity (BMI 25.0–29.9 kg/m^2), or obesity (BMI ≥ 30 kg/m^2), and was retrieved from MBR at the first antenatal clinic visit.

Statistical analyses
All demographic data were presented as mean (SD), median (IQR), or percentage (n) depending on the type and distribution of the data. Incidence analyses for ASD II were performed.

Incidence proportion was assessed based on the number of individuals with diagnosis in each gestational age group per 100,000 live births per year, using data from the Swedish National Statistics Database for live births between 2010 and 2015.

Conditional logistic regression was performed to evaluate the associations between risk factors and ASD II diagnosis. Adjustments were made for potential confounding factors (Table 6). Confounding factors were defined based on clinical importance and time causality, with exclusion of factors arising after development of ASD II. Down's syndrome was not included as a confounding factor for ASD II, due to the low number of children with Down's syndrome among the controls. PPHN and BPD were not included into the regression model, as ASD II is already present before PPHN and BPD develop. Maximum-likelihood estimates of the ORs and 95% CIs were obtained.

Ethics

Approval from the ethical committee in Lund was obtained for Study I, D-nr 2015/559.
Approval from the ethical committee in Umeå was obtained for Studies II and III, D-nr 2015/10-31.
Approval from the ethical committee in Umeå was obtained for Study IV, D-nr 2017/86-31.
For Papers II and III, informed consent was received from the study population.

Results

Paper I. Early complications after percutaneous closure of atrial septal defect in infants with procedural weight less than 15 kg

In total, 252 children were included in the study group, with a mean age of 5.36 years (SD ± 4.44), a median weight of 15.60 kg (range 4.78–87.50 kg), a mean ASD II size of 12.15 mm (SD ±4.31), and a mean ASD II size:weight ratio of 0.70 mm/kg (SD ±0.42). In all, 112 (44%) children had a procedural weight of ≤ 15 kg. Children with major adverse events were lighter, had a higher ASD II size:weight ratio, and a higher ASD II size:BSA ratio compared with children with no major adverse event (Table 8). Furthermore, it was more common among children with major adverse events to have a diagnosis of genetic comorbidities, other comorbidities, and a procedural weight of ≤15 kg compared with children with no major adverse events. Information on gestational age was missing in 36 cases (14%), as these children were born abroad. ASD II size (10.97 ±3.40 mm vs 13.05 ± 4.72 mm, p <0.01), and device size (15.49 ±4.83 mm vs 20.07 ± 6.96 mm, p <0.01) was smaller in children ≤ 15 kg compared with children > 15 kg. ASD:weight ratio (1.00 mm/kg (0.42–2.53) vs 0.47 mm/kg (0.13–1.27) p < 0.01, and ASD:BSA ratios (24.76 mm/m² ±8.61 vs 13.39 mm/m² ± 5.86 p <0.01) was larger among children ≤ 15 kg compared with children > 15 kg. Comorbidities were more common among children with a procedural weight of ≤ 15 kg (n = 42 (38%)) compared with children weighing > 15 kg (n = 23 (16%)) (p < 0.01).

Table 8. Demographic data for children included.

	Major Events	*No Major Events*		*Minor Events*	*No Minor Events*	
	Cases (16)	Controls (236)	*p*	Case (6)	Controls (246)	*p*
Weight (kg) (median, max–min)	9.9 (4.8–64.3)	15.8 (5.1–87.5)	**0.02**	33.3 (11.1–64.0)	15.5 (4.8–87.5)	**0.02**
Age (Years) (mean, SD)	4.8 (±5.3)	5.4 (±4.4)	0.44	5.2 (±4.3)	11.8 (±2.1)	**0.03**
TEE/TTE ASD size (mm) (mean, SD)	14.5 (±6.7)	13.4 (±4.8)	0.36	22.0 (±7.7)	13.3 (±4.79)	**< 0.01**
Gestational age (weeks) (median, max-min)	38 (28–42)	39 (23–43)	0.51	37 (37–39)	39 (23–43)	0.33
Device size (mean, SD)	17.8 (±7.2)	18.1 (±6.5)	0.88	24.0 (±6.1)	17.9 (±6.5)	0.06
ASD:weight ratio (mm/kg) (mean, SD)	1.1 (±0.5)	0.7 (±0.4)	**<0.01**	0.5 (±0.2)	0.8 (±0.4)	0.22
ASD:BSA ratio (mm/m²) (mean, SD)	25.0 (±10.0)	17.8 (±8.8)	**0.01**	14.0 (±4.4)	18.4 (±9.2)	0.34
Cardiac comorbidities	3 (18%)	19 (8%)	0.18	0	22 (9%)	-
Genetic comorbidities	4 (24%)	21 (9%)	**0.05**	1 (17%)	24 (10%)	0.47
Other comorbidities	5 (29%)	27 (12%)	**0.03**	0	32 (13%)	-
Preterm birth	4 (31%)	39 (19%)	0.31	0	43 (20%)	
≤ 15 kg	11 (69%)	101 (43%)	**0.04**	1 (17%)	111 (45%)	0.17

ASD: atrial septal defect, BSA: body surface area

Comorbidity was present in 65 (26%) of the children, stratified by cardiac defects in 22 (9%) children, genetic comorbidity in 25 (10%), and other comorbidities in 31 (12%). In total, 42 (17%) of the children were born preterm.

The majority of children (N =242 (96%)) were discharged the day after the intervention. Six children were discharged within one week and three children within two weeks. One child was discharged 299 days after the closure. Among the late discharged children, five suffered from post-procedural in-hospital complications (four major and one minor) and one child had a fatal device erosion after discharge, five days post-procedure.

Post-procedural adverse events
Post-procedural in-hospital adverse events occurred in 22 (9%) of the children. There were no in-hospital deaths. Major adverse events occurred in 16 (7%) children, whereas minor adverse events occurred in six (2%) children, all on the first post-procedural day.

No risk factor was independently associated with major or minor adverse events following PDC (Table 9).

Table 9. Risk factors for major and minor adverse events.

Univariate	*Minor*		*Major*	
	OR	**95% CI**	**OR**	**95% CI**
Weight ≤ 15 kg	0.24	0.03–2.31	2.94	0.99–8.73
ASD/BSA	0.93	0.81–1.08	1.08	1.03–1.13
BSA	6.31	1.52–25.33	0.37	0.08–1.63
ASD/weight > 1.2	0	-	4.18	1.31–13.35
Gestational age	0.99	0.76–1.29	0.96	0.83–1.11
ASD size	1.14	1.09–1.90	0.98	0.86–1.11
Device size	1.13	1.10–1.27	0.99	0.90–1.07
Cardiac comorbidity	0	-	2.34	0.69–10.01
Genetic comorbidity	1.85	0.20–16.50	3.41	1.01–11.53
Other comorbidity	0	-	2.57	0.77–8.53
Multivariate				
Weight ≤ 15 kg	0	-	1.67	0.38–7.30
ASD Size	1.37	0.99–1.89	-	
BSA	1.64	0.12–23.39	-	
Device Size	0.96	0.78–1.19	-	
ASD/BSA	-		1.05	0.96–1.16
ASD/weight > 1.2	-		0.92	0.13–6.63
Cardiac comorbidity	-		2.13	0.48–9.50
Genetic comorbidity	-		1.91	0.50–7.30
Other comorbidity	-		2.09	0.55–7.97

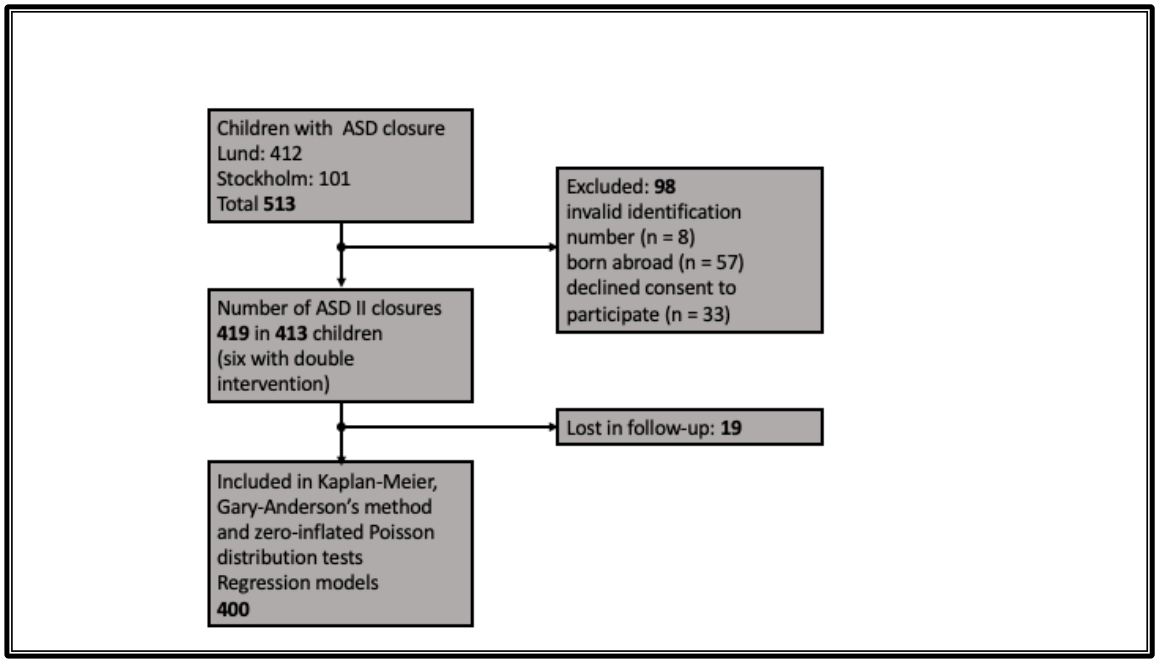
ASD: atrial septal defect, BSA: body surface area.

Paper II. Adverse events within one year after surgical and percutaneous closure of atrial septal defects in preterm children

A total of 511 children with ASD II closure were identified, of which 98 children were excluded due to invalid identification number, having been born abroad or declined consent, leaving 413 children in the study (Figure 6). The study group was stratified by gestational age at birth, with 93 (23%) children stratified to the preterm cohort and 320 (77%) to the term cohort. In the preterm cohort, 63 children (15%) were late preterm, 15 (4%) were very preterm, and 15 (4%) were extremely preterm.

In all, 419 ASD II closures were performed in 413 children. Six children required surgical device removal after (range 1 to 46 days) a PDC was performed with a release of the device, due to persistent arrhythmias, device embolization, or significant residual shunt. These children were included in both the PDC group, where the event of acute surgery was recorded as an adverse event, and the surgical group. Hence, these children occur twice in the study population. In total, 19 ASD II closures were lost to follow-up, leaving 400 ASD II closures to analyse (Figure 6).

Figure 6. Number of children included in Papers II and III.



Number of closures in Studies II and III.

Median age at closure for all children was 3.2 years (range 0.1–17.8 years) and median weight was 14.6 kg (range 3.5–110.0 kg). The median ASD II size was 13.0 mm (range 4.7–37.0 mm).

The preterm cohort was younger, lighter, had smaller ASD II, and a larger ASD size:weight ratio compared with the term cohort (Table 10). PDC was used more often than surgery, with usage being similarly distributed in the two cohorts (Table 10).

The ASD II size in the preterm cohort was 12.2 mm (6.0–24.0 mm) in the late preterm, 10.0 mm (7.5–20.0 mm) among the very preterm, and 9.6 mm (5.2–22.0 mm) in the extremely preterm.

In all, 111 (26.9%) of the children suffered from an additional CHD and this was more common in the preterm cohort than in the term cohort (Table 10). Chromosomal defects were present in 41 (9.9%) of the children, equally distributed between the two cohorts (Table 10).

Indication for ASD II closure was equally distributed between the cohorts, except for PH, which was almost twice as common in the preterm cohort. The indication for the majority of the ASD II closures was signs of a significant ASD II shunt (Table 10).

Table 10. Demographic data and indication of closure (Paper II).

Demographic parameters	*Total*	*Preterm (93)*	*Term (320)*	*p*	*Missing*
Gender (girls/boys)	249 (60%) vs 164 (40%)	54 (58%) vs 39 (42%)	195 (61%) vs 125 (39%)	0.62	
Age at closure (years)	3.2 (0.1–17.8)	2.1 (0.3–17.3)	3.4 (0.1–17.8)	< **0.01**	
Weight at closure (kg)	14.6 (3.5–110.0)	11.6 (3.5–65.0)	15.1 (4.3–110.0)	< **0.01**	3 (1%)
ASD size (mm)	13.0 (4.7–37.0)	12.0 (5.2–21.0)	13.0 (4.1–37.0)	< **0.01**	35 (9%)
ASD size/weight	0.9 (0.1–4.3)	1.1 (0.3–4.3)	0.8 (0.1–3.0)	< **0.01**	35 (9%)
Gestational age (weeks)	39 (22–43)	34 (22–36)	39 (37–43)		
Additional CHD	111 (27%)	35 (38%)	76 (24%)	< **0.01**	
Chromosomal defects	41 (10%)	13 (14%)	28 (9%)	0.13	
Preterm	93 (22.5%)				
Percutaneous closure	266 (63%)	59 (64%)	201 (63%)	0.92	
Device size (mm)	16 (5.0–36.0)	14.5 (4.0–34.0)	16 (5.0–35.0)	< **0.01**	
Surgery	153 (37%)	34 (37%)	119 (38%)	0.92	
Indication for ASD closure (missing 24 (6%))					
Right ventricular or atrial enlargement	307 (73%)	70 (81%)	237 (77%)	0.36	
Qp:Qs > 1.5:1	78 (19%)	14 (17%)	64 (21%)	0.38	
Pulmonary hypertension	19 (5%)	8 (9%)	11 (4%)	**0.03**	

ASD: atrial septal defect, CHD: congenital heart defect.

Adverse events following ASD II closure

Following ASD II closure, 110 minor and 68 major events were recorded. In the preterm cohort, 30 (32%) of the children suffered from adverse events, while in the term cohort, 98 (31%) children did so, with no statistical difference between the cohorts (p = 0.62).

Table 11. Adverse events within the first post-procedure year.

Children	*Minor (%)*	*Major (%)*	*Multiple (%)*	*Missing*
All children (n = 413)	83 (21)	45 (11)	37 (9)	19
Preterm children (93)	19 (20)	11 (12)	8 (9)	6
Term children (320)	64 (20)	34 (11)	29 (8)	13
PDC (260)	18 (7)	13 (5)	5 (2)	6
Surgery (153)	65 (42)	32 (21)	31 (20)	13
Events				
All children, total (419)	110	68		19
Preterm children (93)	21	17		9
Term children (326)	89	51		10
PDC (266)	27	22		9
Surgery (153)	83	46		10
Type of event	**Preterm**	**Term**	***p***	
Minor	19 (20)	64 (20)	0.84	
Major	11 (12)	34 (10)	0.69	
Multiple	8 (9)	29 (8)	0.92	

PDC: percutaneous device closure.

There were no differences, in number or frequency of adverse events, for all ASD II closures, PDC nor surgery separately, nor in time to adverse event between the two cohorts.

Nor was there any difference in types of adverse event between the two cohorts (Tables 11–13, Figures 7–10).

Table 12. Distribution of events between preterm and term cohort.

	Preterm children (%)	*Term children (%)*	$p\chi^2$
Minor events within 30 days			
Percutaneous device closure	4 (6.8)	13 (6.5)	0.93
Surgery	47 (39.5)	14 (41.2)	0.86
Minor events between 30 and 365 days			
Percutaneous device closure	0 (0.0)	1 (1.7)	-
Surgery	4 (3.4)	0 (0.0)	-
Major events within 30 days			
Percutaneous device closure	3 (5.1)	7 (3.5)	0.54
Surgery	6 (17.6)	23 (19.3)	0.83
Major events between 30 and 365 days			
Percutaneous device closure	2 (3.4)	1 (0.5)	0.13
Surgery	3 (2.4)	0 (0.0)	-

Table 13. Kaplan-Meier survival, log rank.

Intervention type, event and time of follow-up	*Log rank*
Both types of closure, Major events within 30 days	0.89
Both types of closure, Major events between 30 and 365 days	0.53
Both types of closure, Minor events within 30 days	0.95
Both types of closure, Minor events between 30 and 365 days	0.92
Percutaneous device closure, Major events within 30 days	0.93
Percutaneous device closure, Major events between 30 and 365 days	0.06
Percutaneous device closure, Minor events within 30 days	0.75
Percutaneous device closure, Minor events between 30 and 365 days	0.06
Surgery, Major events within 30 days	0.88
Surgery, Major events between 30 and 365 days	0.34
Surgery, Minor events within 30 days	0.68
Surgery, Minor events between 30 and 365 days	0.30

Figure 7. Time to first adverse event, all types of ASD II closure.

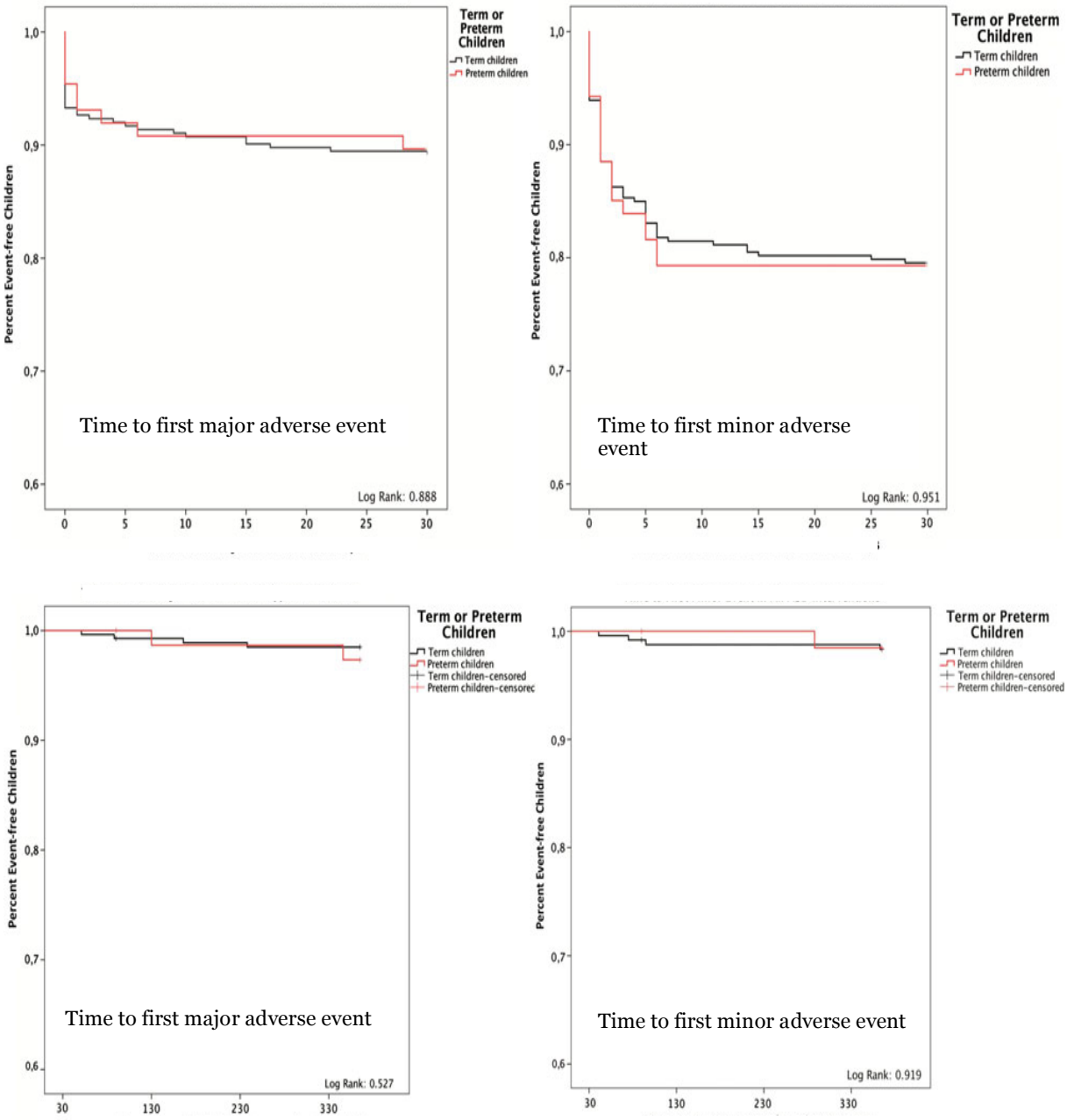


Figure 8. Time to first adverse event, PDC.

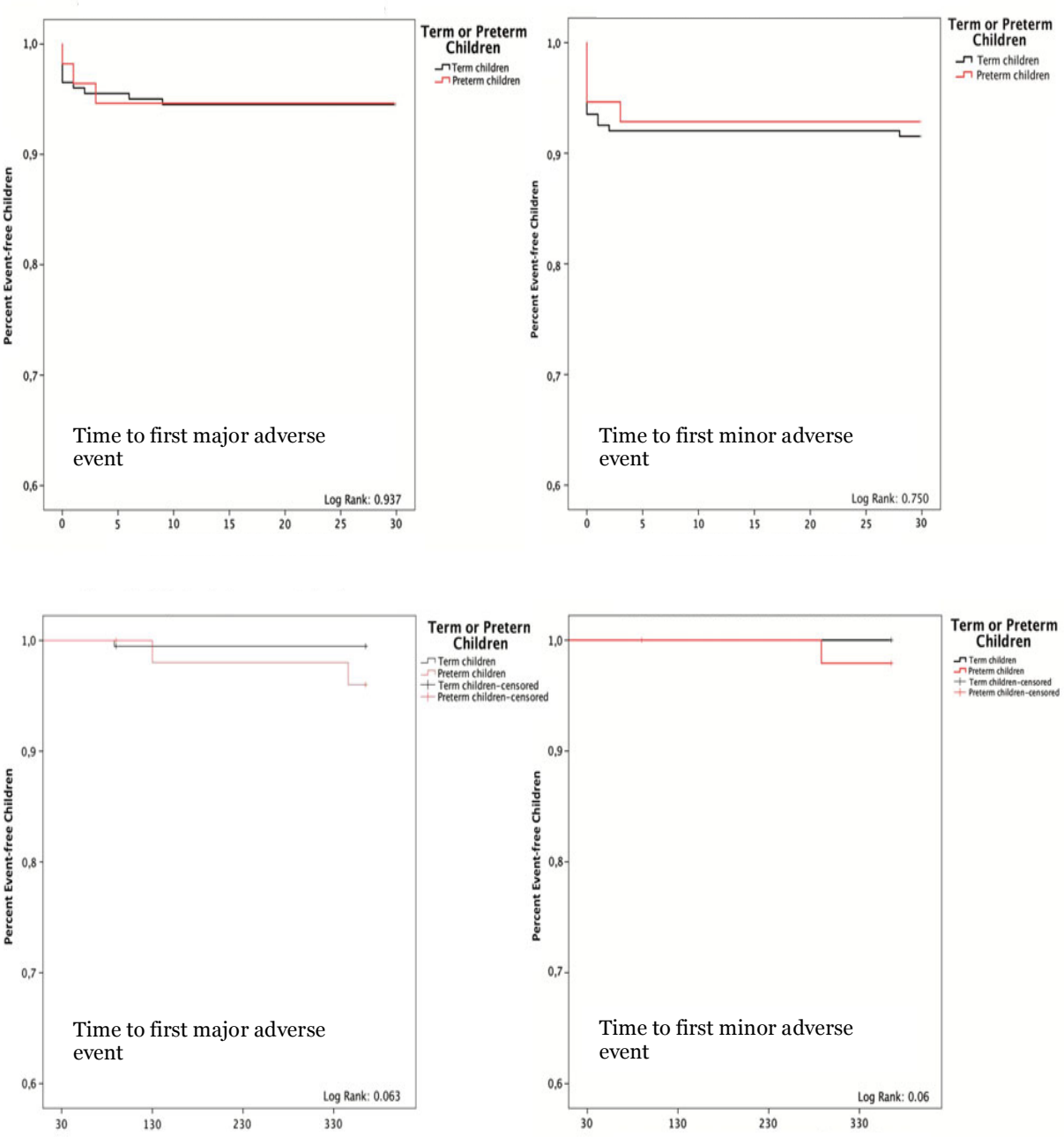


Figure 9. Time to first adverse event, surgery.

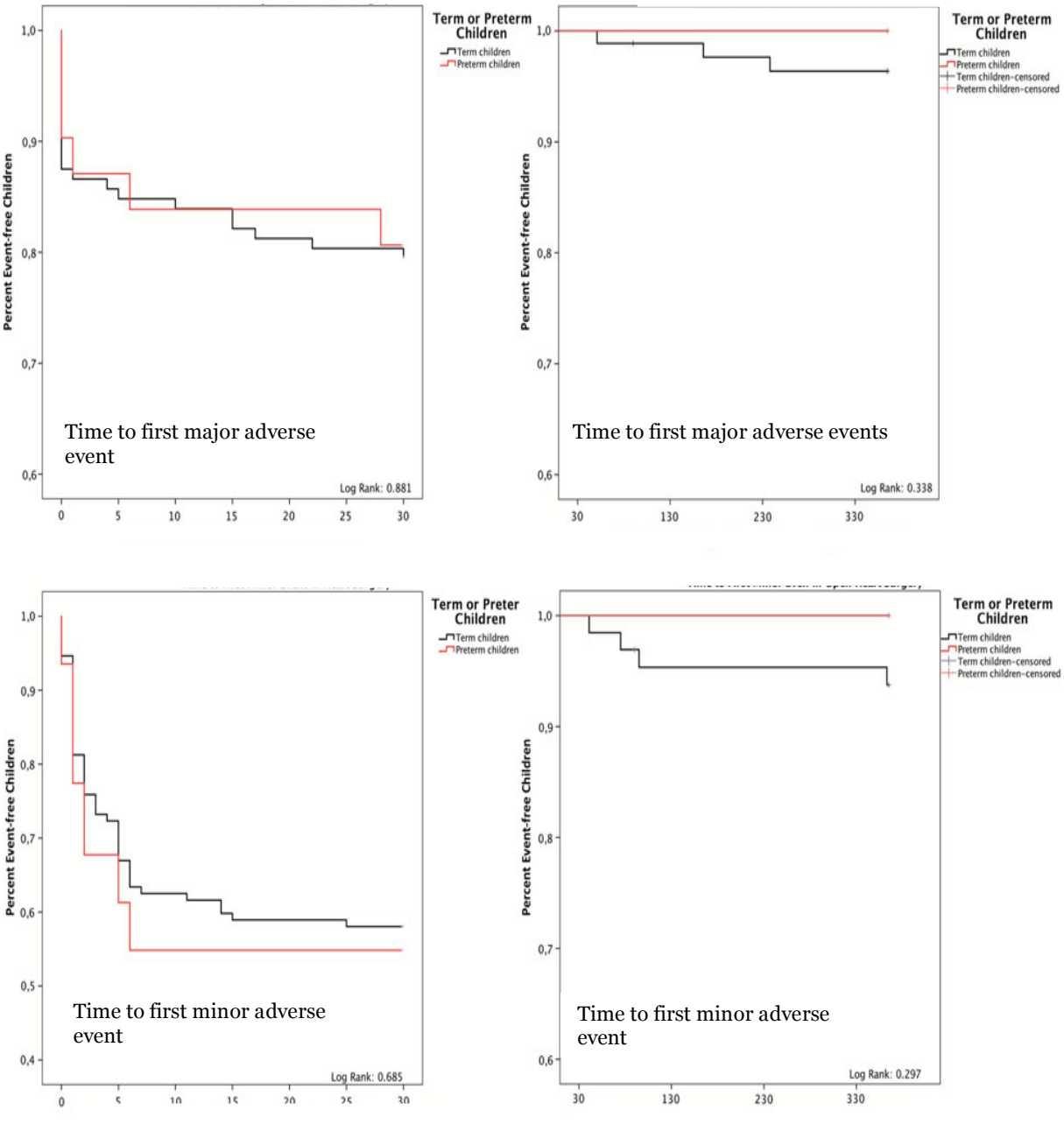
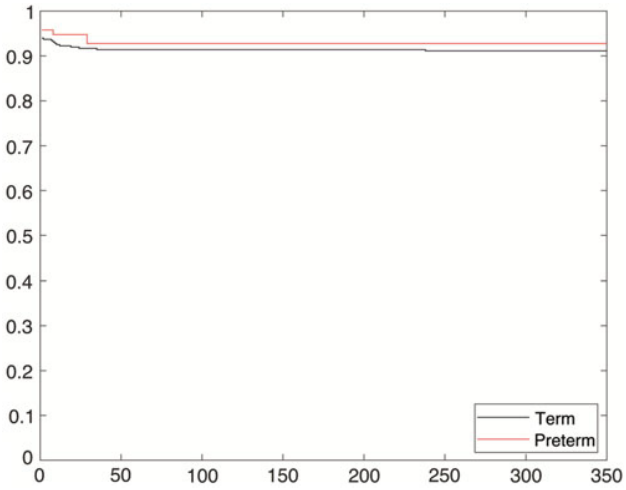


Figure 10. Multiple recurring major adverse events.



Three children in term cohort (1%) and one child in the preterm cohort (1%) died following ASD II closure. In the term cohort, one teenager, aged 17 years, with a 27 mm Amplatzer septal occluder, suffered from pericardial effusion and cardiac arrest five days after ASD II closure and died. Another child in the term cohort had a surgical ASD II closure at the age of 13 months and died from ventricular arrhythmia 237 days after surgery. A third child in the term cohort, aged 12 months, with hypertrophic cardiomyopathy died of septic shock 166 days after surgery.

One child in the preterm cohort, born at a gestational age of 22 weeks, had a surgical ASD II closure at the age of 6 months and died 27 days after surgery due to pulmonary hypertension crisis and multiple organ failure.

Paper III. Risk factors for adverse events within one year after atrial septal closure in children: a retrospective follow-up study

In total, 511 children underwent ASD II closure at one of the two centres. A total of 117 children were excluded from the study group due to invalid identification numbers, having been born abroad, or declined participation, leaving 394 children with 400 ASD II closures for analysis (Figure 6).

The median body weight for children with an ASD II closure was 14.5 kg (3.5–110.0 kg), the median age was 3.0 years (0.1–17.8 years), the median ASD size was 13.0 mm (4.1–37.0 mm), and the median ASD:weight ratio was 0.9 mm/kg (0.1–4.3 mm/kg) (Table 14). The female:male ratio was 1.5:1. Further demographic data are presented in Table 14.

In all, 110 minor adverse events in 87 children and 68 major events in 45 children were recorded. The most common major adverse event was persistent arrhythmia or intra-procedural arrhythmia requiring treatment, accounting for 25 (36.7%) of all major events. The three most common types of minor events were 34 (30.9%) cases of suspected infection, 32 (29.1%) cases with trivial pericardial/pleural effusion but not in need of drainage, and 12 (10.9%) cases of arrhythmia not requiring treatment.

Table 14. Demographic data (Paper III).

Demography Study Population	**Total (n = 400)**	**PDC (n = 257)**	**Surgery (n = 143)**	*P**
Gender (girls/boys)	245 (61%)/ 155 (39%)	161 (63%)/ 96 (37%)	84 (59%)/ 59 (41%)	0.44
Age at closure (years)	3.0 (0.1–17.8)	3.5 (0.3–17.5)	2.5 (0.1–15.7)	**< 0.01**
Weight at closure (kg)	14.5 (3.5–110.0)	15.1 (4.8–110.0)	12.4 (3.5–67.0)	**< 0.01**
ASD size (mm)	13.0 (4.1–37.0)	12.0 (4.1–30.0)	13.5 (5.0–37.0)	**0.04**
ASD-to-weight ratio	0.9 (0.1–4.3)	0.8 (0.1–2.5)	1.1 (0.2–4.3)	**< 0.01**
Gestational age at birth (w)	38.5 (22.0–44.0)	39.0 (23.0–43.0)	38.0 (22.0–44.0)	0.76
Additional CHD	111 (28%)	60 (23%)	51 (36%)	**< 0.01**
Chromosomal defect	45 (11%)	29 (11%)	16 (11%)	0.98
Preterm (< 37 w)	87 (22%)	56 (22%)	31 (22%)	0.98
Late preterm (32 to < 37 w)	59 (15%)	41 (16%)	18 (13%)	0.36
Very preterm (28 to < 32 w)	13 (3%)	8 (3%)	5 (4%)	0.84
Extremely preterm (< 28 w)	15 (4%)	7 (3%)	8 (6%)	0.15
Arrhythmias prior to ASD closure	15 (4%)	8 (3%)	7 (5%)	0.39
Pulmonary disease	45 (11%)	30 (12%)	15 (10%)	0.74
IRDS	24 (6%)	16 (6%)	8 (6%)	0.80
BPD	17 (4%)	10 (4%)	7 (5%)	0.63
Neonatal respiratory ventilation	21 (5%)	11 (4%)	10 (7%)	0.22
Neonatal CPAP	47 (12%)	27 (11%)	20 (14%)	0.31
Neonatal sepsis	24 (6%)	15 (6%)	9 (6%)	0.84
Pulmonary hypertension	33 (8%)	19 (7%)	14 (10%)	0.41
Symptomatic ASD	47 (12%)	19 (7%)	28 (20%)	**< 0.01**

ASD: atrial septal defect, BPD: bronchopulmonary dysplasia, CHD: congenital heart defects, CPAP: continuous positive airway pressure, IRDS: infant respiratory distress syndrome, PDC: percutaneous device closure, w: weeks.
** Comparing percutaneous device closure with surgery.*

Risk factors and adverse events

Preterm birth, regardless of gestational age, was not associated with either minor or major adverse events, following any type of ASD closure (Tables 15 and 16).

Some neonatal comorbidities that are common among children born preterm, such as pulmonary disease, IRDS, need for neonatal respiratory ventilation, continuous positive airway pressure (CPAP), and neonatal sepsis, were also more common among cases with major events compared with controls (Table 15 and 16).

Table 15. Risk factors for major adverse events

	All			*Surgery*			*PDC*		
	Cases (n=45)	**Control**	*P* χ^2	**Cases (n=32)**	**Control**	*P* χ^2	**Cases (n=17)**	**Control**	*P* χ^2
Gender (girls/boys)	33 (73%)/ 12(27%)	207 (59%)/ 143(41%)	0.18	23 (72%)/ 9(28%)	61 (56%)/ 49(44%)	0.10	13 (77%)/ 4(23%)	148 (62%)/ 92(38%)	0.30
Age at closure (years)	1.8 (0.1–16.8)	3.2 (0.3–17.8)	**<0.01**	1.5 (0.1–15.7)	2.7 (0.4–13.6)	0.20	3.2 (0.4–16.8)	3.6 (0.3–17.8)	0.08
Weight at closure (kg)	11.0 (3.5–64.2)	14.6 (4.5–110.0)	**<0.01**	9.2 (3.5–61.5)	12.6 (4.5–67.0)	0.12	11.5 (4.8–64.3)	15.2 (5.1–110.0)	0.12
ASD size (mm)	13.0 (5.0–37.0)	12.3 (4.0–30.0)	0.78	14.0 (5.0–37.0)	13.0 (6.0–28.0)	0.86	12.0 (6.0–24.0)	12.0 (4.1–30.0)	0.62
ASD-to-weight ratio	1.1 (0.3–2.7)	0.8 (0.1–4.3)	**<0.01**	1.1 (0.3–2.7)	1.0 (0.2–4.3)	0.34	1.0 (0.3–1.7)	0.8 (0.1–2.5)	0.16
Gestational age (weeks)	38.0 (22.0–44.0)	39.0 (23.0–23.0)	0.07	38.0 (22.0–44.0)	39.0 (23.0–42.0)	0.18	38.0 (28.0–42.0)	39.0 (23.0–43.0)	0.24
Additional CHD	19 (42%)	89 (26%)	**0.01**	16 (53%)	34 (31%)	**0.02**	3 (18%)	55 (23%)	0.89
Chromosomal defects	5 (11%)	38 (11%)	0.96	4 (13%)	11 (10%)	**0.01**	1 (6%)	27 (11%)	1.00
Preterm	11 (24%)	76 (22%)	0.69	6 (20%)	25 (23%)	0.75	5 (29%)	51 (21%)	0.22
Late preterm	4 (9%)	55 (16%)	0.20	0 (0%)	18 (16%)	**0.01**	4 (23%)	37 (16%)	0.20
Very preterm	3 (7%)	10 (3%)	0.23	2 (7%)	3 (3%)	0.29	1 (6%)	7 (3%)	0.37
Extremely preterm	4 (9%)	11 (3%)	0.10	4 (13%)	4 (4%)	0.07	0 (0%)	7 (3%)	-
Pulmonary disease	10 (22%)	34 (10%)	**0.01**	8 (27%)	7 (6%)	**<0.01**	2 (13%)	27 (11%)	0.73
IRDS	6 (13%)	19 (6%)	**0.04**	4 (13%)	4 (4%)	0.07	2 (13%)	15 (6%)	0.24
BPD	4 (9%)	13 (4%)	0.15	4 (13%)	3 (3%)	**0.04**	0 (0%)	10 (4%)	-
Neonatal respiratory ventilation	8 (18%)	13 (4%)	**<0.01**	5 (17%)	5 (5%)	**0.02**	2 (13%)	8 (3%)	**0.02**
Neonatal CPAP	12 (27%)	35 (10%)	**<0.01**	8 (27%)	12 (11%)	**0.03**	4 (23%)	23 (10%)	0.05
Neonatal sepsis	6 (13%)	18 (5%)	**0.03**	4 (13%)	5 (5%)	0.10	2 (13%)	13 (5%)	0.20
Pulmonary hypertension	8 (18%)	24 (7%)	0.01	7 (23%)	6 (6%)	**<0.01**	1 (6%)	18 (8%)	1.00
Symptomatic ASD	13 (29%)	33 (10%)	**<0.01**	13 (43%)	14 (13%)	**<0.01**	0 (0%)	19 (8%)	-

ASD: atrial septal defect, BPD: bronchopulmonary dysplasia, CHD: congenital heart defects, CPAP: continuous positive airway pressure, IRDS: infant respiratory distress syndrome, PDC: percutaneous device closure

Table 16. Risk factors for minor adverse events.

	All			*Surgery*			*PDC*		
	Cases (n = 86)	**Control**	*P* χ^2	**Cases (n = 65)**	**Control**	*P* χ^2	**Cases (n = 22)**	**Control**	*P* χ^2
Gender (girls/boys)	48 (56%)/ 38 (44%)	197 (63%)/ 116 (37%)	0.26	35 (55%)/ 29 (45%)	49 (63%)/ 29 (37%)	0.33	13 (59%)/ 9 (41%)	148 (63%)/ 87 (37%)	0.72
Age at closure (years)	2.4 (0.4–17.8)	3.2 (0.1–17.4)	0.32	2.1 (0.4–15.7)	2.7 (0.1–13.2)	0.77	4.2 (0.5–17.8)	3.5 (0.3–17.4)	0.38
Weight at closure (kg)	12.6 (4.5–79.0)	14.6 (3.5–110.0)	0.33	12.3 (4.5–67.0)	12.5 (3.5–53.0)	0.65	17.1 (5.6–79.4)	15.1 (4.8–110.0)	0.46
ASD size (mm)	14.0 (5.0–37.0)	12.0 (4.1–31.0)	0.07	14.0 (5.0–37.0)	13.0 (6.0–31.0)	0.69	14.0 (7.0–30.0)	12.0 (4.1–27.0)	0.19
ASD-to-weight ratio	1.0 (0.1–4.3)	0.8 (0.1–3.0)	0.15	1.0 (0.2–4.3)	1.1 (0.4–3.0)	0.83	0.6 (0.1–2.5)	0.8 (0.1–2.4)	0.37
Gestational age (weeks)	38.0 (23.0–42.0)	39.0 (22.0–43.0)	0.77	38.0 (22.0–42.0)	39.0 (23.0–42.0)	0.76	38.0 (24.0–41.0)	39.0 (23.0–43.0)	0.46
Additional CHD	27 (33%)	81 (26%)	0.21	23 (37%)	27 (35%)	0.86	4 (22%)	54 (23%)	1.00
Chromosomal defects	12 (15%)	31 (10%)	0.23	10 (11%)	5 (7%)	0.07	2 (11%)	26 (11%)	0.63
Preterm	19 (23%)	68 (22%)	0.79	14 (22%)	17 (22%)	0.98	5 (28%)	51 (22%)	0.55
Late preterm	11 (13%)	48 (15%)	0.66	8 (13%)	10 (13%)	0.96	3 (17%)	38 (16%)	0.96
Very preterm	3 (5%)	10 (3%)	0.84	3 (5%)	2 (3%)	0.66	0 (0%)	8 (3%)	-
Extremely preterm	5 (6%)	10 (3%)	0.25	3 (5%)	5 (7%)	0.73	2 (11%)	5 (2%)	0.08
Pulmonary disease	9 (11%)	35 (11%)	0.94	6 (10%)	9 (12%)	0.66	3 (17%)	26 (11%)	0.44
IRDS	5 (6%)	20 (6%)	0.91	3 (5%)	5 (7%)	0.73	2 (11%)	15 (6%)	0.35
BPD	3 (4%)	14 (5%)	0.74	2 (3%)	5 (7%)	0.46	1 (6%)	9 (4%)	0.53
Neonatal respiratory ventilation	16 (18%)	5 (6%)	0.74	4 (6%)	6 (8%)	1.00	1 (6%)	10 (4%)	0.57
Neonatal CPAP	13 (16%)	34 (11%)	0.22	11 (18%)	9 (12%)	0.33	2 (11%)	25 (11%)	1.00
Neonatal sepsis	6 (7%)	18 (6%)	0.61	3 (5%)	6 (8%)	0.46	3 (17%)	12 (5%)	0.08
Pulmonary hypertension	10 (12%)	22 (7%)	0.13	8 (13%)	5 (7%)	0.21	2 (11%)	17 (7%)	0.66
Symptomatic ASD	17 (21%)	29 (9%)	**<0.01**	14 (22%)	13 (17%)	0.43	3 (17%)	16 (7%)	0.15

ASD: atrial septal defect, BPD: bronchopulmonary dysplasia, CHD: congenital heart defects, CPAP: continuous positive airway pressure, IRDS: infant respiratory distress syndrome, PDC: percutaneous device closure.

Independent risk factors for adverse events

Neither preterm birth, as a group or by gestational age subgroups, pulmonary diseases, ventilation support, nor neonatal sepsis were associated with major events following ASD II closure after adjusting for potential confounding factors (Table 17). Symptomatic ASD II was an independent risk factor for major adverse events OR = 2.80; (CI 95% 1.23–6.37), and minor adverse events OR = 2.18; (CI 95% 1.05–8.06) following all types of ASD II closure. Symptomatic ASD II was associated with major adverse events OR = 4.50; (CI 95% 1.47–13.80) following surgical ASD II closure, taking into account potential confounding factors (Table 17).

Table 17. Adjusted risk factors.

Adjusted risk factors for adverse events

	All types of ASD closure		PDC		Surgery	
	OR Major events (CI 95%)	**OR Minor events** (CI 95%)	**OR Major events** (CI 95%)	**OR Minor events** (CI 95%)	**OR Major events** (CI 95%)	**OR Minor events** (CI 95%)
Preterm > 32 to < 37 w gestational age†	0.35 (0.10–1.18)	0.80 (0.37–1.76)	1.07 (0.27–4.27)	0.92 (0.23–3.70)	-	0.78 (0.25–2.42)
Preterm < 32 w gestational age†	0.69 (0.18–2.68)	1.23 (0.34–4.45)	0.75 (0.06–9.98)	1.43 (0.14–15.11)	0.59 (0.03–12.66)	1.48 (0.16–13.34)
Pulmonary diseases and general ventilatory support†	2.51 (0.83–7.64)	1.04 (0.41–2.67)	2.17 (0.46–10.15)	0.53 (0.08–3.58)	3.82 (0.28–52.00)	1.45 (0.34–6.15)
Neonatal sepsis†	1.20 (0.34–4.31)	0.77 (0.24–2.48)	2.78 (0.48–16.22)	3.10 (0.60–15.92)	0.56 (0.07–4.54)	0.25 (0.03–1.88)
Pulmonary hypertension†	1.32 (0.48–3.59)	1.07 (0.43–2.68)	0.75 (0.07–8.06)	0.81 (0.14–4.86)	2.50 (0.52–12.03)	1.71 (0.43–6.82)
Symptomatic ASD†	**2.80** (1.23–6.37)	**2.18** (1.05–4.52)	-	1.19 (0.39–8.42)	**4.50** (1.47–13.80)	1.05 (0.39–2.80)

ASD: atrial septal defect, PDC: percutaneous device closure, w: week.
†Included in the regression model

Paper IV. Incidence of atrial septal defect among preterm children and independent risk factors of atrial septal defect diagnosis

In total, 978 cases with ASD II and 8,866 controls were included in the study. Cases had a lower birthweight (3,124.6 g ± 885.3 std) compared with controls (3,511.7 g ± 593.6 std, p <0.001) and were born at an earlier gestational age (38.1 weeks ± 3.6 std) compared with controls (39.7 weeks ± 2.0 std, $p < 0.001$).

The median chronological age at ASD II diagnosis for preterm children was 55.0 days (interquartile range (IQR) 6.0–136.0 days) and for term children 43.0 days (IQR 4.0–212.0 days), $p = 0.927$. Children born very and extremely preterm had a higher chronological age at ASD II diagnosis than term children (Table 18). All subgroups of preterm children were younger (corrected gestational age) at time of ASD II diagnosis compared with term children (Table 18).

Table 18. Age at diagnosis.

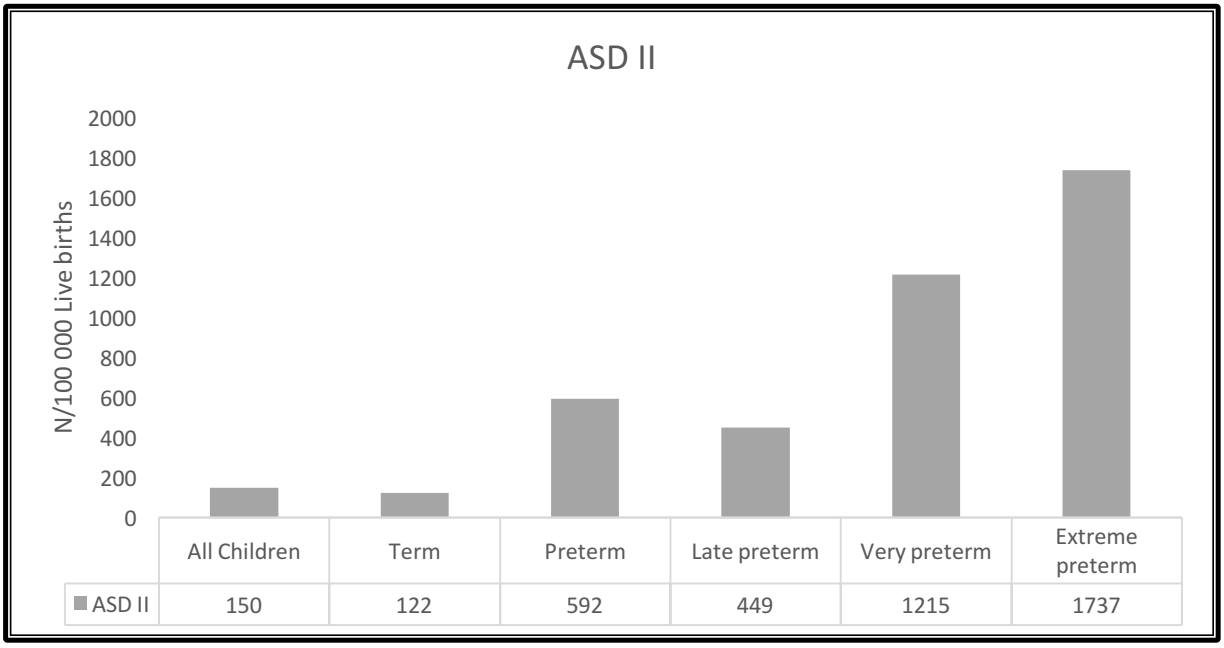
Chronological age at ASD II diagnosis			
	Median (days)	IQR	*p*
Term	43.0	4–212	**0.04**
Late preterm	37.0	5–105	
Very preterm	111.5	25.25–223.25	
Extremely preterm	108.5	11.75–178.75	
Corrected age at ASD II diagnosis			
	Median (days)	IQR	*p*
Term	44.0	4–212	**<0.01**
Late preterm	3.0	-27–60	
Very preterm	40.5	-37.75–145.75	
Extremely preterm	16.5	-82–72.5	

Interquartile range (IQR). Late preterm (32 to < 37 weeks), very preterm (28 to < 32 weeks) and extremely preterm (< 28 weeks). Corrected age: age in days by gestational age at birth.

Incidence

The annual birth rate in 2010–2015 ranged between 110,004 and 115,352 births. Between the years 2010 and 2015, the overall yearly incidence of ASD II was 150 per 100,000 live births (Figure 11). The incidence of ASD II increased with decreasing gestational age, and was more than three times higher among preterm children than term children (Figure 11).

Figure 11. ASD II incidence among term and preterm children.



Risk factors for ASD II diagnosis

Children diagnosed with ASD II were more often born preterm, SGA_w, or with a very low birthweight (VLBW). Associated diseases, such as non-specific neonatal infections, BPD, IRDS, PPHN, persistent ductus arteriosus (PDA), CHD, and Down's syndrome, were more common among cases than controls (Table 19). The female:male ratio for ASD II was 1.3:1.

Smoking at first antenatal visit and diagnosis of diabetes mellitus and epilepsy was more common among mothers of cases than mothers of controls (Table 19).

Table 19. Distribution of risk factors.

Neonatal risk factors	*Cases* *n = 978*	*Controls* *n = 8,866*	p
Girls	556 (56%)	4,061 (49%)	**< 0.01**
Boys	431 (44%)	4,294 (51%)	
Small for gestational age	64 (7.1%)	206 (2.5%)	**< 0.01**
Large for gestational age	39 (4.3%)	288 (3.5%)	0.24
Very low birthweight	65 (6.6%)	72 (0.9%)	**< 0.01**
Over 42 gestational weeks	41 (4.2%)	440 (5.3%)	**< 0.01**
Term	759 (77.0%)	7,858 (94.1%)	**< 0.01**
Late preterm	153 (15.5%)	418 (5.0%)	
Very preterm	40 (4.1%)	44 (0.5%)	
Extremely preterm	34 (3.4%)	35 (0.4%)	
Postnatal risk factors			
Non-specific infections	39 (4.0%)	75 (0.9%)	**< 0.01**
Bronchopulmonary dysplasia	19 (1.9%)	12 (0.1%)	**< 0.01**
Infant respiratory distress syndrome	51 (5.2%)	64 (0.8%)	**< 0.01**
Persistent pulmonary hypertension	32 (3.2%)	20 (0.2%)	**< 0.01**
Persistent ductus arteriosus	47 (4.8%)	25 (0.3%)	**< 0.01**
*CHD**	236 (23.9%)	56 (0.7%)	**< 0.01**
Morbus Down	66 (6.7%)	5 (0.1%)	**< 0.01**
Maternal risk factors			
Maternal smoking at first visit	77 (8.2%)	503 (6.2%)	**0.02**
Maternal snuff use at first visit	13 (1.4%)	112 (1.4%)	0.98
Underweight	16 (1.8%)	185 (2.4%)	0.22
Normal weight	499 (58.0%)	4,545 (55.7%)	
Pre-obesity	236 (25.5%)	1,994 (26.3%)	
Obesity	145 (14.2%)	1,110 (16.2%)	
Maternal chronic renal disease	4 (0.4%)	38 (0.5%)	0.83
Maternal diabetes mellitus	14 (1.4%)	52 (0.6%)	**< 0.01**
Maternal epilepsy	11 (1.1%)	36 (0.4%)	**< 0.01**
Maternal chronic high blood pressure	7 (0.7%)	39 (0.5%)	0.30

**non-ASD congenital heart defects.*

BMI at first antenatal visit: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), pre-obesity (BMI 25.0–29.9 kg/m²), and obesity (BMI ≥ 30 kg/m²).

None of the maternal risk factors were associated with ASD II diagnosis after adjusting for potential confounding factors (Table 20). The risk of ASD II diagnosis was independently associated with a presence of other CHD: OR = 47.71; (CI 95% 34.01–66.94), PDA: OR = 8.11; (CI 95% 2.80–16.69), female gender: OR = 1.39; (CI 95% 1.18–1.63), and $SGA_{w:}$ OR = 1.86; (CI 95% 1.29–2.68). Moderate preterm children had a threefold

independent association with ASD II diagnosis: OR = 3.21; (CI 95% 2.46–4.19) and children born at less than 32 gestational weeks had a fourfold association: OR = 4.02; (CI 95% 2.80–7.12) compared with term children (Table 20).

In this thesis, an additional logistic regression model was performed, incorporating gestational age as a continuous variable, and CHD, SGA_w, gender, and maternal smoking. Excluded factors in this analysis were maternal weight-classes, PDA (as a mediator), and Downs syndrome (due to wide CI in the univariate analyses).
The risk of ASD II was still independent associated with female sex: OR = 1.32; (CI 95% 1.17–1.48), SGA_w: OR = 1.46; (CI 95% 1.12–1.94), CHD: OR = 8.47; (CI 95% 7.05–10.81). For each gestational week of maturity to term, the adjusted risk for ASD II diagnose decreased: OR = 0.86; (CI 95% 0.84–0.88).

Table 20. Risk factors for ASD II diagnosis.

	Uni		*Adj*	
	OR	**95% CI**	**OR**	**95% CI**
Maternal smoking at first visit†	1.36	(1.06–1.74)	1.26	(0.93–1.70)
Boy (ref) †	1		1	
Girl†	1.36	(1.19–1.56)	1.39	(1.18–1.63)
Underweight§ †	0.84	(0.69–1.02)	0.86	(0.49–1.53)
Normal weight§ (ref) †	1		1	
Pre-obesity§ †	0.66	(0.38–1.4)	1.01	(0.84–1.23)
Obesity§ †	0.91	(0.73–1.13)	1.01	(0.80–1.28)
Small for gestational age†	2.93	(2.19–3.91)	1.86	(1.29–2.68)
Term (ref) †	1		1	
Modetate preterm (32 to < 37 weeks) †	3.79	(3.10–4.63)	3.21	(2.46–4.19)
Less than 32 weeks†	9.70	(7.00–13.43)	4.02	(2.80–7.12)
Persistent ductus arteriosus†	16.67	(10.21–27.19)	8.11	(3.94–16.69)
CHD# †	46.57	(34.47–62.91)	47.71	(34.01–66.94)
Morbus down	119.67	(48.09–297.80)		
Very preterm	9.41	(6.09–14.54)		
Extremely preterm	10.09	(6.34–16.22)		

Adj: adjusted, CHD: congenital heart defects, Uni: univariate.
Underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), pre-obesity (BMI 25.0–29.9 kg/m²), and obesity (BMI ≥ 30 kg/m²).
§ Measured at the first antenatal clinic visit.
† Variables included in the logistic regression analyses.
 # Other congenital heart defects.

Discussion

Summary of main results in thesis

The aim of this thesis was to determine risk factors related to ASD II closure, diagnosis, and incidence as well as morbidity and mortality after ASD II closure among small and preterm born children.

The main findings are (Table 21):

- No independent risk factor for major nor minor adverse events following ASD II closure was found. *(Paper I)*
- There was no difference between the preterm and term cohort in the number or time to adverse events following ASD II closure, within one month or within a year, nor in the frequency of multiple events. *(Paper II)*
- No neonatal risk factor was independently associated with adverse events following ASD II closure. ASD II with symptoms was independently associated with major adverse events following ASD II closure. *(Paper III)*
- Children born preterm have a higher incidence of ASD II compared with term children. PDA, CHD, SGA_w, and being born preterm were all independent risk factors for ASD II diagnosis. *(Paper IV)*

Other important findings were (Table 21):

- The overall rate of adverse events following PDC was 8.7%. *(Paper I)*
- The preterm cohort was younger and lighter at ASD II closure. In all, 22.5% of the children with ASD II closure were born preterm. *(Paper II)*
- Children with major adverse events were lighter and younger compared with children without adverse events. *(Paper III)*

Table 21. Summary of main results of papers.

	Aim	*Methods*	*Material*	*Results*
I.	Risk factors associated with PDC ≤ 15kg	Retrospective Case-Control	252 PDC Lund Case: AE Control: no AE	**≤15 kg: OR= 1.67 (CI 95% 0.4–7.3)** ASD/BSA: OR= 1.05 (CI 95% 0.9–1.7) ASD/weight >1.2: OR= 0.9 (CI 95% 0.1–6.6) CHD: OR= 2.1 (CI 95% 0.5–9.5) Genetic comorbidities: OR 1.9= (CI 95% 0.5–7.3)
II.	Compare time to and distribution of AE between preterm and term cohort	Retrospective Cohort	PDC & surgery Lund/STHL Preterm (93) Term (320)	**No difference between the cohorts** Major AE: Preterm 20% vs term 20%, p 0.84 Minor AE: Preterm 11% vs term 10%, p 0.69 Multiple AE: Preterm a 11% vs term 10%, p 0.92 Preterm: younger 2.1 years vs 3.4 years p<0.01, lighter 11,6 kg vs 15,1kg p<0.01.
III.	Paediatric and neonatal risk factors associated with AE after ASD II closure	Retrospective Case-Control	PDC & surgery Lund/STHL Case: AE (45/87) Control: no AE	Major AE **<32 gw: OR= 0.7 (CI 95% 0.2–2.7)** Neonatal sepsis: OR= 1.2 (CI 95% 0.3–4.3) PH: OR= 1.3 (CI 95% 0.5–3.6) **Symptomatic ASD II: OR= 2.8 (CI 95% 1.2–6.4)**
IV.	Incidence and independent risk factors for ASD II diagnosis	Incidence and Retrospective Case-Control	All children in Sweden / ASD II Case: ASD II (987) Control: no ASD II (8,866)	Incidence All children: 150 / 100,000 **Preterm children: 592 /100,000 (449–1737/100,000)** SGA_w: OR= 1.9 (CI 95% 1.3–2.7) **Late preterm: OR= 3.2 (CI 95% 2.5–4.2)** **< 32 gv: OR= 4.0 (CI 95% 2.8–7.1)** PDA: OR= 8.1 (CI 95% 3.9–16.7) CDH: OR= 47.7 (CI 95% 34.0–66.9)

AE: adverse events, ASD: atrial septal defect, BSA: body surface area, CHD: congenital heart defect, gv: gestational weeks, PDA: persistent ductus arteriosus, PDC: percutaneous device closure, STHL: Stockholm,

Methodological considerations of the thesis, strengths and weaknesses

The study population

This thesis is based upon three populations of children (Figure 5). The first three papers partly share the same selected population, and Papers II and III sharing the exact same selected population (Figure 5).

The main objective in the first three studies was to assess associations between adverse events following ASD II closure and perinatal exposures. In order to harmonise the closure procedure at the time as well as indication for ASD II closure, we included children from two collaborating centres (Lund and Stockholm). In Stockholm and Lund, few interventionists perform ASD II PDC, and in Lund, few heart surgeons perform operations (Stockholm patients are referred to Lund for surgery). During the time of the studies, PDC was performed by six interventionists, while surgery was performed by four surgeons (149). The experience of the interventionist or surgeon is associated with mortality and adverse events (56, 150). The study population included a large number of children who underwent ASD II closure performed by few surgeons and interventionists with sufficient experience. This limited both selection bias and allocation bias in the study material.

Paper I included all children born in Sweden, with PDC in Lund during the time period, with no drop outs in the study population. As cases and controls were included from one centre, the risk of selection bias was reduced. In Papers II and III, the two cohorts, including all cases and controls, were retrieved from two centres. However, 33 (6%) of children declined to

participate in the study, which may have introduced a risk of attrition bias and skewness of exposure or outcome. Still, the number of drop-outs was low, which strengthened the results.

To increase the power in Papers II and III, a larger study population could have been selected. The third cardiac PDC and second operative paediatric cardiac centre in Sweden, Gothenburg, performs about one third of PDC and half of the operations in Sweden (149). However, by using the two collaborating centers, a harmonising indication and risk assessment for ASD II closure reduced the risk of selection and allocation bias of confounders and outcome. CRISP assessment score was used in Gothenburg to assess the risk of adverse events following ASD II closure, but was not used by the centres included in this thesis at the time of studies. Age, body weight, and medical conditions and morbidity are variables used as prognostic factors for intervention in CRISP, and small children are considered to be at a higher risk score by CRISP, and may be assessed differently in Gothenburg compared with at the centres included in this thesis (49). This might induce an allocation bias due to an increased number of interventionists and surgeons and different assessments for ASD II closure. Taken together, the study groups in this thesis include more cases and controls than other international studies on small or preterm children with ASD II (63, 104, 151).

Paper IV was a national register-based study including all children with an ASD II diagnosis and matched controls with no ASD II diagnosis. The timespan of 2010–2015 was chosen, as this was optimal, wiht regard the ascertainment of an ASD II diagnosis, as well as other CHD diagnoses, by ultrasound, and to achieve reliable coverage of CHD in the national register SWEDCON (16, 149). Most children born between 2010 and 2015 would have had the possibility of being diagnosed during the three-year timespan of data retrieval. It can be regarded as a limitation that some ASD II might not have been diagnosed during this period, especially among asymptomatic term children, which could introduce a selection bias and an overestimation of the incidence difference between term and preterm children. However, national coverage of SWEDCON and a sufficient timespan of retrieval will strengthen the study and reduce the risk of selection bias.

In Paper IV, all children with an ASD II diagnosis born in Sweden, and registered in SWEDCON, were matched to controls, born at the same hospital and during the same month and year. Thanks to this inclusion criterion, a similar TTE accessibility was present for cases and controls, leading to an equal possibility of diagnosis. In hospitals with few births, matching of three controls born within the same month may have been difficult, and case-controls might have been lost.

Study methods

All studies included in this thesis are limited by the retrospective design, with a risk of selection, recall, and attrition bias (145, 152). However, missing data was well below 20%, especially in Papers I–III, which is considered valid by others, and reduces the risk of bias and strengthens the reliability of the results (145).

Logistic regression models are highly dependent on choosing the right dependent and independent variables and adequate power. In this thesis, unusual dependent variables, such as IRDS or need of ventilatory support, were assessed, which would increase the risk of underpowering of the models. Furthermore, when studying the association between an

independent variable (preterm birth) and a dependent variable (ASD II diagnosis), the independent variable may affect the dependent variable directly as well as indirectly by influencing a third variable (the confounders, CHD), which in turn may influence the dependent variable (ASD II diagnosis). Thus, the relationship between variables is often complex and cannot be well-modulated in a single regression model (143). The natural diversity and maturation of physiology at different ages in paediatrics makes assessment of risk factors of ASD II closure difficult. The low incidence of reported major adverse events further limits the possibility to assess a large number of potential risk factors (143). In Studies III and IV, we stratified some variables into groups with shared morbidities. This can be regarded as a limitation, as the results become less specific. On the other hand, this increases the power and enables assessment of variables with synergistic effects. Preterm birth can be a potential risk factor for ASD II diagnosis as well as for adverse events following ASD II closure, but is also highly associated with maternal risk factors, intrauterine growth retardation, and other comorbidities, which may in turn be influenced by CHD and ASD II (72, 75, 77, 94, 95, 121, 153, 154). Thus, assessing risk factors for ASD II diagnosis and adverse events following ASD II closure can be difficult, as these factors may also be regarded as confounding or mediating factors in the logistic regression model. The true influence can be debated. It is important to remember that the causality of a risk factor to a disease or event can never be studied with regression models, which are used only to indicate associations between exposures and diseases or events.

Sample size power analyses in Paper IV indicated that with $\alpha = 0.05$, an estimated power of >80, eight individual risk factors in the logistic regression model, and a detected OR of 1.8, a minimum of three controls matched to each case was needed. Ten individual risk factors were used in this study, all with clinical relevance. The high number of risk factors assessed may have introduced a risk of spurious significant associations. However, the main result above four a threshold calculated by the power analysis, indicated that there was a low risk of overestimating (type I error) these risk factors. In Paper I, post hoc power analyses were performed for the conditional regression model. Based on the most common risk factors and the incidence of major adverse event, using Shieh-O'Brien's approximation of $\alpha = 0.05$, the study provided a power of 0.996. This showed that the risk of an unstable regression model was limited. Thus, the studies had good power and sufficient possibility to assess an association between outcome and risk factors.

In Paper II, Kaplan-Meier curves were used with a log rank test, which is a univariate method for analysing differences in time to first event between two cohorts. The primary aim of this study was to assess timing and frequency of adverse events in the preterm cohort compared with the term cohort. For this, Kaplan-Meier survival curves were sufficient.

Data retrieval, exposure and outcome

The three first studies assessed paediatric and neonatal factors associated with adverse events, using valid data sources. To reduce the risk of missing data as well as to verify the data, data were retrieved from medical records as well as registries. This also reduced the risk of subjective allocation to non-adverse events. By using predefined stratification of adverse events, the risk of observational bias was reduced.

National registries are not established primarily for research purposes and some risk factors

or outcomes may not have been included in the registries. Data cleaning, checking of data quality, and handling of outliers are important when using register-based data. The quality of the registers can never be better than the data recorded, and researchers have to rely on knowledge and uniformity in the method of recording, such as the diagnosis of ASD II . The linkage between MBR and SWEDCON, two national registers, further strengthened the thesis.

Crosschecking of data between medical records and registries on demographic data, exposure data, and outcomes, when possible, limited the risk of selection, allocation, and recall bias.

SWEDCON is a quality register based on demographic and clinical data and aims to improve medical practices and treatment for children with CHD. This registry has recently been validated with good coherence of data between the registry and medical records (139). MBR was established in 1973 and covers pre- and perinatal data, such as maternal data and neonatal factors, for more than 99% of all births in Sweden (141). The use of various data sources with high reliability decreased the risk of missing data and increased the validity of data, and is a strength of this thesis.

Using the European paediatric cardiac code (EPCC: 05.04.02) used in SWEDCON, which distinguishes ASD II from PFO, instead of using the ICD code, where ASD II and PFO share the same classification (Q21.1), reduced the risk of misclassification of diagnosis (139, 155). The diagnosis of PFO (EPCC code: 05.03.01) with regard to preterm birth, was not assessed in this thesis. PFO is often considered a normal variation and of no clinical significance. PFO was registered in SWEDCON for 1,146 children during the study period, indicating that the risks of misclassification to ASD II and of overestimating ASD II incidence in Paper IV were low.

By using a predefined definition of adverse events, also used by others, the risk of observational bias was reduced (45). The short follow-up time of one year may be regarded as a limitation. However, results from Paper II indicated that the majority of adverse events occurred within the first 30 days, which is in line with previous reports (156). Few late adverse events occured and the risk of this to influence our results must be regarded as limited.

A CHD is always evaluated through a TTE, and an ASD II diagnosis in SWEDCON is registered only after such evaluation. The TTE is done after a referral to a paediatric cardiologist, indicated by clinical signs. Small, asymptomatic ASD II might not be diagnosed among healthy full-term children, as they do not need a cardiac assessment and do not undergo a TTE evaluation. There is a risk of an overestimation of the incidence difference between preterm and term children, as preterm children may have several cardiac assessments during the neonatal period. The prospectively collected data in this large cohort enabled us to assess multiple risk factors for an association with ASD II diagnosis and the risk of overestimation was limited.

The partly similar selection of a study base for cases and controls in Papers I and III strengthened the thesis. Exposures and outcome after ASD II closure, retrieved from the same source, reduced the risk of selection and allocation bias. This also applied to the two cohorts in Paper II.

Ethical considerations

Using information retrieved from registers and medical records may be regarded or perceived as a violation of personal integrity. However, cases included in Studies II and III in this thesis were all subject to informed consent, with the option to decline participation. Information on cases and controls was retrieved from registers such as MBR, Statistics Sweden, and SWEDCON. The identities of the included subjects were anonymised by the Swedish National Board of Health, Statistics Sweden, and SWEDCON, and the risk of violation of personal integrity must be regarded as limited. Personal identification numbers were excluded from the data sent to the research team.

By the linkage between governmental national and quality registers, using individually assigned personal identification numbers, it was possible to assess the research questions of this thesis. Thus, the gains were expected to be significant, justifying the small risks of handling personal data.

Findings and implementation

Diagnosis of ASD II

The overall incidence of ASD II in children born in Sweden between 2010 and 2015 was 150 per 100,000 live births, two to three times higher than in previous studies (15, 16). The diagnostic and reporting routines may have changed over time. Previously, an asymptomatic and small ASD II with insignificant murmur during childhood might have been diagnosed later in life. Today, there is a possibility that such an ASD II is diagnosed during childhood (17-19, 157). The growing availability of TTE at Swedish hospitals and paediatric clinics may explain the increased reporting and diagnosing of ASD II (7, 158).

ASD II is highly associated with other types of CHD; in this thesis, the risk of an ASD II diagnosis in the presence of an additional CHD was increased by 8–40 times. This association has also been reported by others (9, 20). Some studies on ASD II assess the incidence only when the diagnosis is described as solitary, thus potentially underestimating the actual incidence of ASD II (16). SWEDCON reports all CHD diagnoses individually, and the reported ASD II diagnoses, regardless of an association to another CHD, which strengthens the thesis. Association with another CHD increases the possibility of detection due to cardiac symptoms during infancy. Accordingly, CHD is a known confounding factor for both preterm birth and ASD II, and ASD II is a mediator for some CHD. Including CHD in the regression model enabled an evaluation of neonatal risk factors and impact on ASD II diagnosis.

Preterm children have a three to 14 times higher incidence of ASD II diagnosis compared with term children in this thesis (Figure 11). Incidence estimates for all types of CHD are higher in preterm children even when ASD II is excluded (159). The known high prevalence of atrial septal communication found in children under three months of age may contribute to the high incidence of ASD II in preterm children seen in Paper IV (9). Preterm children are more likely to undergo TTE examinations compared with term children. The calculated corrected age at diagnosis for preterm children indicated that the diagnosis of ASD II was set

at a younger age, although the chronological age (days between birth and diagnosis) was well past the first three months of life (Table 18). This implies that the diagnosis of an ASD II is given after initial care at the neonatal intensive care unit (NICU), and thus it is less likely that a PFO could be misclassified as an ASD II. The increased incidence rates of ASD II in preterm children might therefore not only been influenced by the likelihood of echocardiography. An atrial septal communication might have been identified at the neonatal care unit as part of an overall cardiac evaluation related to preterm morbidity, and followed with several TTE evaluations before an ASD II diagnosis was set. This potential careful follow-up could reflect a delayed spontaneous closure of ASD II in preterm children, which in turn may have influenced the incidence rates. On the other hand, some studies report an increased number of preterm children among those with an early ASD II closure, and so the ASD II diagnosed in preterm children may be regarded as clinically relevant and the increased incidence rate in this thesis can be perceived as accurate (65, 98).

PDA usually creates a left-to-right shunt, increasing pulmonary blood flow which stretches the atrial wall separating of the PFO "flap" (9). It can be speculated that a stretched PFO may develop into an ASD II or possibly be incorrectly diagnosed as an ASD II. Symptomatic PDAs, combined with the high incidence of atrial septal communication in preterm children, may contribute to the high incidence of ASD II reported in paper IV. PDA may be regarded as a mediating factor, and attenuating the true effect of preterm birth as a risk factor for ASD II diagnosis. For this reason, additional assessments were made in which PDA was included as well as excluded as a confounding factor, and still ASD II diagnosis was independently associated with preterm birth.

Neonatal pulmonary conditions, could contribute to poor RV compliance and elevated RA pressure, while a residual PPHN could keep the PFO "flap" open. Neonatal pulmonary conditions, which can be regarded as mediator factors, were not included in the regression model in Paper IV (9).

Reduced pulmonary compliance in preterm infants could lead to greater phasic respiratory intrathoracic changes, and higher LA and RA pressures, creating shunts in correlation with the respiratory cycle, preventing soldering of the two atrial septa (12). Speculatively, these factors may displace a PFO to an ASD II, which would lead to overestimation of the incidence of ASD II diagnosis in preterm children. However, it must be kept in mind that ASD II arises in the uterus, at the time of the atrial septation, and that pulmonary diseases develop postnatally. The incidence of ASD II diagnosis may be accurate and it is even possible that ASD II is an independent risk factor for pulmonary diseases (94, 131).

The underlying causes of the potential increased overall incidence in ASD II are not known, and were not possible to assess with the epidemiological methods used in this thesis. One could speculate that increased diagnostic possibilities, allocation disparities, younger age at diagnosis compared with in other studies, and new TTE advances may all contribute to overcoming a past underestimation of the true incidence of ASD II in preterm children. On the other hand, a study of the same study population as this thesis, along with one previous study, reported an increased proportion of preterm children among those with an early ASD II closure, indicating clinical relevance and pathology of the diagnosed ASD II (65, 98). This, and the increased survival rates among preterm children, may indicate that the incidence of ASD II diagnosis in this thesis may be more accurate than that previously described.

The combination of high incidence and an associated increased adjusted risk of ASD II diagnosis in preterm children, along with pre-interventional comorbidities, suggest that a structured follow-up programme in preterm children is indicated. This would include assessing the development of cardiac and pulmonary morbidities and evaluating the need of ASD II closure.

The risk of adverse events after ASD II closure among small and preterm children

Both preterm and SGA_w children have an increased adjusted risk of ASD II diagnosis (Table 20) and a reported risk factor of early intervention, and being overrepresented in the group of children with PDC (23%) compared with that in the general population (6%) (65, 98).

This thesis indicate that preterm children were younger and lighter at the time of ASD II closure compared with term children (Table 10). Hence, it can be speculated that this subgroup is more exposed to ASD II closure at a potentially vulnerable age, with a higher risk of adverse events at less favourable weight and body size for PDC and therefore more often referred to surgery (36, 48, 49). Surgery is considered safe, but risks for adverse events following closure have been reported (41, 156). In line with previous results by others, none of the previously known risk factors, nor weight ≤ 15 kg, gestational age, or comorbidities, were independently associated with adverse events following ASD II closure by PDC and surgery in this thesis (Tables 9 and 17) (45, 64, 65, 67, 71, 160).

The heterogeneous preterm cohort in this thesis included a wide range of gestational ages at birth. CHD, and PH as indication for ASD II closure, were more common in the preterm cohort than in the term cohort (Table 10). This heterogeneity may have induced bias when assessing the association of specific risk factors with the outcome. The total number of children included in the studies was large, but the number of preterm children (n = 93 (23%)) was smaller. This limited the analyses of specific subsets of confounding factors and reduced the overall power. However, findings in this thesis support those of other studies, and indicate that small or preterm children, regardless of gestational age at birth, having a lower body weight and age at the time of ASD II closure, were comparable to larger and term children with regard to the associated risk of adverse events and time to adverse event (61-63, 65, 161).

In Paper III, stratification of independent variables with synergistic effects into merged "risk factor groups" was performed, with a focus on neonatal comorbidities and gestational age, and in order to assess synergistic risk factors with the association to adverse events (Table 6). This model was used to reduce the risk of over-adjustments and to reduce the risk of missing clinically linked risk factors. None of these merged risk factors were independently associated with adverse events following ASD II closure. On the other hand, children with a clinical symptomatic ASD II had an almost three to four times higher risk of major adverse events following ASD II closure. Children with ASD II and clinical symptoms, as stated in the medical records, and/or in need of medication for heart failure, were more common in the preterm group compared with the term group (20.4% vs 10.1%, $p = 0.008$). There were also more children with a symptomatic ASD II in the surgical group compared with in the PDC group (20.1% vs 7.9%, $p < 0.001$). This may explain the increased risk of major events for children with symptomatic ASD II, as surgery has a higher risk of adverse events (41, 156).

Preterm children with symptomatic ASD II may be a specific subgroup of children. These symptomatic preterm children in our population might share characteristics, such as pulmonary comorbidities, PH, and cardiac alterations, with the population that benefits from an early ASD II closure, as reported by others (33, 34, 70, 102-104).

In contrast to the hypothesis presented in this thesis, no elevated risk of adverse events could be found associated with preterm birth, despite the known altered RV and LV function and morphology, and additional pulmonary comorbidities and PH. These cardiac and pulmonary vessel alterations persist into adulthood, and cardiac interventions in childhood might carry less risk of adverse events than interventions in infancy(162). The age-related association of adverse events and timing of ASD II closure for preterm children was not studied in this thesis and further studies are needed.

None of the neonatal risk factors were independently associated with adverse events, although additional CHD, neonatal respiratory support, pulmonary comorbidity, and neonatal sepsis were more common among children with major adverse events following ASD II closure, paper III. The timing of ASD II closure may have an impact on the risks of adverse event and even on future cardiac morbidity(162). Few (n = 22 (23%)) of the children in our preterm group had an ASD II closure before the age of one year. The cardiac morphological alterations are associated with lower gestational age (107, 163). The study populations in this thesis included few very preterm (n = 13 (3%)) and extremely preterm (n = 15 (4%)) children, and associations between preterm risk factors, the origin of known cardiac alteration, and additional pulmonary comorbidities, and adverse events following ASD II closure might have been overlooked due to few included cases. Children with neonatal and pulmonary morbidity may be a special group of patients, requiring careful assessment and risk stratification; this has yet to be studied in larger cohorts.

Assessing mortality rates after ASD II closure is difficult, as the causes of death are heterogenic and sometimes not certainly linked to the ASD II closure. Four deaths were identified in children of different ages, with diverse comorbidity and causes of death. The frequency of death in this thesis was increased compared with other studies, but this must be interpreted with caution, as the number of deaths included was low, and assessing the associated risk of mortality was not possible. Much larger study groups, uniform definitions, and unbiased reviewers would be needed to assess mortality following ASD II closure.

Small and preterm children with ASD II and comorbidities

A growing population of preterm children with BPD, CHD, PH, altered cardiac functions, and morphology is seen (164). These children may potentially benefit from early ASD II closure, which raises a question regarding new indications for ASD II closure and guidelines for follow-up. This has also been discussed by others and is the clinical target of this thesis (70, 94-96, 104, 131).

Indications for ASD II closure are based on signs of a significant left-to-right shunt, RV volume overload, and a potential secondary morbidity, such as decreased growth or PH, but do not include comorbidities associated with preterm birth (31). The combination of reduced pulmonary function and PH could contribute to altered RV maturation, as well as vascular remodelling. Several of the diseases that are associated with preterm birth are challenging to treat during infancy, while an ASD II can be approached more easily. Some studies indicate

that preterm or small children with BPD, PH, and signs of enlarged RV due to pulmonary over-circulation, clinically improve after an ASD II closure (33, 65, 70, 104, 136). However, it can be hard to assess the effect of ASD II closure, as some improvements may be caused by the postnatal normalisation of pulmonary vascular resistance and pulmonary blood flow (165). A careful pre-closure assessment is crucial and the benefits must exceed the risk of major adverse events. Further, as preterm children may suffer from an altered cardiac and pulmonary dysfunction for several years, and the possibility of spontaneous closure or decreased ASD II size, a pulmonary normalisation may occur (17, 99, 125, 166, 167). All these aspects must be evaluated prior to closure. Previous studies of the benefits of early ASD II closure have not assessed the potential associated risks for adverse events in preterm children with neonatal morbidity (33, 104). Thus, this thesis may contribute to the overall risk assessment of ASD II and ASD II closure in preterm children.

Prematurity, a risk factor in early ASD II closure, and associated morbidity – including BPD, feeding problems, and frequent respiratory tract infections – may mimic the symptoms of a significant ASD II (6, 98, 124, 125, 168). Together with TTE signs also commonly described in preterm children, such as RV dysfunction, clinicians may incorrectly interpret the symptoms to be caused by the ASD II, and suggest an unnecessary ASD II closure (95, 118, 124, 169). The natural history of ASD II, which is not fully known in preterm children (other than the known delayed spontaneous closure), may further complicate the decision to treat an ASD II (99, 136, 170). The studies in this thesis indicated that risk factors associated with adverse events were more common among preterm children, although not independent risk factors, and thus these issues require further assessment.

The increased incidence of ASD II diagnosis and the few statistically significant risks of adverse events following ASD II closure in preterm children suggest that these children may have pre-interventional, rather than post-interventional, problems. Thus, preterm birth should not be regarded as a contraindication for ASD II closure. The benefits and timing of an early ASD II closure are important and have yet to be studied.

Clinical implications

The trend toward early ASD II closure in small children with new types of comorbidities linked to preterm birth, reported in the literature and also seen in the clinic, creates the need for new instruments of evaluation. Risk assessment prior to closure requires the application of a holistic view on this specific group of patients. Some risk assessment scores, such as CRISP, include physiological and medical history data, and have been used successfully. Results in this thesis add specific knowledge regarding preterm children, and that gestational age and additional conditions and symptoms does not impact on the risk of adverse events following ASD II closure.

In combination with previous risk assessments, the findings improve the potential risk estimate when discussing the benefits of ASD II closure among clinicians in an evaluation setting or with families of children with ASD II. Further, these findings can add information regarding the need for special resources and the level of post-operative care.

The knowledge regarding a higher incidence and risk of ASD II diagnosis in preterm children, especially in children born before 32 gestational weeks, may aid clinicians in assessing and optimising the follow-up of preterm children after the neonatal period.

Future research

One conclusion in this thesis is that there are no increased risks of adverse events after ASD II closure in small and preterm children, but these children have an increased risk of ASD II diagnosis. However, preterm children is a heterogeneous group with altered cardiac function, risk of neonatal pulmonary disease, such as BPD, and risk of early ASD II closure. The impact of these conditions may be present during early infancy and even more prominent in very and extremely preterm children (< 32 gestational weeks) (94, 97, 112, 117, 163, 168, 171). Assessing risks and risk factors for adverse events following early ASD II closure in very and extremely preterm children is yet to be assessed along with an evaluation of the clinical course of ASD II in these children.

Among children with ASD closure, 22.5% were born preterm, compared with 6% in the general population. The risk of ASD II interventional closure, the need for pre-interventional medical treatment, or a prolonged time to spontaneous closure or risk of early ASD II closure in preterm children were not assessed in this thesis and need to be further evaluated. Severe CHD and ASD II may increase morbidity and mortality in preterm children, especially in very preterm children (87, 90, 92, 94, 95). Few studies assess the impact of ASD II in preterm children with regard to morbidity and mortality.

Future studies suggest to assess the following:

- The association between age at ASD II closure and the risk of adverse events after ASD II closure for preterm children born at < 32 gestational weeks.
- Risk factors associated with adverse events and medication prior to and after ASD II closure in preterm children with clinical symptoms associated to preterm birth, compared with in asymptomatic preterm children.
- The optimal timing of ASD II closure in preterm children with BPD in a prospective cohort study, compared with in preterm children without BPD.
- The association between ASD II diagnosis in infancy and mortality and morbidity of preterm children later in life, compared with the mortality and morbidity preterm children without and ASD II diagnosis.

Conclusions

Preterm children have a high incidence of ASD II diagnosis. Low gestational age at birth is an adjusted independent risk factor for ASD II diagnosis. Adverse events occur in children following ASD II closure, but there was no association between neonatal nor paediatric risk factors (including low procedural body weight or gestational age) and adverse events following ASD II closure. A clinical symptomatic ASD II was independently associated with major adverse events after closure.

Despite younger procedural age, larger ASD II size to weight ratio, and comorbidity, preterm children appeared to have comparable risks of adverse events to those of term children during the first year after ASD II closure.

Preterm children and children with symptomatic ASD II need careful management prior to and after ASD II closure. A new, structured follow-up programme encompassing assessment of indications, timing of treatment, and type of interventional closure should be considered for children born preterm.

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