Outcomes following PDA surgery in extremely preterm born subjects

Focusing on left vocal cord paralysis and associated short- and long-tem outcomes

Merete Salveson Engeset

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The present work was carried out between August 2015 and February 2022 and the thesis originated from the PhD programme of the Department of Clinical Science, Faculty of Medicine at the University of Bergen, Norway. The main research environment was the research groups Westpaed Research, Department of Pediatric and Adolescent Medicine at Haukeland University Hospital, Bergen, Norway and Movement and Function at the Faculty of Health and Social Sciences, Institute of Health and Functioning at the Western Norway University of Applied Sciences.

My supervisors for this work were:

Ola Drange Røksund, physical therapist, professor, main supervisor.

Thomas Halvorsen, medical doctor, professor.

Hege Synnøve Havstad Clemm, medical doctor, associate professor

Silje Mæland, physical therapist, assoiciate professor

The statistical analysis in Study #I–III was carried out in collaboration with Associate Professor Adam Goode, Department of Orthopaedic Surgery at Duke University, Durham, NC, USA, Associate Professor Roy M. Nilsen, Faculty of Health and Function, Western Norway University of Applied Sciences and Karl O. Hufthammer, Centre for Clinical Research at Haukeland University Hospital, Bergen, Norway, respectively.

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Introduction to the thesis

A patent ductus arterious (PDA) is a frequent complication of prematurity[1,2], which allows left to right shunting of blood from the descending aorta and back into the pulmonary circuit. While the PDA have closed spontaneously in most term-born infants within a week after birth, the ductus is still open in 42%–69% of infants born extremely preterm (EP <28 weeks of gestation)[3], and in up to 66% of infants born with extremely low birth weight (ELBW <1000g at birth)[3,4]. The management of a PDA is under continuous debate[5-10], and current treatment options include conservative treatment, pharmacological closure or surgical closure[11]. Injury to the left recurrent laryngeal nerve (LRLN) is a well known complication of PDA surgery[12], which may result in left vocal cord paralysis (LVCP)[13]. A paralysed vocal cord may have impact on vocalisation and impair a full opening of the larynx during inspiration[14].

In 2010, Westpaed Research (previously known as the Research Group for Paediatric Follow-Up Studies) published results from a regional cohort of adults born EP/ELBW in the early 1980's, where 7/11 subjects with a history of neonatal PDA surgery had left vocal cord paralysis (LVCP)[15]. LVCP was associated with dysphonia, reduced lung function at rest and airway obstruction during heavy exercise, but not with impaired exercise capacity. To the best of our knowledge, this was the first and only study investigating long-term outcomes associated with LVCP in adults with a history of neonatal PDA surgery. However, as the sample size was small and the 95% confidence intervals (CIs) were wide, the results may have been inconclusive. Therefore, we wanted to repeat the study in a larger sample of EP/ELBW-born adults. A national population-based cohort study, Project Extreme Prematurity 1999–2000, provided our group with this opportunity. This thesis provides increased knowledge on the incidence and prevalence of LVCP after neonatal PDA surgery as well as short- and long-term outcomes associated with PDA surgery and LVCP.

Summary of thesis

Background: Extremely preterm born (EPB) infants are at risk of a range of complications, among them a patent ductus arteriosus (PDA). If a conservative approach does not reduce the cardiopulmonary compromise imposed by the PDA, pharmacological or surgical closure is required. The rate of PDA surgery has declined over the last decade, in part due to reports of postoperative complications such as left vocal cord paralysis. The incidence and prevalence of LVCP and outcomes associated with left vocal cord paralysis (LVCP) after neonatal PDA surgery has not been sufficiently described.

Aim: The aims of this thesis were to investigate incidence and prevalence of LVCP after surgical PDA closure in EPB subjects, and to study associations between PDA surgery with or without LVCP versus outcomes in the neonatal period and later, focusing on respiratory and voice related symptoms, exercise capacity and lung function.

Methods: In Study #I, we conducted a systematical review and meta-analysis to investigate previous reports of LVCP incidence after PDA surgery and associated outcomes using the Newcastle-Ottawa Scale for quality assessment of individual studies. Study #II and #III were both based on a national prospective cohort study, enrolling all infants born at gestational age (GA) <28 weeks or with birthweight (BW) <1000 grams during 1999–2000. In Study #II, we compared parental reports on voice and exercise related respiratory symptoms in three groups of EPB schoolchildren who either underwent neonatal PDA surgery, received other management for PDA or did not have PDA. In Study #III, EPB young adults with a history of neonatal PDA surgery, EPB controls, and term-born controls underwent spirometry, maximal treadmill exercise testing and answered questionnaires including questions about voice and exercise related respiratory symptoms. The PDA surgery-group also underwent laryngoscopy examination at rest and during the exercise test, allowing the scoring of exercise induced laryngeal obstruction.

Results: The systematic review showed an overall incidence of LVCP following surgical closure of PDA was 9%, with a wide dispersion (0–67%). The incidence was highest in a subanalysis of studies where all subjects underwent laryngoscopy examinations after PDA surgery (overall: 32%, range 11–67%), and heterogeneity decreased with stratification based on study design. LVCP was associated with dysphonia, stridor, and adverse neonatal outcomes, such as chronic lung disease and feeding difficulties. In Study #II, surgical closure of a PDA was associated with an increased crude odds ratio of parental reports regarding voice and exercise related respiratory symptoms compared to other methods of managing PDA. However, days on mechanical ventilation was identified as a potential confounder in multivariate analyses. Study #III revealed a 53% prevalence of LVCP in the PDA surgery group. LVCP was associated with increased laryngeal obstruction during physical exertion and subjective reports of voice symptoms, but not with lung function ($zFEV_1$), exercise capacity ($peakVO_2$) or subjective reports of exercise related respiratory symptoms. PDA surgery was associated with impaired lung function, also after adjusting for BPD. Exercise capacity was not associated with LVCP nor PDA surgery, but all EPB groups performed poorer compared to term-born subjects, even after adjusting for gender. However, low levels of physical activity among those born EP may have impacted the results.

Conclusion and implications: We found that reported incidence of LVCP after PDA surgery in EPB subjects varied across studies and study designs, and that the prevalence of LVCP in our national cohort was high compared to the pooled incidence from the systematic review. Despite associations between LVCP and adverse neonatal outcomes, exercise induced laryngeal obstruction and frequent reports of voice and exercise related respiratory symptoms, LVCP was not associated with poor lung function or exercise capacity. PDA surgery was associated with increased rates of voice- and exercise related respiratory symptoms, but not with exercise capacity. However, the average lung function in the PDA surgery group was below the 5^{th} percentile, and these individuals might represent a group in need of extra pulmonary follow-up in the future. To ensure correct diagnosis and follow-up of patients with LVCP, laryngoscopy examination should be performed routinely after

PDA surgery in EPB neonates. Further, EPB adults with a history of PDA surgery who complain of voice problems or respiratory symptoms should undergo laryngoscopy examination to look for LVCP. Despite a nationwide recruitment, relatively low sample size may have contributed to some of the results being inconclusive. To further enlighten our research questions on incidence, prevalence, and outcomes of LVCP after PDA surgery in the EPB population, an international longitudinal multicentre study is warranted to enable recruitment of a sample with power to detect any true between-group differences.

List of Publications

The thesis is based on three published papers, which will be referred to as studies and numbered using Roman numerals (I–III).

Paper #I. Engeseth MS, Olsen NR, Maeland S, Halvorsen T, Goode A, Røksund OD. Left Vocal Cord Paralysis After Patent Ductus Arteriosus Ligation: A Systematic Review. Paediatric Respiratory Reviews. 2018; 27: 74–85. doi: 10.1016/j.prrv.2017.11.001

Paper #II. Engeseth MS, Engan M, Clemm H, Vollsæter M, Nilsen RM, Markestad T, Halvorsen T and Røksund OD. Voice and Exercise Related Respiratory Symptoms in Extremely Preterm Born Children After Neonatal Patent Ductus Arteriosus. Frontiers in Pediatrics. 2020; 8 (150). doi: 10.3389/fped.2020.00150

Paper #III.* Engan M, Engeset MS, Sandvik L, Gamlemshaug OCO, Engesæter IØ, Øymar K, Vollsæter M, Røksund OD, Hufthammer KO, Halvorsen T, Clemm H (2021) Left Vocal Cord Paralysis in Young Adults Born Extremely Preterm – A national cohort study. Frontiers in Pediatrics. 2022; 9 (1507). doi:10.3389/fped.2021.780045

*Engan and Engeset contributed equally as first authors in Paper #III

Abbreviations

BPD	bronchopulmonary dysplasia
BW	birth weight
CI	confidence interval
CLD	chronic lung disease of infancy
CLE-test	Continuous Laryngoscopy during Exercise test
COX	cyclooxygenase
CPET	cardiopulmonary exercise test
DA	ductus arteriosus
ELBW	extremely low birth weight (<1000 g)
EP	extremely preterm (<28 weeks GA)
EPB	extremely preterm-born
FEV_1	forced expiratory flow during the first second of expiration
FVC	forced vital capacity
GA	gestational age
ISAAC	International Study of Asthma and Allergy in Childhood
IMV	Invasive mechanical ventilation
LMP	last menstrual period
LVCP	left vocal cord paralysis
MBRN	Medical Birth Register of Norway

MD	Mean difference
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
OR	Odds ratio
PA	physical activity
peakVO_2	peak oxygen consumption
$PEP_{99/00}$	Project extreme prematurity 1999–2000
PDA	patent ductus arteriosus
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
RR	Risk ratio
SGA	small for gestational age
VHI	Voice Handicap Index

Contents

1. Background

1.1 Preterm birth

Definitition

The World Health Organisation (WHO) have defined preterm birth as *all births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman`s last menstrual period*[16,17]. Subcategories of preterm birth are based on gestational age (GA) or birth weight (BW). Extremely preterm (EP) infants are born before 28 weeks of gestation[17]. As GA and BW are colinear, extremely low birthweight (ELBW, <1000g) is also a measure of extreme prematurity[16]. However, a birth weight of <1000g is not a certain indication of EP birth as some infants are born small for gestational age (SGA)[18].

A global health issue

Preterm birth complications is the leading cause of death among neonates worldwide[19]. In 2014, the overall estimated preterm birth rate was 10.6%[20], ranging from 10–12% in Asia and Sub Saharan Africa to 8.7% in Europe[20]. The global rate of infants born EP was reduced from 5.1% in 2010[21] to 4.1% of children born preterm in 2014[20]. In Norway, the rate of children born preterm (22–36 weeks GA) was 5.5% in 2020, while 0.3% were born EP (22–27 weeks GA)[22].

Etiology and risk factors of preterm birth

Three main obstetric precursors of preterm birth are 1) induced labour or prelabour caesaran section for maternal or fetal indications (30–35%), 2) spontaneous preterm labour with intact membranes (40–45%), and 3) preterm premature rupture of the membranes (PPROM) (25–30%)[23]. Pre-eclampsia, eclampsia and intrauterine growth restriction are frequent reasons for inducing preterm birth, while spontaneous preterm births including PPROM commonly rise from multiple mechanisms such as infection or inflammation, vascular disease or uterine overdistension[24].

Among risk factors associated with preterm birth are maternal ethnicity[25], socioeconomic and educational status, body mass index, age, previous preterm

delivery, medical disorders (asthma, thyroid disease, diabetes, hypertension), adverse behaviours, psychological characteristics (stress, depression), nutritional and marital status, short inter-pregnancy intervals, vaginal bleeding, biological and genetic markers[23] and in vitro fertilisation[24,26].

1.1.2 From survival to life long health

Advances in obstetric and neonatal medical care have led to a decrease in mortality and lowering of the threshold of viability in extremely preterm born (EPB) infants. Currently, infants born before week 22^0 do not survive (irrespective of efforts to resuscitate) and decisions regarding management of infants born at 22–23 weeks of gestation are made based on a range of factors pertaining to the perceived viability of the fetus as well as individual clinical circumstances, and the families` attitudes towards the institution of the extensive measures required to improve the potential for survival of the newborn[27]. The survival rate of EPB varies between low-income and high-income settings, and also between centres with modern NICUs[28]. Within the EPB population, the survival rate increases with each week of GA, ranging from 6%–67% in infants born at 22–24 weeks GA to 84–95% in infants born at 26–28 weeks of GA when advanced neonatal care is available[3]. In countries with highly developed health care systems, a plateau in survival of EPB infants may have been reached[29,30], and focus has turned from increasing survival to reducing severe impairment and promoting life-long health[31]. However, in addition to the need of prolonged neonatal intensive care, which imposes high societal costs[32], caring for a critically ill infant may impose profound emotional and financial burdens on families[33,34].

1.1.3 Complications and outcomes after extremely preterm birth

Born on the limit of viability, EPB infants are vulnerable to a range of complications which may be associated with the underlying cause(s) of premature birth[23,24], extreme immaturity in itself, or complications that paradoxically may be caused by the life saving treatment they receive during their first critical period of life[23].

Although a range of organs and organ systems may be affected by preterm birth and lifesaving treatment, the ability to obtain gas-exchange through immature lungs is

crucial for immediate survival after birth. Formation of the lungs starts in the first eight weeks of the fetal development, called the embryonic period (Figure 1). Further maturation and growth through the fetal period start with the main bronchi and bronchioles, which branches out into terminal bronchioles. During the last few months of the fetal period, the alveoli, which is the main site for gas-exchange develops, and up towards term the lungs are increasingly equipped for the ventilation and gas-exchange necessary for surviving extra uterine life[35]. The most immature surviving infants are born at the end of the canicular stage, where the terminal respiratory bronchioles are developed and may contribute to gas-exchange, but the development of alveolar ducts has barely (if at all) started. Infants born between 24–28 weeks of GA are born at the saccular stage of lung development, and with alveolar ducts they are better equipped for gas exchange[35]. However, with structurally and functionally immature lungs (including immature production of surfactant), EPB infants are at risk of hyaline membrane disease, also known as respiratory distress syndrome (RDS), where surface tension in the alveoli is increased, resulting in microatelectasis and impaired lung volumes, reduced compliance and reduced capacity for gas-exchange[31,35].

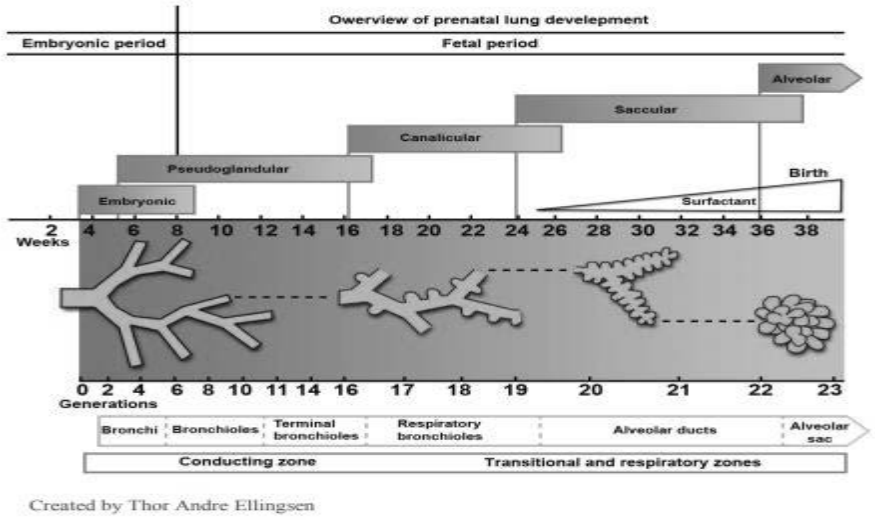

Figure 1. Overview of prenatal lung development. Previously published by Clemm (2015), Exercise capacity after extremely preterm birth. Development from childhood to adulthood (thesis), Department of Clinical Science, University of Bergen, reproduced with permission.

When it comes to the treatment algorithm for infants born before 28 weeks of gestation, the first line treatment includes assessment and resuscitation, i.e providing adequate and gentle ventilation using positive pressure ventilation or nasal continuous positive airway pressure ventilation, oxygen supplementation, avoiding hypothermia, avoiding hypoglycemia, and administering antibiotics to fight possible infections. Surfactant treatment, drug therapy for hypotension, and the use of prostaglandins or COX-inhibitors are indicated in some cases[36].

Short-term outcomes – neonatal morbidity

Up to 93% of EPB infants are affected by RDS[31]. Clinical signs of RDS are respiratory distress including tachypnea, nasal flaring, grunting, and subcostal, intercostal, and/or suprasternal retractions[37]. Administration of surfactant in combination with invasive mechanical ventilation (IMV) or non-invasive-ventilatory support are therefore strongly recommended[38]. The diagnosis of bronchopulmonary dysplasia (BPD) is given to EPB infants who are dependent on oxygen supplementation at 28 days of age, and further sub classified into mild, moderate, or severe based on the percentage of oxygen requirement at 36 weeks GA[39]. As the prevalence of BPD increase with EPB survival, it remains the most common complication of extreme prematurity[40]. The change from 'old' to 'new' BPD reflected a reduction and a change of the injuries (inflammation, fibrosis, bronchial muscle hypertrophy) imposed on the immature lungs by positive pressure ventilation and oxygen toxicity, which vere commonly seen in the pre-surfactant era[39]. With provision of exogeneous surfactant (introduced in the 1990`s) a milder form of BPD also emerged, mainly characterised by disruption of lung development, with reduced alveolar septation with fewer and larger alveoli, as well as abnormal microvasculature development resulting in increased pulmonary vascular resistance and a potential for reduced gas-diffusion capacity[41]. The term BPD is often used interchangeably with chronic lung disease (CLD)[40].

Within the EPB population, incidence and severity of morbidities decreases for each week of gestation[3,30,31,42]. Variation in study designs, inclusion criteria and possible selection bias may have contributed to a dispersion in the rate of reported outcomes

across studies. The decrease in incidence of morbidities by increasing GA at birth is demonstrated in the following rates of important short-term outcomes of EP birth, published in the Canadian Neonatal Network's 2020 annual report, here presented as overall percentage range in those born from before 25 weeks GA to those born at 28 weeks GA[3]: Chronic lung disease (moderate/severe: 72–38%) intraventricular hemorrhage (IVH, 50–13%), sepsis (here, late onset; 36–8%), necrotising enterecolitis (NEC, 13–3%), rethinopathy of prematurity (ROP, 92–29%). Alone or combined, BPD/CLD, ROP and/or brain injury may predict poor long-term outcomes such as death or neurosensory impairment in ELBW infants[43].

Long-term outcomes associated with extremely preterm birth

Allthough the lungs have remodelling potential and lung growth may continue into adolescence[40,44], abnormalities in lung function and structure may persist[40]. Previously published studies from the Project Extreme Prematurity 1999–2000 ($PEP_{99/00}$) cohort have reported increased respiratory morbidity and more respiratory complaints (i.e wheezing during exercise and more use of asthma medications) in EPB children[45,46]. Results from pulmonary testing and respiratory questionnaire in another population based longitudinal follow-up study (the EPICure study) support these findings of impaired lung function and higher rates of self-reported breathing difficulties during exercise among EPB children[47,48]. However, respiratory complaints[45] have been found to decline by age, and the comparison of pulmonary outcomes in cohorts born in the early nineties vs. 1999–2000 have suggested that better neonatal management may improve long-term pulmonary outcomes[49]. Only recently, larger populations of EPB survivors have reached adult age, and an increasing number of studies describing long-term pulmonary outcomes into early adulthood have been published, along with with systematic reviews focusing on the impact of neonatal BPD[50,51], which is associated with increased lung function impairment in EPB adults[51]. EPB subjects surviving BPD have been found not to reach their expected peak lung function in their early 20`s, implying increased risk of developing chronic obstructive pulmonary disorder with age compared to term born subjects (Figure 2)[52,53].

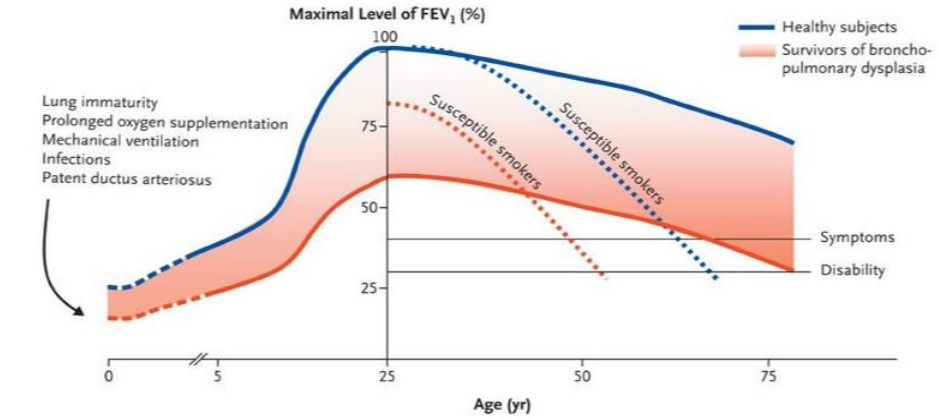

Figure 2. Theoretical model of changes in forced expiratory volume in 1 second (FEV_1) in survivors of bronchopulmonary dysplasia and healthy subjects according to age. Reproduced with permission from the New England Journal of Medicine, Baraldi & Filippone (2007), Copyright Massachusetts Medical Society.

Several studies have reported reduced exercise capacity in EPB children and adults compared to term born[54-56]. The reduced exercise capacity has been associated with a range of possible mechanisms, such as impaired respiratory outcomes[57], adverse cardiovascular health[55,56], reduced cardiomyocyte proliferation and left ventricular function[58-61], reduced lean body mass[62], poor growth and development[47] and reduced fine and gross motor skills[63,64].

Extremely preterm birth is associated with increased readmission rates[46], higher costs for the public sector which include health, social and education services in schoolchildren and adolescents[65,66]. Children and adults born EP have higher rates of cerebral palsy, autism, cardiovascular disease, diabetes, chronic lung disease, mental health problems, impaired skills in motor and social adaptive tasks and increased levels of academic underachievement[66-70]. Learning and attention problems may contribute to poorer health related quality of life[71], and preterm born young adults have increased early mortality rates associated with chonic health conditions[68]. However, most of the EPB survivors *without* severe medical disabilities are well functioning adults[67].

1.2 Patency of the ductus arteriosus

From fetal to neonatal circulation

In utero, the fetus is supplied with nutrients and oxygen from the placenta, which also clears out waste products. The ductus arteriosus (DA) is one of three fetal vascular connections that allows blood to bypass the lungs and liver, organs that are not fully functional before birth[72]. The DA is kept open through complex processes, in which prostaglandins (PG, with E_2 being the most potent subtype) produced by the placenta and the DA itself, plays a crucial role[73]. During fetal development, the pulmonary vascular resistance is high while the systemic vascular resistance is low. The DA provides a connection between pulmonary artery, close to its left origin, to the descending aorta, opening for right to left shunting of blood oxygenated in the placenta[74]. Clamping of the umbilical cord after birth leads to increased systemic vascular resistance, while pulmonary vascular resistance decreases with ventilation of the lungs and clearance of fluid from the alveoli. This reverses the blood flow through the DA, and in term-born infants the shunt is predominantly left to right within ten minutes[75].

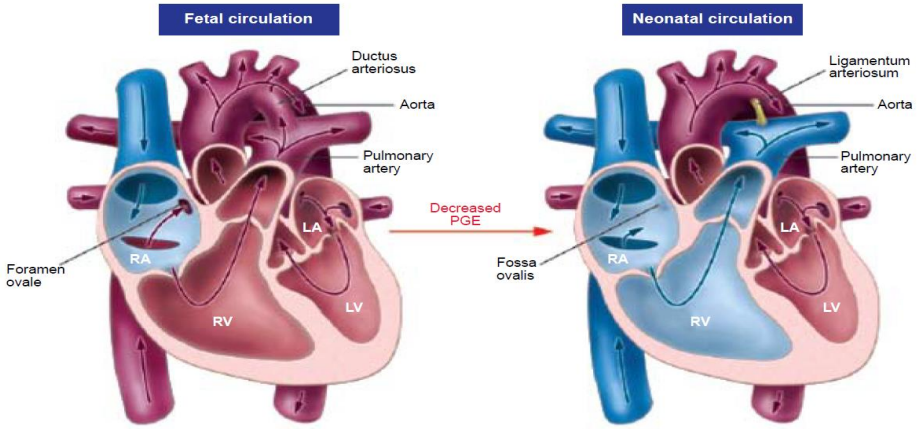

Figure 3 illustrates the ductus arteriosus during fetal circulation (left) and the conversion of the ductus atreriousu into Ligamentum arteriosum in normal neonatal circulation (right). RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle. The paradoxical patent ductus arteriosus. Republished with permission of the American Society for Clinical Investigation, from The paradoxical patent ductus arteriosus, Ivey & Srivastava, 116:2863-2866. Copyright © 2006; permission conveyed through Copyright Clearance Center, Inc.

Mechanisms of ductal closure and patency

In most term born infants, constriction of smooth muscle fibres in the lumen and shortening of DA length results in a functional closure of the DA within the first days of life[76]. This functional closure is mediated mainly by a rise in oxygen tension after exposure to oxygen rich ambient air, a reduction in concentration of prostaglandins following removal of the placenta, and increased catabolism of prostaglandins in the lungs[77]. Over the next three weeks, this muscular vessel is permanently converted into the ligamentum arteriosum[78]. When the DA fails to close within the first days following birth, this is called a patent ductus arteriosus (PDA). Several factors may contribute to maintaining ductal patency: concentration of ductal mediators through the use of antenatal and postnatal medication, maturity of the DA and postnatal condition, and ductal sensitivity to mediators[73,79]. The programming of DA closure normally advances with GA and is interrupted by premature birth. Thus, the rate of PDA increases with lower birth weight and lower gestational age[29,80-82]. Respiratory distress syndrome (RDS) and mechanical ventilation are associated with a PDA requiring treatment[83].

Clinical manifestations of a PDA

Whereas a small DA may not have any clinical manifestations, a moderate or large PDA causes increased pulmonary blood flow[84]. Increased preload from the lungs may lead to elevated pressure in the left ventricle and atrium, which in turn inhibits pulmonary venous return. Subsequently, pulmonary compliance is reduced while work of breathing increase, and the infant may have increased need of respiratory support be difficult to wean from respiratory support. The infant may present with cardiac murmur, bounding peripheral pulses, widened pulse pressure, hypotension, and later signs of congestive heart failure or complications such as RDS, BPD, and pulmonary hemorrhage[84-86]. Systemic infection is associated with ductal reopening, and in interaction with PDA it may increase the risk of chronic lung disease[87]. The ductal steal phenomenon, caused by left to right shunt through the DA, resulting in reduced systemic blood flow and decreased renal, mesenteric, and cerebral perfusion[5], may explain reported associations between PDA and severe outcomes such as renal failure, NEC and IVH[88,89]. Prolonged exposure to a PDA is associated

with increased neonatal mortality[90,91]. However, evidence supporting a causal relationship or the direction of causation between a PDA and associated comorbidities is lacking[92].

Diagnosis of a PDA

Clinical signs of left to right shunting of blood through a PDA may not be evident during the first days of life[93], but manifest later. Echocardiography is currently the standard method for early identification or confirmation of a PDA diagnosis[94], allowing measurement of ductal size and flow[95], pressure gradient across the PDA, signs of increased pulmonary blood flow or systemic hypoperfusion, and impact on cardiac structure and function[93,94]. The PDA should be considered in relation to clinical parameters such as the size and maturation of the infant[96]. Therefore, a hsPDA may simply be defined as a PDA with hemodynamical impact on the heart and circulation[97], and treatment decisions must be based on a combination of clinical signs and diagnostic imaging[97,98].

1.3 Treatment strategies for PDA closure

1.3.1 Short historical view

In 1939, Gross & Hubbard were the first to report successful surgical closure of a PDA[99]. Twenty five years later, Powell described surgical closure of a PDA in a premature infant with RDS[100], and in 1978 Cotton and colleagues published results from a randomised controlled trial demonstrating superior benefits of surgical closure vs. medical management (not cyclooxygenase inhibitors) of symptomatic PDA in infants < 1500g[101]. Surgical ligation was the only curative treatment for PDA until the 1970`s, when cyclooxygenase inhibitors (COX-inhibitors) such as indomethacin were introduced as effective constrictors of the DA, also in preterm infants[102,103]. Around the turn of the millennium, increased knowledge regarding the risk of NEC and bowel perforation in premature infants managed with indomethacin[104], and lack of improvement in long-term morbidities[105] contributed to a decrease in the use of COX-inhibitors in prophylactic treatment[106]. Subsequently, the rates of surgical ligation again increased and peaked in 2006/2007[77,107,108]. Allthough randomised controlled

studies on the effect of PDA surgery vs. medical treatment were lacking[109], several observational studies described associations between PDA surgery and negative outcomes[110-112], and the rate of PDA surgery again declined. Meanwhile, alternatives to the use of indomethacin for pharmacological closure were explored, such as ibuprofen and paracetamol[77,107,108]. Studies reporting relatively high rates of spontaneous closure of PDA in EP/ELBW neonates within the first week (31–34%) and year (75%) after discharge from hospital[4,81,113] contributed to an increased use of a more permissive approach, which, in several studies did not result in increased rates of morbidity or mortality[114-117], whereas other authors found that rates of BPD, mortality and periventricular leukomalacia (PVL) did not change proportionally with the reduction in active PDA closure (Figure 4)[107]. These results contributed to a discussion about whether the permissive approach towards a hsPDA or the increased survival among the most immature infants could explain the lack of improvement regarding adverse outcomes.

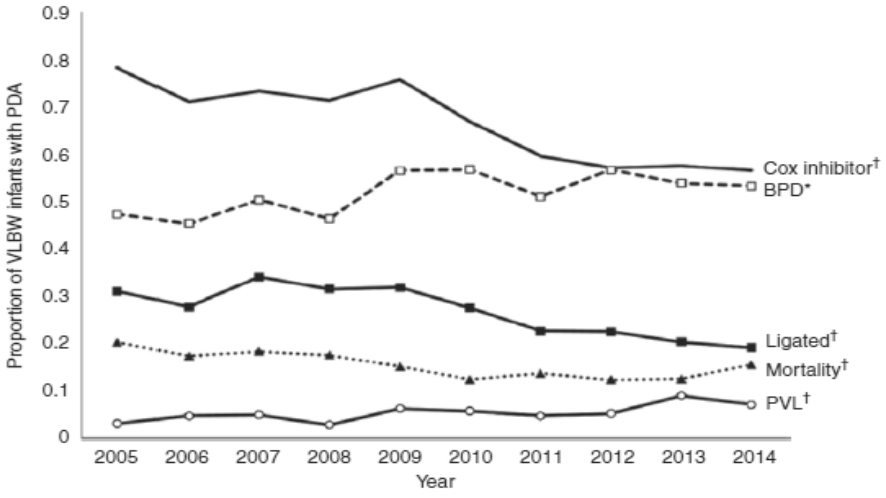

Figure 4 illustrates trends in impairment and outcomes among 5.719 very low-birthweight infants with PDA at 19 US referral children`s hospitals from 2005–2014[107]. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Pediatric Research, Trends and variation in management and outcome of very-low-birthweight infants with patent ductus arteriosus, Hagadorn et al., Copyright © 2016, International Pediatric Research Foundation, Inc.

Recent studies have reported an increased risk of severe negative outcomes such as BPD and death in the EP infants who received expectant management, particularly among EP < 26 weeks GA[118,119]. Attention has now shifted towards predicting for which infants the PDA is not expected to close spontaneously and thus expected to require active management[92]. Infants born at 23–24 weeks GA have the highest risk of developing a PDA that does not close in response to pharmacological treatment[9], and a case control study of EPB infants with PDA, matched for GA and BW, showed that need for surgery was predicted by larger ductal diameter and lack of decrease in diameter in response to pharmacological treatment[120]. Several authors underscore the urgency of a more individualised and targeted approach when treating EPB infants with hsPDA to ensure that the benefits of PDA closure may outweigh the possible side-effects[9,119]. Thus, a moderate and targeted approach towards PDA treatment in EPB infants may be more appropriate compared to both low and high treatment rates, which may lead to adverse outcomes related to a longstanding hsPDA or side-effects of PDA treatment, respectively[121].

Today, surgical ligation is rarely performed, and particularly not as the only form of active treatment for closing a PDA in EPB infants. In the 2020 annual report published by the Canadian Neonatal Network, only three out of 881 (0.3%) neonates born ≤28 weeks gestation received surgical ligation without pharmacological treatment, whereas 6.5% received a combination of pharmacological and surgical treatment[3]. However, the mode and rate of PDA treatment in EPB infants vary between countries and NICUs[121,122]. In a recent multinational cohort study including 139 NICUs and 39 096 EP/VLBW infants, the overall treatment rate of PDA was 45% (range: 13–77%), with variation between NICUs and countries in both pharmacological (overall 43%, range: 7–77%) and surgical management (overall 10%, range: 0.5–28%)[121].

1.3.2 Current guidelines for management of a PDA in preterm infants

Treatment algorithms of PDA in very or extremely preterm infants vary between institutions, as well as between cardiologists and neonatologists[107,108,123]. The following treatment algorithm is recommended for PDA in premature infants by

UpToDate[11], an evidence based clinical resource. These recommendations are also in line with the current treatment algorithm for PDA developed by the University Hospital of Northern Norway[124], which is widely used in NICUs in Norway today.

Prophylactic treatment is not recommended due to few important short-term or long-term benefits[105,125,126]. Difficulties predicting in whom the PDA will close spontaneously may unnecessarily expose a large proportion of infants to medications with negative side-effects[11,127].

First line treatment: In premature infants with a hsPDA, a stepwise management approach is recommended. Step one is conservative care including moderate fluid restriction, a neutral thermal environment and respiratory support for adequate oxygenation, while diuretic therapy may be considered. If respiratory status is compromised and the infant remains dependent on mechanical ventilation at one week of age, pharmacological closure using COX inhibitors (indometacin, ibuprofen) or paracetamol is recommended[11].

Second line treatment: Surgery may be performed when the infant does not respond to pharmacologic therapy and still show significant symptoms of a hsPDA/requires maximal ventilatory support, or when COX inhibitors are contraindicated in an infant on maximal ventilatory support[11].

Pharmacological treatment of a hsPDA

COX-inhibitors, acting trough inhibition of prostaglandin synthetase, are commonly used for active closure of a hsPDA. Indomethacin provides effective closure of a PDA in preterm infants[128], but its vasoconstrictor qualities may lead to side effects such as transient renal failure, gatrointestinal bleeding and perforation[104]. Ibuprofen is a COX inhibitor with effectiveness similar to indomethacin for PDA closure, but with reduced risk of NEC and transitient renal insufficiency[129]. More recently, paracetamol, also acting through inhibition of synthetase of prostaglandins, have been introduced as a third alternative for PDA treatment. Moderate quality of evidence suggests that paracetamol is as effective in closing a PDA as ibuprofen or indomethacin, while also resulting in fewer renal and gastrointestinal side effects[130].

Surgical closure of a PDA

Surgical closure of a PDA provides an immediate and definitive closure of the DA, and can be performed through open thoracothomy, video assisted thoracoscopic (VAT) procedure (less invasive, fewer side effects and shorter healing time compared to open thoracotomy), or by percutaneous transcatheter occlusion, which are now also available for infants <1000g[11]. Surgical closure of a PDA may lead to blood pressure fluctuations, respiratory compromise, infection, scoliosis, chylothorax, diaphragma paresis, left recurrent laryngeal nerve (LRLN) paralysis, and it has also been assossiated with increased risk of BPD, ROP, NEC and IVH[83,110,112,120,131-133]. Side effects of transcatheter occlusion include groin hematoma, arrhytmia, bleeding, pseudo aneurism, device embolisation and complications with sedation for the preocedure[134*p84*].

Expectant management of a PDA

An initial supportive approach includes moderate fluid restriction (120–130 ml/kg per day), a neutral thermal environment (>26 degrees Celsius), minimal respiratory support necessary to obtain adequate oxygenation (90–95% measured with pulse oxymetry) and keeping pH values within the normal range. Efforts to avoid pulmonary injury and atelectases include small tidal volume ventilation and positive end expiratory pressure (PEEP) at 5–7 cm H_2O. Hematocrit should be maintained above 35% as it may reduce left to right shunting due to an increase in pulmonary vascular resistance. Diuretic therapy (thiazide diuretic) can improve short-term pulmonary mechanics and may be considered in cases of fluid overload or signs of interstitial pulmonary edema. However, furosemide and other loop diuretics should be avoided as they stimulate synthesis of PGE_2 and may contribute to ductal patency[11,135].

1.4 Left vocal cord paralysis (LVCP) after neonatal PDA surgery

The larynx is a complex organ, crucial in modulating airflow to the lungs, adjusting the vocal cords during phonation, and in the protection of the lower airways from aspiration[14]. Paralysis of the left recurrent laryngeal nerve (LRLN) and a paralysed

left vocal cord (LVCP), often in paramedian or intermediate position, may lead to increased airway resistance during ventilation, incomplete closure of the vocal cords during vocalisation[13,136] and impaired regulation of acoustic quality[137].

1.4.1 The recurrent laryngeal nerve and intrinsic muscles of the larynx

The major framework of the larynx consists of the thyroid, the cricoid, the epiglottic and the paired arytenoid cartilages[14]. Three branches of the tenth cranial nerve (vagus) innervates the larynx with motor, sensory and autonomic fibres: The superior laryngeal nerve (SLN), and the left and right recurrent laryngeal nerve (RLN). The superior laryngeal nerve leaves the vagus nerve high in the neck (at the level of the thyrohyoid membrane and the superior thyroid artery) and enters the larynx directly, whereas the right and left RLN loops around the right subclavian artery and the arch of aorta, respectively, before running back into the larynx[138] (Figure 5). The LRLN is frequently located immediately medial and inferior to the PDA, an area normally in close proximity to where the suture/clip application is positioned when the PDA is closed surgically[139].

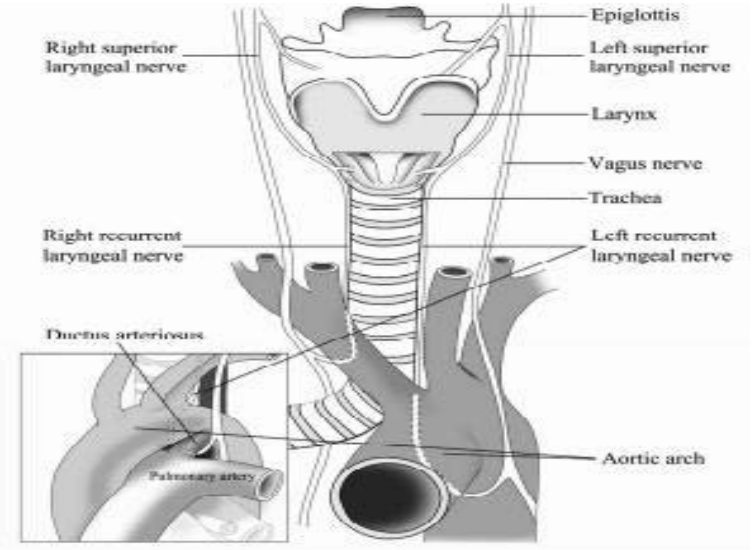

Figure 5. The anatomy of the larynx and other relevant vascular structures and nerves. Created by Thor Andre Ellingsen. Previously published by Røksund (2012), Larynx in exercising humans. The unexplored bottleneck of the airways (thesis). Department of Clinical Science, University of Bergen, reproduced with permission.

The left and right RLN provides sensation to the sub glottic area and ipsilateral innervation of four out of five intrinsic muscles/muscle groups in the larynx[13]: 1) The thyroarytenoid muscles (including the vocalis muscle), which acts to relax the vocal cords and allows a softer voice (Figure 6, left). 2) The posterior cricoarytenoid (PCA) muscles, which are the only abductors of the vocal cords and responsible for widening the rima glottidis during ventilation (Figure 6, right).

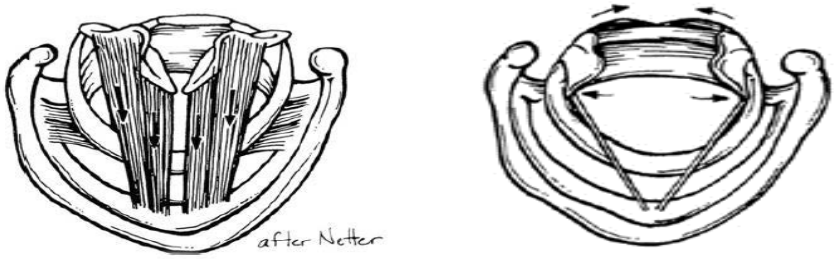

Figure 6. Left: Action of the vocalis and thyroarytenoid muscles. Right: Action of the posterior cricoarytenoid muscles. From Professional Voice: The Science and Art of Clinical Care, Fourth Edition (Vol. 1) (pp. 1-555) by Sataloff, R.T. Copyright © 2017 Plural Publishing, Inc. All rights reserved. Used with permission.

3) The lateral cricoarytenoid muscles are major adductors of the vocal cords, and through narrowing of the rima glottidis they modulate tone and volume of speech (Figure 7, left). 4) The transverse and oblique arytenoid muscles, which adduct the arytenoid cartilages, resulting in closure of the posterior area of the rima glottidis and narrowing of the laryngeal inlet (Figure 7, right).

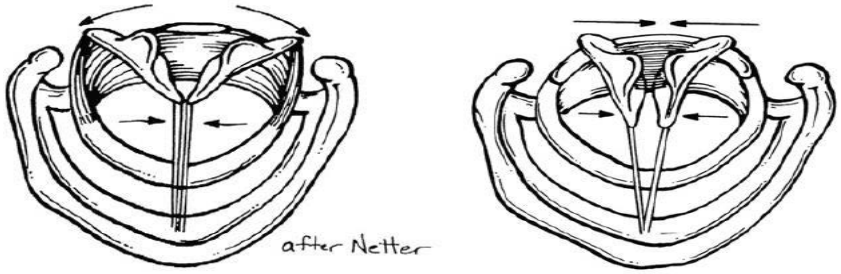

Figure 7: Left: Action of the lateral cricoarytenoid muscles. Right: Action of the arytenoidius muscle. From Professional Voice: The Science and Art of Clinical Care, Fourth Edition (Vol. 1) (pp. 1-555) by Sataloff, R.T. Copyright © 2017 Plural Publishing, Inc. All rights reserved. Used with permission.

The cricothyroid muscles, however, are innervated by the left and right SLN. These muscles stretches and tenses the vocal cords, which is important for achieving high voice pitch, but also contributes to enhance the glottic cross sectional diameter in cooporation with the widening action of the PCA muscles[137]. As the SLN leaves the vagus nerve high in the neck, at the level of the crossing of the hypoglossal nerve, it would not be affected by damage to the LRLN during surgical closure of a PDA, and it may be important following an injury to the LRLN and reinnervation[13].

Airway resistance through larynx during ventilation and incremental exercise

During inspiration, the PCA muscle and the diaphragma work in a close co-operation, modulated by the vagus and phrenicus nerves and the medullary respiratory centre, which is stimulated by hypercapnia and ventilatory obstruction and depressed by hypocapnia and hyperventilation[137]. The PCA muscle rotates, tilts and slides the vocal processes outwards, which widens the rima glottidis just before the diaphragm contracts, and when this is combined with forward tilting of the thyroid by the cricothyroid muscle, a simultaneous lengthening and abduction of the vocal cords increase glottic diameter, allowing air to flow to the lungs with as little resistance as possible though the larynx[140]. Airway resistance normally increase with increased airflow[141], as a consequence of elevated ventilatory demands during physical exercise.

The glottis is the narrowest part of the respiratory tract, accounting for 16% (16–24%) of total airway resistance in adult men at a flow rate of 1 liter/sec[141], and the flow resistance in the upper airways account for 12–30% of the total respiratory work[142]. Normal glottic cross-sectional area in men and women is approximately 2.31 cm^2 and 2.07 cm^2, respectively, and normally largest at total lung volume and decreasing towards rest volume[143]. According to Bernoulli`s principle, when airflow passes through an area with reduced diameter such as the glottis, this will result in increased flow velocity and a drop in the intraluminal pressure, a process that may compromise the patency of the glottis[144]. Considering the turbulent flow through the glottis, the relationship between the severity of airflow limitation and the degree of anatomical obstruction, at least in subglottic stenosis patients, may be described by

the Bernoulli obstruction theory, where a two-fold reduction in cross-sectional area is associated with a two-fold reduction in airflow[145]. Injury to the LRLN impairs movement of the PCA muscle and left sided abduction of the vocal cords. Unopposed by the left PCA muscle, the adducting action of the cricothyroid muscle often leave the left vocal cord in paramedian position[137], which further narrows the glottic cross-sectional area[146] (Figure 8).

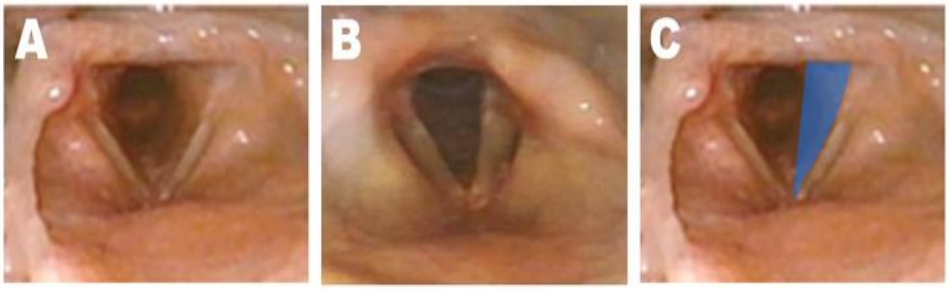

Figure 8. A) Superior view of a normal larynx at moderate exercise intensity, with vocal cords in symmetrically abducted position. The wide part of the V-shaped opening is the posterior part of the rima glottidis. B) A larynx with left vocal cord paralysis at moderate exercise intensity. C) Illustrates the larynx in Figure A with the glottic space partially shaded in blue, representing the reduction of the glottic cross-sectional area imposed by a paralysed left vocal cord. Created by Thor Andre Ellingsen.

The relation between cardiac output (heart rate x stroke volume) and oxygen uptake (VO_2) during exercise have been expressed in Fick`s equation: VO_2= CO x C (a-v); indicating that the oxygen uptake is related to the product of cardiac output (CO) and the difference in arterial-venous oxygen content[147]. Impairments at any level of the oxygen transport chain (including ventilation, gas exchange, gas transportation, and peripheral gas exchange and utilisation) may impair oxygen uptake and exercise capacity. In healthy subjects, maximal exercise capacity is generally limited by cardiac factors[147], whereas patients with severe lung disease may be limited by impaired lung function[148]. Adults with acute LVCP have presented with effort dyspnea and reduced exercise tolerance due to shortness of breath during minimal physical exertion, despite normal lung function[136,138,149]. However, the exact degree of glottic narrowing which results in subjective breathing symptoms is unknown[150]. Røksund et al. found that LVCP in EPB adults with a history of PDA surgery had more airway obstruction, expressed by poorer FEV_1/FVC (% of predicted), but not

reduced exercise capacity compared to a control goup without LVCP[15]. However, so far these results have not been confirmed by other studies.

1.4.2 Risk factors and mechanism of LRLN injury and LVCP

While cancer, trauma and surgery are the most common causes of damage to the LRLN in adults[151], surgical closure of PDA is the most significant risk factor for LVCP in preterm infants[152] and have been reported in 11–67% of EPB subjects post PDA surgery[107,153-159]. However, prolonged intubation (<1 week) also poses an independent risk factor for paralysis of the vocal folds[152]. The occurence of LVCP after PDA surgery increases inversely with gestational age and birth weight [153,157,160]. However, within the EPB population, GA and BW may not be predictive for development of LVCP[159].

The mechanisms of injury to the LRLN during surgical clipping or suture of the DA include a completely or partly disrupted nerve or stretching of the nerve in an effort to avoid the nerve[161]. LRLN injury in macroscopically intact nerves may be intermittent or permanent depending on the type of intraneural injury, which could include conduction block, only affecting the Schwann cells (myelin injury, neuropraxia), or axonal injury where axons are disputed (axonotmesis)[162]. After peripheral injury to the recurrent laryngeal nerve there is a risk of misdirected reinnervation (synkinesis) in laryngeal muscles, which may impair vocal fold mobility and voice control[163].

1.4.3 LVCP: Symptoms, comorbidities and potential of recovery

Common symptoms of LVCP in neonates include a weak cry, hoarseness/dysphonia, or stridor[153,155,158-160,164-166], the latter being a high-pitched, monophonic breath sound associated with obstruction at the larynx, glottis, or subglottic area[37]. Feeding problems, swallowing difficulties and aspiration are other outcomes frequently reported in association with LVCP[154,155,159,160,164,165], as well as respiratory distress and prolonged duration of mechanical ventilation[154-156,160,164]. Similar to neonates with LVCP following PDA surgery, adults with acute LVCP (not related to PDA surgery) often present with dysphonia (hoarse, weak or breathy voice, impaired high

pitch) and swallowing difficulties (dysphagia, regurgitation, aspiration)[149]. Moreover, unilateral vocal cord paralysis is associated with more impaired health related quality of life than other causes of dysphonia in adults[167,168], in part due to dyspnea[167].

Although laryngoscopic recovery of LVCP after PDA surgery in EPB infants has previously been reported in 3%[165] to 33%[158] at mean follow up periods of 3.0 years and 4.5 months (respectively), recovery is rather uncommon[12,154,155]. However, clinical recovery of dysphonia, respiratory symptoms and dysphagia are reported in several of these follow-up studies[154,155,165], implying functional compensation by the normal vocal cord[165]. The low rate of recovery suggests that injury to the LRLN during PDA surgery at neonatal age may also present as LVCP with or without symptoms in adulthood.

1.5 An updated search for previously published studies

Incidence and prevalence of LVCP

In epidemiology, two important measures of disease are commonly used. The incidence is the number of new cases with a certain disease within a specified period of time divided by the number of subjects at risk of the disease. Prevalence is the proportion of the population with a disease at a specific point in time, and it reflects both the incidence rate and the duration of a disease[169].

As a systematic review of the incidence and associated outcomes of LVCP is included in this thesis (Paper #I), another detailed overview of the current knowledge will not be presented here. Rather, results from an updated, but more specified search will be presented: i.e., articles that aim to investigate incidence or prevalence of LVCP and associated outcomes in EP/ELBW born subjects with a history of PDA surgery. In the updated search performed on 21/01/22, the search strategy described in Paper #I (Supplementary File 4) was used, but with additional search terms such as vocal cord paresis or vocal cord paralysis, vocal fold paresis or vocal fold paralysis (limited to humans) (Appendix 1).

Only one retrospective cohort study published in 2017 by Pharande et al. aimed to find the incidence and predictive factors of LVCP and other associated outcomes after PDA surgery in children born EP[159]. The total LVCP incidence of 11/35 (31%) was higher than the pooled proportion of 16% (95%CI: 9%–25%) in the subanalysis of studies that performed laryngoscopy examination only in symptomatic infants, included in Paper #I. This study could have been included in a future updated search and analysis of the incidence of LVCP.

In a case-control study from 2017, Jabbour et al. aimed to find the prevalence of vocal fold paralysis (VFP) in preterm (<37 weeks GA) infants and to identify risk factors for the development of VFP. Although this study included preterm infants (<37 weeks GA), a subgroup of infants born <26 weeks of GA was also presented, in which the incidence of vocal fold paralysis was 18%. However, although 70% of VFP cases were left sided and VFP was associated with PDA surgery in multivariate analysis, the authors did not report the incidence of left sided VFP after PDA surgery in EPB infants. We would therefore have to contact the authors to get more information about the study and the incidence of LVCP in the EPB infants following PDA surgery, before potentially including the study in an update of the SR.

Vocal cord paralysis was also evident among outcomes reported in a recent retrospective single centre cohort study by Foster et al., that aimed to find the incidence of short-term complications of PDA surgery in infants born ELBW during the period of 1989–2015, identify factors associated with those outcomes and their impact on long term outcomes[133]. LVCP was the most common medical complication affecting 16/180 (9%). This study could have been included in the subcategory of studies only examining symptomatic infants in Paper #I, and the 9% incidence was lower than the pooled estimate of 16%, but still within the 95%CI (9%; 25%). Thus, this could have been grouped into the same sub-analysis category as Pharande et.al, but in the lower range of the previously reported incidence of LVCP in this sub-analysis (5%–40%). However, the study is not included in Table 1 or 2 as the authors did not aim to investigate the incidence of LVCP in particular, and they did not report outcomes after LVCP.

Author, year, study design, year of birth	Population demographics	Diagnostic method (LVCP)	Incidence of LVCP (%)
Studies included in the systematical review (Paper #I)			
Zbar, 1996* Retrospective 1991 – 1994[157]	ELBW (N=22/68), all PDA ligated. 5/22 with LVCP were EP. +LVCP (N=6): GA, 26.3 wk; BW, 900g - LVCP (N=62): GA, 33.8 wk; BW, 2300g	Laryngoscopy if symptoms (N=Not reported)	5/22 (22.7%)
Pereira, 2006 Prospective 2001 – 2004[155]	Premature (N=100), all PDA ligated. GA, 25 wk; BW, 740g	Laryngoscopy (N=61/100)	7/61 (11%)
Smith, 2009* Prospective 2004 – 2007[153]	EP (N= 60/86), all PDA ligated. All LVCP < 28 wk GA. +LVCP (N=14): GA, 25.4 ± 1.2 wk; BW, 829 ± 205g - LVCP (N=72): GA, 26. 9 ± 2.6 wk; BW, 1033 ± 414g	Laryngoscopy (N=86/89)	14/60 (23.3%)
Spanos, 2009 Prospective 1995 – 2005[158]**	ELBW (N=55/105), all PDA ligated. All with LVCP were EP. Suture: GA, 25.0 ± 2.0 wk; BW, 740 ± 288g. Clip: GA, 24.7 ± 1.3 wk; BW, 561 ± 169g.	Laryngoscopy (N=68/105)	13/55 (23.6%)
Clement, 2008* Retrospective 2003 – 2005[154]	ELBW (N= 18) and VLBW (N=5) infants, all PDA ligated. All with LVCP were EP. +LVCP (N=12): GA, 24.8 (24–26 wk); BW, 725 (580–887g) - LVCP (N=11): GA, 27 (25–31 wk); BW, 1040 (7001540g)	Laryngoscopy (N=20/23)	12/18 (66.7%)
Røksund, 2010 Retrospective 1982 – 1985/ 2008 – 2009[15]	EPB adults, PDA-ligated (N=13) +LVCP (N=7): GA, 27.1 ± 1.5 wk; BW, 874 ± 138g - LVCP (N=4): GA, 27.0 ± 2.9 wk; BW, 982 ± 283g	Laryngoscopy (N=11/13)	7/11 (63.6%)
Rukholm, 2012§ Retrospective 2003 – 2010[156]	EP (N=111), all PDA ligated. +LVCP (N=19): GA, 25.4 (24.8-26.0 wk) BW, 744 (665-822g) - LVCP (N=92): GA, 26.7 (26.0-27.5 wk); BW, 990 (858-1122g)	Laryngoscopy if symptoms (31/111)	19/111 (17.1%)
Studies identified through additional search, January 2022			
Pharande, 2017 Retrospective 2006 – 2014[159]	EP infants (GA<29 wk, N=35), all PDA ligated GA (median, IQR): 25 wk (24–27)	Laryngoscopy if symptoms (N=Not reported)	11/35 (31.3%)

*Table 1 provides information about the eight identified studies that aimed to find the incidence or prevalence of LVCP post-PDA surgery in EPB subjects, the first seven were included the SR (Paper #I), whereas one was published in 2017, after completion of the search (December 20th, 2016). *Indicates that the incidence of LVCP was calculated based on a subgroup of EP/ELBW subjects, not the complete study population. Results are given in mean (range) or mean (SD) unless otherwise specified.** Results presented in median (mean, absolute deviation).§ Results presented as mean (95%CI). Some of the content in this table have previously been published in Paediatric Respiratory Reviews: Left vocal cord paralysis after patent ductus arteriosus ligation: A systematic review. Engeseth et al. Copyright © 2017 The Authors. Published by Elsevier Ltd.*

Neonatal outcomes associated with LVCP after PDA surgery in EPB

Adding Pharande et al. to the seven studies included in Study #I, eight studies have previously aimed to describe short-term outcomes associated with LVCP after PDA

surgery in EPB neonates. However, Nichols et al. did not have a group without LVCP for comparison. The neonatal outcomes BPD, aspiration, gastroesophagal reflux, tube feeding/gastrostomy, IVH and RAD were most frequently reported in association with LVCP, and known symptoms of LVCP such as stridor, a hoarse cry and dysphonia were reported in six out of eight of the studies (Table 2). Most of the studies had 1-2 years follow-up, and only one of the studies reported outcomes after three (± 2) years of age.

Author, year Follow-up	LVCP, Symptoms	LVCP, Outcomes
Studies included in the systematical review (Paper #I)		
Pereira, 2006 **6-13 months**[155]	Stridor Weak cry	Feeding difficulties, tube feeding.
Clement, 2008 **3-12 months**[154]	Not reported	Ventilator support, supplemental oxygen, chronic lung disease, BPD, tube feeding, gastrostomy, hospital stay, readmission.
Spanos, 2009 **1-18 months**[158]	Stridor Hoarseness	Episodes of decreased oxygen saturation, aspiration.
Benjamin, 2010 **18-22 months**[160]	Stridor Hoarse/ absent cry Unable to wean from respiratory support, Cardiorespiratory distress	Days of mechanical ventilation, BPD, reactive airway disease, gastrostomy tube, Nissen fundoplication, neurodevelopmental impairment, intraventricular hemorrhage.
Røksund, 2010 **24 years**[15]	Stridor Dysphonia Wheezing	Ventilator treatment, oxygen treatment, measures of lung function and exercise capacity.
Rukholm, 2012 **NR (Post-op.)**[156]	Not reported	BPD, gastroesophageal reflux syndrome, gastric feeding tube, pneumonia, sepsis, anemia of prematurity.
Nichols, 2014 **Mean 3** **(±2 years)**[165]	Stridor Dysphonia	BPD, tube feeding, laryngomalacia, subglottic stenosis Intraventricular hemorrhage, retinopathy of prematurity
Studies identified through additional search, January 2022		
Pharande, 2017 **1 year**[159]	Stridor Dysphonia	Days on respiratory support, chronic lung disase, home oxygen, tracheostomy, vocal cord medialization, tube feeds at discharge, age reaching full sucking feeds, anti-reflux treatment, gastrostomy/ fundoplication Intraventricular hemorrhage, chronic lung disease, hospital stay, death, postnatal steroids, neurodevelopmental outcomes at 1 year.

Table 2. Summary of symptoms and outcomes reported by studies aiming to report outcomes associated with LVCP after PDA surgery. Some of the content in this table have previously been published in Paediatric Respiratory Reviews: Left vocal cord paralysis after patent ductus arteriosus ligation: A systematic review. Engeseth et al. Copyright © 2017 The Authors. Published by Elsevier Ltd.

Lung function and exercise capacity

Advanced searches in Medline and Embase (21.01.22) (Appendix 2) only resulted in one hit for a combination of the keywords and phrases: premature, ductus arteriosus, left vocal cord paralysis and lung function OR exercise capacity; namely the previously described study by Røksund et al. (2010)[15]. No additional articles reporting voice and respiratory symptoms in subjects with LVCP after PDA surgery were found.

Short summary of background

To summarise, vast improvements in obstetric and neonatal medicine have led to increased survival in EPB infants, and focus is now directed towards promoting lifelong health. Previous studies have shown that EPB children and young adults have a higher risk of dysphonia, impaired lung function and reduced exercise capacity compared to children and young adults born full term. Causal pathways between exposure and outcomes in this population are difficult to assess, namely due to the complexity of multiple exposure variables, including the reason(s) for extremely preterm birth, immaturity per se, and the lifesaving treatment they receive. Whereas dysphonia has been associated with prolonged and repeated intubation, impaired lung function is often associated with neonatal BPD, which is further associated with PDA and PDA surgery. A range of variables have also been associated with reduced exercise capacity in EPB subjects, however these mechanisms are still unclear.

LVCP may impair vocalisation and increase airway resistance through the larynx. The reported rates of LVCP after PDA surgery vary between studies and little is known about whether PDA surgery or LVCP contributes to poorer long-term outcomes among EPB subjects.

2. Aims and research questions of the thesis

The overall aim of this thesis was to provide new knowledge on outcomes following PDA surgery in EPB children and adults, with emphasis on exploring the incidence, prevalence, and outcomes of left vocal cord paralysis in particular.

Aims and research questions of the individual studies

Study # I: To investigate previous reports of incidence and associated comorbidities of LVCP following PDA surgery in EPB subjects, and to identify knowledge gaps.

> **Research question #1:** What is the reported incidence of LVCP after surgical PDA ligation in EPB infants?
>
> **Research question #2:** Which study level characteristics may explain the wide incidence variation reported by different studies?
>
> **Research question #3:** What are the short and long-term consequences and/or associated comorbidities of LVCP in EPB infants?

Study #II: To identify associations between different methods of managing PDA and parental reported voice and exercise related respiratory symptoms in a national cohort of EPB schoolchildren.

> **Research question #4:** Is the odds ratio of having voice symptoms increased among EPB schoolchildren who underwent PDA surgery as neonates compared to EPB schoolchildren who received pharmacological or conservative PDA management?
>
> **Research question #5:** Is the odds ratio of having exercise related respiratory symptoms increased among EPB schoolchildren who underwent PDA surgery as neonates compared to EPB schoolchildren who received pharmacological or conservative PDA management?

Study #III: To investigate the prevalence of LVCP and outcomes associated with LVCP and/or PDA surgery in a national population-based cohort of EPB young adults who underwent PDA surgery as neonates.

Research question #6: What is the prevalence of LVCP in EPB young adults who underwent neonatal PDA surgery in Norway during 1999–2000?

Research question #7: Does the rate of self-reported voice and exercise related respiratory symptoms differ between EPB adults presenting with and without LVCP after PDA surgery?

Research question #8: Does lung function, exercise capacity and laryngeal obstruction during exercise differ between EPB adults presenting with- and without LVCP after PDA surgery?

Research question #9: Does lung function and exercise capacity differ between adults who underwent neonatal PDA surgery compared to EPB controls and term born controls?

3. Material and methods

A description of the material and methods used will be provided in this section, as well as a short reasoning for the choice of methods. Details on measurements and testing conditions are described in the methods sections for the individual Papers (#I–III) and will not be repeated here.

3.1.1 Study design

To address the aims of the thesis, we first conducted a systematic review including a meta-analysis to synthesise the available knowledge on incidence and associated outcomes of LVCP after PDA surgery in EPB subjects (Study #I) and to identify knowledge gaps. Next, we analysed parent reported data from a prospective national cohort of EPB children, Project Extreme Prematurity 1999–2000 ($PEP_{99/00}$), to explore associations between different modes of PDA management and voice or respiratory symptoms (Study #II). Finally, we recruited EPB adults from the same national cohort ($PEP_{99/00}$) and investigated the prevalence of LVCP after PDA surgery. Moreover, we used self-reported questionnaires, and performed spirometry and exercise testing to explore whether PDA surgery or LVCP were associated with voice and exercise related respiratory symptoms, alterations in lung function and exercise capacity (Study #III).

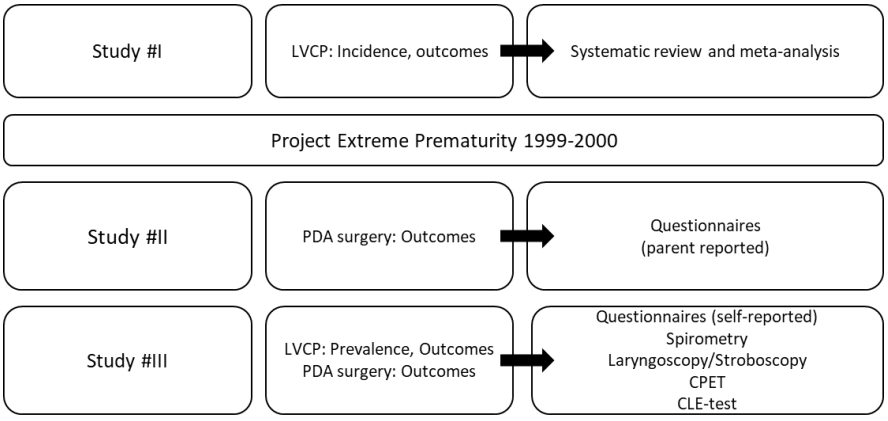

Figure 9 provides a short overview of the aims and methods used for assessment in Study #I–III.

3.1.2 Definitions

In $PEP_{99/00}$, information on the neonatal characteristic and clinical course in the NICU was collected by obstetricians and neonatologists with forms developed for the study and linked with compulsory reported data from the MBRN[170], while other background data was obtained from medical charts or by questionnaires during follow-up assessments. GA (completed weeks) was primarily (94%) determined by ultrasound scans in week 17–18, but the mothers last menstrual period (LMP) was used if consistent with clinical findings when scans were not available. Small for gestational age (SGA) was defined according to Norwegian growth curves[171]. Bronchopulmonary dysplasia (BPD) was defined as still dependent on oxygen supplementation at 36 weeks' GA. Diagnosis and management of a PDA was determined at the discretion of the neonatologists responsible for neonatal care at the different NICUs and was based on clinical signs and echocardiographic evaluation. Infants with a diagnosed PDA were treated either conservatively with fluid restriction, diuretics, or unspecified symptomatic support, or the PDA was actively treated with either indomethacin or surgical closure. Surgical ligation was the first line causal treatment for PDA in EPB infants at our institution (Haukeland University Hospital) during the recruitment of infants to the $PEP_{99/00}$ study[172]. In descriptions of study #I-III in this thesis, the abbreviation EPB (extremely preterm born) is not only referring to subjects born at GA ≤28 weeks, but also include those born at BW ≤1000g.

3.1.3 Participants

Index subjects

In Study #I, we included studies reporting incidence or rate of LVCP after PDA surgery, either from a sample of only EPB subjects, from a sample with >80% EPB subjects or from a defined subgroup of EPB subjects. If included studies reported any outcomes associated with LVCP, those outcomes were extracted and included in the analysis.

Study #I

1) PDA surgery, LVCP: EP/ELBW-born subjects with a history of PDA surgery and who were diagnosed with LVCP.

Study #II and #III in this thesis are based on the cohort $PEP_{99/00}$, for which all infants born in Norway from 1999–2000 with a gestational age of 22^0 to 27 completed weeks and/or a birth weight of 500 to 999g were eligible for inclusion (n=638, 0.53% of all births)[173]. Of 485 live born infants, 464 infants were admitted to 15 different NICUs, parents of two infants declined to participate in the study, and 462 where eligible for inclucion. None with GA under 23 completed weeks survived. Among those admitted, 96 were more than 27 completed weeks GA, and 72 were more than 1000g. 376 infants were discharged from the NICUs and 373 was alive at 2-year follow-up[174], while 372 children were alive and eligible for follow-up at five[46,175] and eleven[45] years of age (Figure 10). Descriptions and results from the follow-up assessments of the $PEP_{99/00}$ cohort at ages two, five and eleven have been published previously[45,46,49,69,174-177].

Out of the 51 infants who underwent neonatal PDA surgery, three died before the age of two, leaving 48 subjects eligible for inclusion at 11 and 19 years of age. Of note, during recruitment of participants for Study #III, we detected that one participant who had undergone PDA surgery had been misclassified as not having PDA/PDA surgery in our data set, and thus, was wrongfully placed in the No PDA and no PDA surgery groups in Study #II, which explains the discrepancy between number of eligible subjects in the PDA group (143 vs. 144), and no PDA group (229 vs. 228) and the PDA surgery group (47 vs. 48) presented in Paper #II vs. in Study #III, respectively.

Study #II

1) PDA surgery: 11-year-old EP/ELBW-born subjects with a history of PDA surgery.

Study #III:

1) PDA surgery: 19-year-old EP/ELBW-born subjects with a history of PDA surgery.

2) PDA surgery, LVCP: The EP/ELBW-born subjects from the PDA surgery group who were diagnosed with LVCP.

Control subjects

Study #I: In the analyses of outcomes associated with LVCP, we included studies that presented data from a control group:

1) PDA surgery, no LVCP: EP/ELBW-born subjects with a history of PDA surgery, but who were not diagnosed with LVCP.

Study #II: Both control groups consisted of 11-year-old EP/ELBW-born subjects from the national $PEP_{99/00}$ cohort:

1) No PDA: EP/ELBW-born subjects with no history of PDA.
2) PDA, no surgery: EP/ELBW-born subjects who did have neonatal PDA but received conservative or pharmacological treatment.

Study #III: At 11 years of age, a regional sub cohort of the national $PEP_{99/00}$, where those born EP in the Western region of Norway were eligible for inclusion, was established for a longitudinal study describing lung function trajectories[49]: This sub group included 57 out of 61 eligible EPB children and 54 age and gender matched term-born controls (Figure 10). The follow-up of this regional cohort coincided with Study #III, and thus, some of the participants were recruited for both studies. In Study #III, the EPB from the regional $PEP_{99/00}$ with no history of neonatal PDA surgery were eligible as EPB controls, and their matched term-born controls were eligible as term-born controls, whereas the EPB with a history of PDA surgery who did not have LVCP were eligible for the PDA surgery, no LVCP group. Thus, we had the following three control groups in Study #III:

1) PDA surgery, no LVCP: EP/ELBW-born adults who underwent PDA surgery as neonates, but who were not diagnosed with LVCP.
2) EPB controls: EP/ELBW-born adults (with and without PDA) who did not have a history of PDA surgery.

3) Term-born controls: Term-born adults (GA >37 weeks and BW >3000g). Matched with the EPB controls for age and gender.

Table 3 provides an overview of study designs and study populations (Study #I–III):

	Study #I	**Study #II**	**Study #III**
Design	Systematic review and meta-analysis	Prospective population-based cohort study	Prospective population-based cohort study
Population	Infants, children, adults born extremely preterm	Schoolchildren born extremely preterm in Norway in 1999–2000	Adults born extremely preterm in Norway in 1999–2000
Gestational age	<28 weeks completed	<28 weeks completed	<28 weeks completed
Birth weight	<1000g	<1000g	<1000g
Exposure	PDA surgery LVCP	PDA surgery	PDA surgery LVCP
Comparison (control)	No PDA surgery No LVCP	No PDA surgery No PDA	No PDA surgery No LVCP Not EPB (term-born)
Outcome	Incidence of LVCP Any reported outcomes associated with LVCP	Subjective voice and exercise related respiratory symptoms	Prevalence of LVCP Subjective voice and exercise related respiratory symptoms Laryngeal obstruction during exercise, lung function, exercise capacity
Follow-up age	0 months–24 years	11 years	19 years

3.1.4 Systematic review and meta-analysis

In the 1990`s the narrative review as a method of combining results from multiple studies was disregarded in favour of the systematic review and meta-analysis to summarise the findings of studies relevant to a particular research question[178]. The narrative review is limited by its inherent subjectivity and lack of transparency, whereas the systematic review is characterised by transparency in the search strategy and decision-making process used to synthesise the data and arrive at a conclusion. However, a systematic review also has elements of subjectivity, such as in setting the criteria for inclusion and exclusion, modifications in use of the quality assessment tool and conclusions drawn from the synthesis of data[178].

Meta-analysis is the statistical combination of results from two or more separate studies[179]. Thus, meta-analyses may lead to an improvement in the precision of estimates compared to those derived from individual studies, allow investigation of consistency of evidence across studies, and the exploration of variation (heterogeneity) across studies[179]. Two commonly used measures of dispersion and

heterogeneity are the Q statistic (a measure of weighted squared deviations used to test the null hypothesis that all studies share a common effect size) and the I-squared (I^2; the ratio of true heterogeneity to total observed variation)[178]. It is important to assess and consider heterogeneity in effect sizes when interpreting the data. With consistent effect sizes and low heterogeneity across studies, the summary of effects is often robust. However, with increased dispersion of effect sizes and moderate (I^2 >50%) to high heterogeneity (I^2 >75%), the focus shifts from discussing the summary of effects to attempts to explain the dispersion itself[178,180].

3.1.5 PROSPERO and PRISMA, Study #I

To ensure transparency, avoid duplication and reduce the chance of reporting bias[181], we registered the protocol for our systematic review in the initial phase of the study in an international database of prospectively registered systematic reviews (PROSPERO). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and flow-chart[182] were useful tools in the systematic reporting of our review (Paper #I, Suppl. 1 & 2). Details on eligibility/ exclusion criteria and search strategy are described in Paper #I (Suppl. 3 & 4).

3.1.6 The Newcastle Ottawa Scale for quality assessment of individual studies, Study #I

Assessing risk of bias in individual studies is a fundamental step in the process of conducting a systematic review. The choice of assessment tool depends on the study design of the included studies, which are, in turn chosen depending on the research question. Prospective/longitudinal cohort studies are appropriate for studies investigating incidence, whereas a cross-sectional design would be more suitable when investigating the point prevalence of common, long-term conditions, however, this is not applicable for temporary or rare diseases[183]. Several tools have been developed for the quality assessment of cohort studies in systematic reviews[184], including the Newcastle Ottawa Scale (NOS) for cohort studies[185], which were used in Study #I. Despite being criticised for having low inter-rater and test-retest reliability[186,187], uncertain validity[188] and forbeing vague and difficult to use[189], the NOS was among the most commonly used tools for assessing quality in cohort

studies in 2020[190]. In a systematic review of methodological assessment tools by Zeng et al. in 2015, the NOS was recommended for cohort and case-control studies[191]. In 2017, the NOS was also recommended by the Cochrane Scientific Committee as an alternative to their own tool, ROBINS1, which was under development for the assessment of non-randomised observational studies[192,193].

The NOS assesses methodological quality by assigning points up to a maximum of nine points for the least risk of bias in three domains:(1) selection of study groups (four points); (2) comparability of groups (two points); and (3) ascertainment of exposure and outcomes (three points). Descriptions of how each domain were adapted for study #I are provided in Paper #I (Suppl. 5). To reduce performance bias during the assessment, two authors independently evaluated the included studies before comparing the individual assessments. We experienced high consensus on the rating between the two reviewers. Any disagreements were discussed thoroughly, and a third party was included if needed.

3.1.7 Questionnaires, Study #II and #III

Paper surveys providing information on demographic variables and the previous and current health status were filled in by the caregivers for each subject in Study #II (Appendix 3). In Study #III, all subjects were asked to fill in electronic versions of questionnaires providing information on several health issues (Appendix 4), but only subjects in the PDA surgery group filled in additional paper surveys which included all the questions used for information regarding voice and exercise related respiratory symptoms (Appendix 5). One of the questions used in Study #II (*Does the child have problems with shouting or talking with a loud voice?*) was not included in the paper questionnaire in Study #III. As only the question on hoarseness *(Is your voice hoarser compared to others of the same age?)* was included in the electronic questionnaire, we did not have data on other voice characteristics in the control groups in Study #III. All questions were translated into Norwegian language.

The six questions about voice characteristics (a voice that is hoarse compared to peers, that affects participation in singing, cracks when shouting, problems shouting

or talking with a loud voice, a weak or unclear voice or voice limiting social- or school participation) were based on questions sourced from the functional and physical scale in the Voice Handicap Index (VHI) questionnaire[194]. This questionnaire was the most widely published instrument employed to measure the impact of voice related diseases on activities in 2011[195]. A more LVCP disease-specific questionnaire such as the Voice Outcome Survey[196] could have been used in Study #III, but we wanted to collect information comparable with the previously collected data. However, VHI's physical scale has strong and significant correlations between objective acoustic measures (jitter, shimmer, and harmonics to noise ratio) in adult patients with unilateral paralysis[197].

The participants originally answered on a 5-point Likert scale (from 0=not at all to 5 =extremely) for the questions about voice, whereas the alternatives for answering questions about exercise related respiratory symptoms was three (i.e "no", "a little", "a lot"). In our analyses, the categories were reduced to a dichotomous variable (yes/no).

The questions regarding exercise related wheezing, current asthma, history of asthma (referred to as 'asthma ever') and use of asthma medications in Study #II were obtained from the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC)[198]. Allthough several asthma related questions were included in the questionnaire, only the question about having used asthma medications over the last 12 months was used in Study #III. Two questions were custom made for $PEP_{99/00}$ and adapted to the repondents who were either caregivers of the EPB children (Study #II) or the adult participants (Study #III)*; 'Does the child/do you have breathing problems beyond what is normal during physical exertion?'* and *'Does the child/Do you make "scraping sounds" or other abnormal sounds from the throat during physical exertion?'* The question on weekly hours of physical activity (PA) in Study #III were adapted from the European Community Respiratory Health Survey II questionnaire (question number 34)[199] and answers were reduced from the original six categories to three categories in our analysis.

3.1.8 Measurements and testing conditions, Study #III

Spirometry

Spirometry is the most common type of pulmonary function test, widely used to assess lung function[200]. In Study #III, maximal expiratory flow-volume loops were obtained using a Vyntus® PNEUMO spirometer (Vyaire Medical GmbH, Leibniztrasse, Hoechberg, Germany), according to guidelines[201]. After visual inspection, the highest forced expiratory volume in first second (FEV_1) and the highest forced vital capacity (FVC) obtained from technically acceptable flow-volume loops were recorded. Raw data were normalised for height, age, gender, and ethnicity by using the Global Lung Function Initiative online spirometry calculator[202], which is the set of reference equations recommended for use in the Norwegian adolescent and adult population[203]. The z-values for FVC, FEV_1 and FEV_1/FVC were calculated and reported for the studies of this thesis.

Laryngoscopy

Endoscopic examination of the larynx with laryngoskopy and/or strobovideolaryngoscopy are widely used and considered the gold standard in observing asymmetries of laryngeal motion and to diagnose LVCP[204]. In Study #III, diagnosis of LVCP or other laryngeal pathology were determined at rest by an experienced otolaryngologist, who performed video-laryngoscopy including strobe light illumination (Pentax Medical Laryngeal Strobe Model 9400, Video Recording Module 9310 HD).

Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing (CPET) allows for the simultaneous study of the responses of the cardiovascular and ventilatory systems to a known exercise stress through measurement of gas exchange at the airway[147]. Electrocardiogram (ECG), heart rate, blood pressure and oxygen saturation are commonly measured as well. Common symptoms that may lead to early abruption of an exercise test is fatigue, dyspnea and pain[147].

Peak exercise capacity was measured performing an incremental treadmill (Woodway PPS 55 Med, Weil am Rhein, Germany) exercise test according to a modified Bruce protocol[205]. Speed and elevation were increased every 90 seconds from an initial slow-walking phase. Oxygen consumption was measured breath by breath using a face mask connected to a Vyntus CPX unit powered by SentrySuite software (Vyaire Medical GmbH, Leibnizstrasse, Hoechberg, Germany). The test was stopped when the subject indicated severe exhaustion or if it was not considered safe to continue the test. Achievement of maximal intensity by the test-person was supported by a respiratory exchange ratio (RER) of 1.05 or greater, and/or maximum heart rate of 95% of maximal predicted or greater[206], preferably supported by a plateau in oxygen consumption[207]. PeakVO_2 was reported as ml/kg/min and as % of predicted peak VO_2, calculated with reference equations for age and gender based on a treadmill exercise study in a large sample of Norwegian subjects[208]. Exercise performance was described by the completed distance (metres) on the treadmill. The percentage inspiratory time to total time in a respiratory cycle (Ti/Ttot%) was used to describe the breathing pattern. Peak respiratory rate was recorded as breaths per minute, breathing reserve was the difference between maximal voluntary ventilation (FEV1 x 35) and peak minute ventilation, reported as the percentage of maximal voluntary ventilation.

Continuous laryngoscopy exercise (CLE) test

The participants who had undergone PDA surgery performed a continuous laryngoscopy exercise (CLE) test to investigate if the LVCP which was observed to be present at rest resulted in increased laryngeal obstruction during incremental exercise. The same exercise protocol as described under 'Cardiopulmonary Exercise Testing' was used, but with concomitant continuous transnasal flexible video-laryngoscopy (ENF TYPE V2, video processor CV-170, OLYMPUS, Tokyo, Japan) as described by Heimdal et al in 2006[209]. Our group has previously shown that CPET testing with and without equipment for CLE testing produces similar results[210]. The video recording of the laryngeal inlet was assessed and later scored for laryngeal obstruction. Because of laryngeal asymmetry in subjects with LVCP, a modified version of the visual score classification described by Maat et al.[211] was used. The

Maat score (CLE score, 0–12 points) was originally developed for assessment of exercise induced laryngeal obstruction (EILO), and thus for the scoring of a bilateral condition that is not present at rest and which increases with exertion, contrasting this present situation with a hemiparetic larynx, apparent also at rest[212]. The modified CLE score (0–24 points) assessed the right and left glottic and supraglottic areas separately (Paper #III, Figure 5).

Measurement and recording of age, weight and height

A stadiometer was used for height (cm) measurement, with the subject standing erect without shoes, heels to the wall, looking straight forward. Weight (kg) was measured with the subject standing on a digital weight without shoes and wearing light clothing (t-shirt, tights/shorts, underwear, socks). Values were recorded in patient examination forms and in the software used for lung function measurement and exercise testing. Age was calculated as the difference between examination date and birth date.

3.1.9 Statistical methods, Study #I–III

The statistical methods used in Study #I–III are given in Table 4:

Statistical methods	Study #I	Study #II	Study #III
Chi-square test		**x**	**x**
Fischers exact test		**x**	**x**
Binary logistic regression (crude and adjusted OR 95%CI)		**x**	
Mann-Whitney U test			**x**
Students t-test (independent samples)		**x**	**x**
Linear regression			**x**
Analysis of covariance			**x**
Analysis of interaction terms			**x**
DerSimonian and Laird random effect model with inverse variance weighting	**x**		
Freeman–Tukey Double Arcsine Transformation	**x**		
Cochrane's Q	**x**		
I-squared (I^2)	**x**		
Funnel plot and Egger's test	**x**		

Study #I: The pooled proportion of the incidence of LVCP including 95%CIs was reported. Assuming that the different studies were estimating different, yet related, measures of incidence, the DerSimonian and Laird random effect model with inverse

variance weighting was used for all analyses. A Freeman–Tukey Double Arcsine Transformation was used to stabilise the variances prior to pooling for incidence estimates. For the analysis of associated co-morbidities, we pooled studies when ≥2 studies reported the same outcome using random effects models estimating risk ratios and 95%CIs. Heterogeneity between studies was tested for incidence proportion and consequences with Cochrane's Q and I-squared (I^2). A Q p-value <0.10 or I^2 >50% indicated high heterogeneity, and we attempted to explain heterogeneity through stratification. Publication bias was assessed by visual inspection of the funnel plot and an Egger's test for the main analysis of occurrences of LVCP. Results were synthesised descriptively if a quantitative synthesis was not feasible. All analyses were conducted using Stata 14.0 (College Station, TX).

Study #II: We investigated binary outcome variables (voice characteristics and exercise related respiratory symptoms) in relation to a neonatal history of PDA vs. no PDA, and in relation to the mode of treatment given to the children with a neonatal history of PDA. Group differences were tested using independent samples' t-tests and chi-square test or Fischer's exact test, as appropriate. We further investigated associations by odds ratios (OR) with 95%CIs using binary logistic regression. The ORs were estimated with crude and adjusted models (adjusted for days on IMV and GA). An online tool, DAGitty, was used to produce directed acyclic graphs (DAGs) and to derive minimally sufficient adjustment sets for confounding variables[213]. All analyses were performed using IBM SPSS statistics version 24 for Windows.

Study #III: Group comparisons were performed using the independent samples t-tests (equal variance not assumed) with 95%CIs, Mann-Whitney U tests, or Fisher's exact tests, as appropriate. We performed an analysis of covariance to adjust for possible confounders affecting associations between group exposure and associated outcomes, whereas an interaction term for gender and group affiliation was included to examine whether the mean difference in peakVO_2 between all EPB and term-born controls differed by gender. Linear regression was used to investigate whether peakVO_2 was associated with the CLE score after adjusting for gender. The data was analysed using

the statistical software SPSS version 26 (IBM SPPS Statistics, NY, USA) and MedCalc version 19.5.3 (MedCalc Software Ltd, Osted, Belgium).

3.1.10 Ethical approval

The Regional Committee for Medical and Health Research Ethics in Western Norway approved Study #II (REC number 2009/2271) and #III (REC number 2009/2271, 2017/1174 and 2017/628). Informed written consent was obtained from all participating subjects or from the caregivers of participants if said subjects were too young to give consent (Study #II) or did not have the competence to give consent (Study #III). All participants were informed of the opportunity to withdraw at any time during the studies.

4. Results

This chapter presents a condensed summary of the results from three published papers based on Study #I–III, respectively.

4.1 Paper #I

Paper #I: Left vocal cord paralysis after patent ductus arteriosus ligation: A systematic review

Subjects

21 publications including 2067 infants were studied. Except for one case-control study they were all based on cohort studies. The pooled mean GA at birth between the 21 included studies was 25.6 weeks (range of means 24.5–27.1 weeks) and the pooled mean BW was 817g (range of means 679–1040g). GA and BW were lower among the subjects with LVCP.

Main findings

Seven out of 21 studies included in the analysis aimed to detect the incidence of LVCP. The overall pooled summary estimate of LVCP incidence was 9.0% (95%CI 5.0; 15.0) and high heterogeneity (I^2 =92%, Q<0.00) was present. The pooled incidence of LVCP increased to 32% (95%CI: 16.0; 50.0) and the heterogeneity was reduced, but still high (I^2=84%, Q<0.00), in a sub-analysis of the five studies that aimed to perform laryngoscopy exams of all (not only symptomatic) infants postoperatively. Further stratification of this subgroup based on study design reduced heterogeneity (retrospective; I^2=74%, Q=0.05 vs. prospective: I^2= 49%, Q=0.14) and showed that the incidence of LVCP was higher in the retrospective studies compared to the prospective studies (61% vs. 19%).

Seven of the studies aimed at investigating outcomes associated with LVCP, and eight studies reported such outcomes. However, only six studies were included in the pooled meta-analysis as two studies did not have a control group. The overall risk ratio (RR) indicated that the LVCP group was two times more likely to have adverse

neonatal outcomes compared to the non-LVCP group (RR:2.20, 95%CI:1.69; 2.88). The LVCP group had an increased risk of BPD, tube feeding/gastrostomy, stridor and asthma, and spent on average 16.5 days longer on IMV. However, the number of included studies in analysis for separate neonatal outcomes were low (ranged from two to four) and the CIs were wide. The additional analyses found increased rates of dysphonia, sepsis, Nissen fundoplication, and prolonged hospital stay in subjects with LVCP. One study reported significantly more airway obstruction, but not impaired maximal oxygen uptake in the LVCP group.

4.2 Paper #II and Paper #III

Paper #II: *Voice and Exercise Related Respiratory Symptoms in Extremely Preterm Born Children After Neonatal Patent Ductus Arteriosus*

Paper #III: *Left Vocal Cord Paralysis, Lung Function and Exercise Capacity in Young Adults Born Extremely Preterm with a History of Neonatal Patent Ductus Arteriosus Surgery – A National Cohort Study*

Subjects

From the national $PEP_{99/00,}$ 327 children were eligible for inclusion at 11 and 19 years of age. Among these were 144 who had been diagnosed with a neonatal PDA, and 48 who had a history of PDA surgery. In addition, 57 EPB controls recruited from the regional $PEP_{99/00}$ and and 54 age- and gender matched term-born controls were eligible for inclusion in Study #III (Figure 10). The overall response rates in Study #II and #III were 61% (228/372) and 60% (96/159), respectively, whereas the response rates in the PDA surgery groups in Study #II and #III were 72% (34/47) and 63% (30/48), respectively. Response rates in the control groups were 59% and 60% in Study #II while we recruited 30 EPB and 36 term-born adults in the control groups in Study #III (53% and 66% response rate).

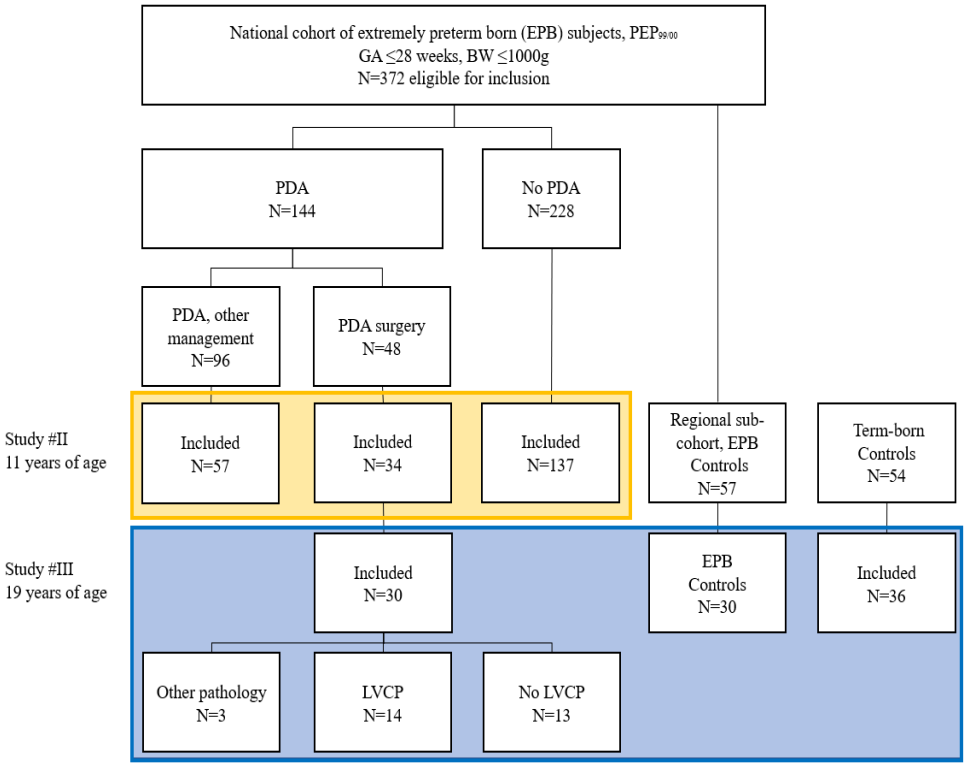

Figure 10. Overview of the study population eligible for inclusion and patients included in Study #II and #III. The yellow and blue rectangles represent the subjects assessed in Study #II and #III, respectively. During recruitment of participants for Study #III, we detected that one participant who had undergone PDA surgery had wrongfully been registered in the no PDA group in Study #II, this explains the discrepancy between number of eligible subjects presented for the PDA, no PDA and PDA surgery groups in Paper #II vs. the figure above/Study #III.

In both studies, the PDA surgery group had lower GA, received more postnatal steroids, and they spent more days on IMV compared to the EPB control groups who did not undergo PDA surgery (Study #II; EPB with PDA, other management, Study #III; EPB, with and without PDA). The rates of BPD and SGA, however, were increased in the PDA surgery group only in Study #III. Increased rate of postnatal steroids in the LVCP group was the only difference between those with and without LVCP in comparison of background variables and adult height and weight measurements. However, those born EP, in particular males in the PDA surgery

group, had lower height and weight compared to term-born young adults in Study #III. Body mass index, however, was similar across groups.

Table 5: Subjects recruited from $PEP_{99/00}$ with a history of PDA surgery

	Study #II	Study #III
PDA surgery, n (% of eligible)	34 (72)	30 (63)
GA, weeks (SD)	25.6 (1.4)	25.4 (1.5)
SGA, n (%)	1 (3)	4 (13)
BW, grams (SD)	832 (173)	792 (178)
IMV, days, median (range)	10 (0–83)	13 (1–87)
BPD, n (%)	27 (79)	24 (80)
Females, n (%)	13 (38)	14 (47)

Table 5 shows background variables of the included subjects who were recruited from the PDA surgery group, indicating that the subjects included in Study #II and #III were overlapping, but not identical.

Paper #II

Main findings

Compared to the EPB children who had PDA but were treated with indomethacin or conservatively, the crude odds ratio (OR, 95%CI) increased in regard to having exercise related respiratory problems (3.4, 1.3; 9.2), a hoarse voice (16.9, 2.0; 143.0), a voice that breaks when shouting (4.7, 1.3; 16.7), a voice that disturbs singing (4.6, 1.1; 19.1) or having problems with shouting or speaking loudly (3.7, 1.1; 12.3) in the children who had been treated surgically. Adjustment for days on IMV left all associations between exposure to PDA surgery and outcomes as not statistically significant ($p > 0.05$), whereas the association between PDA surgery and hoarse voice or a voice that breaks when shouting was still statistically significant after adjustment for GA. However, although not statistically significant, the ORs were still high after these adjustments were made, and the 95%CIs were wide.

Paper #III

Main findings

Sixteen out of 30 (53%) EPB adults who had undergone PDA surgery as neonates presented with LVCP during the laryngoscopy examination. Compared to the group without LVCP, the subjects with LVCP did not have increased rates of breathing

problems during physical exertion, but rates of voice symptoms (a hoarse voice or a voice that affected participation in singing) were increased (8% vs. 57% for both variables).

The groups with and without LVCP did not differ in our measurements of lung function (z-scores for FVC, FEV_1 and FEV_1/FVC) or exercise capacity (peakVO_2 or completed distance on the treadmill), but participants with LVCP used a higher percentage of the total breathing cycle on inspiration during incremental exercise testing (Ti/Ttot, %). The participants with LVCP had a higher modified CLE score than the participants without LVCP, but the dispersion of scores were wide in both groups and CLE score was not associated with peakVO_2. The PDA surgery group had reduced z-scores for FVC, FEV_1 and FEV_1/FVC compared to the EPB and the term-born control groups. Exercise capacity (peakVO_2) was not associated with PDA surgery, but it was reduced in both EPB groups compared to term born controls.

5. Discussion

In this section, I will first summarise the principal results from the three studies on which this thesis was based, then outline some of the strenghts and limitations of the methods used and follow this with a discussion of the main results.

In summary, the principal findings of this thesis were that the incidence of LVCP in EPB subjects with a history of PDA surgery varied internationally between studies and study designs, and the rate of LVCP (53%) in our Norwegian cohort study was higher than the pooled incidence of LVCP (32%) reported in our systematic review. Differences in how the studies were performed, such as whether all infants underwent laryngoscopy after PDA surgery, contributed to differences in the reported incidence of LVCP across the studies included in the systematic review. Further, the systematic review showed that LVCP was associated with adverse respiratory and feeding outcomes in neonates, whereas in study #III the only neonatal variable associated with LVCP was (more use of) postnatal steroids. Allthough possibly confounded by prolonged duration of IMV, the crude OR for voice and exercise related respiratory symptoms were increased in the PDA surgery group, and in study #III, LVCP was associated with voice symptoms, but not with not exercise related respiratory symptoms. Further, LVCP was associated with increased laryngeal obstruction during exercise in study #III, but not with reduced lung function or exercise capacity. PDA surgery, however, was associated with impaired lung function, but not with reduced exercise capacity.

5.1 Methods discussion

Study design and sample size

Epidemiology is defined as the study of the distribution and determinants of health related states or events in human populations, and the knowledge derived from epidemiological studies may be applied to prevent and control health problems[214]. While the sampling of data on the full target population is desirable, it is rarely possible, and a sample of the target population is therefore commonly used. Among

factors influencing our confidence in the results and inferences drawn from this sample is the size of the sample and number of events. A small sample could be influenced by random errors, and this often results in wide confidence intervals in statistical analyses[214]. Statistical power describes the study`s ability to detect a difference between two groups, and power calculations are used to determine how many participants that are needed to answer the research hypothesis[215]. Several factors can impact power calculations, including: the precision and variance of measurements, the magnitude of a clinically meaningful difference, the accepted probability level for rejecting a 0-hypothesis when it is correct (type I error or a false positive test) and the choice of statistical test. When a study has low power, it may not have the ability to detect a difference even though a true difference may exist (type II error or a false negative test)[215].

One strength of the systematic reviews is the pooling of results from all available (and comparable) studies, where studies with small, inconclusive results may also contribute to the overall estimate. In the meta-analysis (Study #I), we used a random effects model (assuming that the true effect size varied between studies), in which the summary effect is the mean of the distribution of effect sizes[178]. In the random effects model, studies with high presicion are assigned more weight in the weighted mean[178], and the precision is primarly driven by sample size, but this is also affected by study design, such as the matching of groups[178]. Looking at Table 4 in Paper #I, the weighting of individual studies range from 3.41% to 5.37%, representing studies with wide and narrower 95%CIs, repectively. A major strength of Study #II and #III is that they were both cohort studies based on $PEP_{99/00}$, which is a national population based prospective cohort study aiming to '*examine short-term and long-term physical and neurodevelopmental outcomes in a national birth cohort*'[173]. The cohort included all NICU`s in Norway and all infants born extremely preterm or with extremely low birth weight during 1999–2000. However, $PEP_{99/00}$ was not designed to investigate outcomes of rare exposures such as PDA surgery and LVCP (n=16). As the number of eligible subjects was restrained by the number of subjects who underwent PDA surgery in the $PEP_{99/00}$ cohort (n=51, 48 survived and were eligible for inclusion), we

did not perform a power analysis in advance, but we did aim to recruit as many of the eligible subjects who had gone through PDA surgery as possible within the $PEP_{99/00}$ cohort. For some outcomes we found not statistically significant between-group differences (i.e p >0.05), allthough large differences in effect size in combination with wide 95%CI`s suggested inconclusive results. To our knowledge, Study #III is still the largest study reporting outcomes related to lung function and exercise capacity in EPB adults with a history of neonatal PDA surgery.

5.1.2 Internal validity

Internal validity refers to the *validity of the inferences drawn as they pertain to the members of the source population*[216p128]. With the exception of one case control-study, all studies in Study #I–III were cohort studies, referring to a group of people who share a common experience or condition, for example being born EP or having been exposed to PDA surgery[217]. Systematic errors related to selection, information and confounding are common concerns threatening internal validity and precision, which should be considered in cohort studies in general[214,216].

Selection by indication

Selection bias results from the methods used to include study participants or from factors that influence participation in the study[217], and selection by indication is a challenge in observational studies for which the subjects are not randomly allocated to exposure or control group[217]. This is an issue in cohort studies reporting outcomes after PDA or PDA surgery, in which a number of characteristics, including GA, BW, gender, Apgar score, use of steroids or cause of EP birth may have impact on the outcome[92]. Further the treatment algorithm for PDA indicates (or rather dictates) selection of the most vulnerable of the EP/ELBW infants for PDA closure, often presenting with symptoms of compromised respiratory and cardiac function and contraindications of COX-inhibitor treatment, and PDA surgery is used as rescue treatment after failing other treatment modes[92,132].

Study #I may be affected by said selection by indication as all of the included studies were observational studies without random allocation to PDA surgery, and only two

studies were assigned points for comparability of groups[15,218] (Paper #I, Suppl. 7). In Study #II and #III, associations between outcomes and PDA ligation might have been biased by selection of the most vulnerable infants for PDA surgery, as the children undergoing PDA surgery were of lower GA, spent more days on IMV, and received more postnatal steroids compared to the EPB groups who did not undergo PDA surgery. Similar neonatal background data in Study #II and #III are not surprising due to a large overlap between study participants (Results section, Table 5). We tried to identify and control for possible confounders in the analysis (described in the methods section under 'statistical methods' (3.1.9) and in the methodological discussion under 'confounding').

Information bias

Information bias occurs as a result of incorrect measurement or misclassification, which refers to inaccuracy in the assignment of exposure or disease status[214]. Misclassification may be random (non-differential) or non-random (differential)[217]. Random misclassification occurs when the value of the exposure and outcome variables does not depend on the other, i.e when a misclassified outcome variable is equally distributed between exposed and non-exposed groups. By making the groups more similar, random misclassification may lead to underestimation of the strength of the true association between exposure and disease. Non-random misclassification occurs when misclassification of the exposure or outcome depends on the value of the other, and may result in over- or underestimation of the true association[214].

In Study #I–III, there may have been inaccuracies in assignment of status as exposed to EP/ELBW birth. Use of the mother's last menstrual period (LMP) to determine gestational age (GA) is less precise compared to estimates provided through an early ultrasound[219,220], and differences between the two measurement methods may exceed a week in up to 50% of infants[30]. A limitation of Study #I was that we did not systematically assess how GA was determined in the individual studies (i.e LMP or early ultrasound), but rather assumed that information from medical journals was reliable. Furthermore, the inclusion of studies reporting >80% EP/ELBW infants contributed to inclusion of infants who were above 28 weeks GA. Fortunately,

ultrasound scan in week 17-18 is provided as part of the public health service in Norway and in $PEP_{99/00}$ (Study #II and #III) GA was based on results fom ultrasound scans in 94% of the infants and on LMP in the remaining subjects, with full agreement between the results from ultrasound scans and LMP in 41%[173]. As the risk of LVCP after PDA surgery and other adverse neonatal outcomes increase inversely with GA and BW[3,157], inaccuracies in classification of EP birth that led to inclusion of subjects with higher GA/BW in Study #I may have contributed to an overall underestimation of the ratio of cases presenting with LVCP, whereas between-group differences for neonatal outcomes in the LVCP vs. no LVCP group may have increased as those with GA >28 weeks were overrepresented in the no LVCP group.

Our use of the term 'extremely preterm born' (EPB) to describe the EP/ELBW-born study participants in this thesis may be a weakness as GA and BW should not be used interchangeably[17]. Although weight and age normally increase in a co-linear pattern during foetal development, a birth weight <1000g does not necessarily only occur in infants born at GAs below 28 weeks. Approximately 11% of preterm babies in high-income countries are born SGA, indicating a birth weight below the 10^{th} percentile[18,221]. Further, in Study #I–III, the inclusion criteria of GA <28 weeks and/or BW <1000g opened the opportunity for the inclusion of infants born SGA at GAs exceeding 28 weeks. Premature children born SGA due to intrauterine growth restriction have increased risk of death and major morbidities[222,223], but we had no information of whether those born SGA in study #II-III had been under intrauterine growth restriction or not. However, the only between-group difference detected for SGA was an increased rate of children born SGA in the no PDA group compared to the PDA group in Study #II. Thus, it seems that children born SGA were less likely to have PDA in this study, possibly reflecting that the programming of ductal closure depends on GA[73], rather than BW. However, the impact of including children born SGA in Study #II-III is uncertain as we found no other between-group differences for SGA.

Confounding

'*Confounding occurs when the relationship between an exposure and a disease outcome is influenced by a third factor, which is related to the exposure and, independent of this relationship, is also related to the health outcome*'[214p. 227]. In observational studies, confounding must be considered as a possible explanation for an observed association – a confusing of effects[214]. Neonatal intensive care is highly complex, and an unknown number of factors, including the cause of EP birth[224], might have influenced the exposures and/or the disease outcomes in Study #I–III. In logistic regression analyses, the number of events per variable should not exceed 1/10[225], we therefore identified the most important confounders through cross-analysis of neonatal background variables, outcomes and associated exposures and then adjusted for these potential confounders one by one. We considered the confounding effect of variables that were associated with the exposure and a risk factor for the outcome, but not an intermediate step in the causal pathway between the exposure and outcome[217]. In addition, we considered adjusting for variables other comparable studies had found important to adjust for (i.e., BPD). We found directed acyclic graphs (DAGS) helpful in identifying possible confounders and mediators in complex datasets with multiple variables, and to derive minimally sufficient adjustment sets[213].

In Study #II, GA and days on IMV were identified as possible confounders for the association between exposure to PDA surgery and voice and exercise related symptoms. As difficulties weaning off IMV is an indication for surgical closure of a PDA[11], and prolonged IMV is a risk factor for outcomes such as dysphonia and stridor[226,227], the number of days on IMV may have confused the association between PDA surgery and voice and exercise related respiratory symptoms (Study #II), suggesting that prolonged use of IMV, rather than PDA surgery itself, may have contributed to voice and exercise related respiratory symptoms.

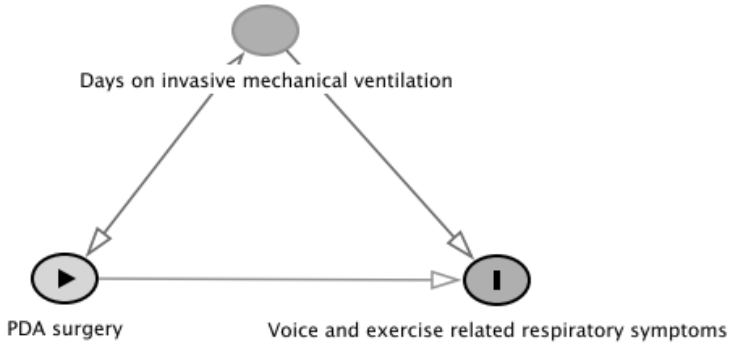

Figure 11 illustrates a simplified relationship between the three variables (Study #II).

As indicated by the doble arrow between PDA surgery and Days on invasive mechanical ventilation (IMV) in Figure 11/12, there is also a possibility of an opposite directed relationship. Post operative complications related to the PDA surgery, such as LVCP or traumatic laryngeal injury during intubation, could have contributed to an increase in the number of days spent on ventilatory support. We were unable to disentangle these issues, as we unfortunately did not have information on when IMV started and stopped, only the total number of days spent on IMV.

When we investigated the association between PDA surgery and lung function (zFVC, $zFEV_1$, $zFEV_1/FVC$) in Study #III we chose to adjust for BPD instead of days spent on IMV as we had to make the choice between these often, but not necessarily always, correlated variables. The rate of BPD was increased in the PDA surgery group (80% vs. 37%) compared to the EPB control group, and BPD was associated with reduced zFVC and $zFEV_1$ (Paper #III, Table 1). We also knew from other publications that BPD was associated with PDA surgery and reduced lung function in EPB subjects[50,228]. However, after adjusting for BPD the association between PDA surgery and lung function ($zFEV_1$) was still statistically significant with a mean difference of 0.89 (95%CI: 1.17; 1.61) compared to the EPB control group.

Adjusting for BPD may be a weakness to the analysis as BPD, diagnosed at 36 weeks of GA, is unlikely to be an ancestor of PDA surgery which in our study was performed

at a median age of 11 days after birth (range 11–34 days). In addition, a previously published study by Vollsæter et al. found that neonatal BPD was not a predictor for future FEV_1-values among 11-year-old children from $PEP_{99/00}$[49].

An effect modifier is an extrinsic factor that influences the assossiation between two other variables in an informative way and should be described rather than controlled for[214]. Effect modifiers can be evaluated by stratification and the inclusion of interaction terms. Interaction is of interest when researchers want to find the joint effect of two or more exposures on a disease or outcome[229]. It is possible that handling the BPD variable as an effect modifier, and dividing those with BPD into a PDA surgery vs. a no-PDA surgery group would have been more appropriate, i.e similar to what Røksund et al. did when they didived the subjects with BPD into groups with and without LVCP, and found that within the BPD group, those with LVCP had more airway obstruction than those without LVCP[15].

We did use stratification based on study design and method for investigating LVCP in Study #I, and when investigating interaction between gender and EP birth on exercise capacity in Study #III (Paper #III, Figure 2). Although the overall reduction in peakVO_2 (% of predicted) in the EPB subjects apparently seemed to be explained by poor results in the male EPB subjects (Paper #III, Table 5), we found no significant interaction effect between gender and group affiliation (all EPB and term-born) on peakVO_2. It is possible that other factors previously reported in association with exercise capacity in EPB subjects, such as reduced lean body mass[62] may have had higher impact on the difference in peakVO_2 than gender per se.

5.1.3 Reliability and validity of tools and measurements

Reliability refers to the repeatability of a measurement or test, whether it produce reliable results over time, across locations or populations[214]. A tool with high validity measures exactly what it intends to measure[230].

Use of the Newcastle Ottawa Scale (NOS) for quality assessment of cohort studies in Study #I

In addition to having low inter-rater and tes-retest reliability[186,187], the NOS has been critisised for having unknown validity[188]. Before performing the quality assessment, we had challenging discussions on how to adapt the NOS to assess the quality of the included studies, and it might have been too vague, but at the same time flexible in use (Paper #I, Suppl. 5). Our adaptation of the NOS was not an ideal choice for assessing quality in all included studies considering the diversity in aims and study designs. Assessing quality the same way in studies who aimed to find the incidence of LVCP after PDA surgery and in studies that (aimed to) report outcomes following PDA surgery may not have led to valid conclusions about the quality of all the individual studies. We defined PDA surgery as the main exposure, and to earn a star for assessment of the outcome (LVCP), all subjects (not only symptomatic subjects) had to undergo laryngoscopy examinations. Instead of defining PDA surgery and LVCP as exposure and outcome in assessment of all the studies included, we could have adjusted the NOS to a second quality assessment tool for the studies reporting outcomes of LVCP, where LVCP was defined as exposure. Further, we could have described how to ascertain that each of the outcomes reported (i.e BPD, dysphonia, IVH. etc) were not present before exposure and provided definitions on how to earn a star for proper assessment for each outcome. Interestingly, the scores in NOS did not reflect this limitation in the assessment, as there was no apparent difference in scores between studies aiming to detect LVCP vs. those aiming to report outcomes of LVCP (Paper #I, Suppl. 7). This may be because few studies earned a star for describing a non-exposed group (comparability), none of the studies demonstrated that LVCP was not present before surgery, and because of our strict criteria for earning a star in the assessment of outcomes (the studies only examining symptomatic subjects for LVCP did not earn a star).

Biases related to self-report (Study #II and #III)

There are several sources of measurement bias when using self-reported data, which should be taken into consideration when interpreting the results of Study #II–III, such as selective reporting, social desirability, and recall bias[231,232]. Selective reporting bias

may occur when a patient, consciously or unconsciously, does not report issues they consider irrelevant to their illness[231]. For example, previous use of asthma medications may not be reported if the participant does not experience exercise related respiratory symptoms or does not believe that asthma is the source of their complaints. Reporting based on perceptions of what is the most socially appropriate answer may not reflect reality, for example overestimating one's level of physical activity, compliance with treatment recommendations or not reporting that they smoke. When recall bias is present, the answer may be influenced by other factors such as current mood or social desirability[231]. Other factors that may impact the answers are the phrasing and proceeding of questions or who the respondents perceive as peers if asked to compare themselves (or their children) with peers[231].

Previous studies have shown that collecting self-reported exercise related respiratory complaints is not a reliable method for diagnosing exercise induced asthma in 11-year-old children[233], and a poor predictor of exercise-induced bronchoconstriction or exercise induced laryngeal obstruction in adolescents[234]. The parent-reported ISAAC questionnaire has previously underestimated the prevalence of asthma[235]. Further, the questions used to investigate level of leisure-time physical activity[199] in Study #III could have been influenced by social desirability bias or recall bias, and adding direct measures of activity, such as accelerometry, could have provided more reliable results[236]. However, use of accelerometry would have demanded more resources, it could have affected the level of physical activity (i.e increased motivation for PA), and could be accompanied by other challenges, such as compliance. Moreover, French et al.[226] reported that 58% of 154 school aged children born at <25 weeks GA presented with moderate to severe hoarseness when assessed by a speech pathologist, whereas the pediatric VHI resulted in only 12% having voice difficulties on the physical scale. Thus, it is possible that we could have had identified an even higher rate of participants with a hoarse voice in Study #II and #III if a speech pathologist had examined the participants in our study instead of using self-reported symptoms.

Testing and measurements, Study #III

The same team, including a physician and a physiotherapist, performed all measurements of weight, height, lung function, and exercise tests with continouous laryngoscopy examination, whereas two otolaryngologists performed the laryngeal examinations of the participants included in the PDA surgery group. In addition, a group of researchers with extensive experience in using the Maat score[211] contributed to the development of the modified CLE score and in scoring of participants based on videos of the larynx captured during the CLE test. As the subjects in the control groups were also part of a regional follow-up study, many of these were examined and tested by another experienced research team. Thus, we believe that we have produced reliable results, but we may have unknown issues with inter-rater reliability as the PDA surgery group and the control groups were assessed by different teams, and some from the control groups were also examined in a different laboratory.

In general, the participants' ability to cooperate with the testing was adequate, but due to neurodevelopmental disabilities, one patient could not perform the spirometry and two were unable to run on the treadmill. The inspiratory curves from the spirometry measurements were not of good enough quality in some of the tests, possibly resulting from suboptimal effort and/or too little emphasis on the inspiratory phase from the instructor (me), which is unfortunate for the analysis of the spirometry results, and for inspiratory flow curves in particular. However, although truncation of the inspiratory curve on the flow-volume loop have been described as a sign of vocal cord dysfunction[237], others have reported that resting inspiratory flow values and the shape of the inspiratory loop could not distinguish between subjects with and without inspiratory stridor[238,239]. In one patient, laryngoscopy examination was impossible due to triggering of the pharyngeal 'gag' reflex, and flexible nasopharyngoscopy was therefore used when assessing functionality of the vocal cords also at rest. Some participants needed more than three attempts to aquire lung function measurement of acceptable and reproducable quality. In addition, the helmet with the flexible fibreoptic laryngoscope attached to it fell out of position in one patient near the end of incremental exercise testing, however, this was after peakVO_2 was obtained.

Reference values support the clinical interpretation of data and should reflect the characteristics of the population being tested, as well as the equipment and methodology used[240]. In 2021, the Association for Respiratory Technology and Physiology recommended using reference values developed by Edvardsen et al. (2013) for adult CPET testing[241]. According to the Edvardsen et al.[208] reference values, which were based on a large sample of Norwegian subjects of relevant age, and also used an incremental treadmill protocol, the PDA surgery group and the EPB control group in Study #III presented with respectively 80% and 83% of predicted peakVO_2 (Paper #III, Table 5). However, as the term born group only scored 90% of predicted (95%CI: 85.5; 94.9), it is possible that the reference values were not applicable for the young adults in our study or that some form of systematic measurement bias affecting all groups was present. In previously published studies reporting exercise capacity in EPB children and young adults from our research group[15,242], the reference values provided by Jones et al.[243] were used to report the percentage of predicted peakVO_2, and despite reporting only slightly higher values for peakVO_2 compared to the results in Study #III, the EPB participants in Clemm et al.'s study achieved higher percentages of predicted (above 100% of predicted peakVO_2)[242]. However, the reference values by Jones et al. was based on values from cycle ergometer testing, and therefore probably have provided too low predicted values for treadmill exercise testing[244]. However, in another study[245] where Clemm et al. used the reference values by Edvardsen et al.[208], a lower % of predicted were reported in the EPB children (89.6%), and the term born children obtained values at almost 100% of predicted. We have no good explanation for why our control group had subnormal peakVO_2.

External validity

External validity can be defined as the validity of the inferences drawn from internally valid results in the sample population as they pertain to people outside that population, often referred to as generalisability[216]. Representativeness is not only a possible threat to internal validity, but it is also relevant to generalisability as it may refer to whether the study population is representative of the target population[217]. Errors in representativeness which arise from the method used to recruit or include

subjects in the study is problematic, and efforts to prevent such errors should be implemented in the study design as this is hard to correct[214].

In Study #I, we assigned all the included studies a star for representativeness of the cohort exposed to PDA surgery during quality assessment, as the participants in all of the studies consisted of more than 80% EP/ELBW-born subjects or presented results from a defined subpopulation of EPB subjects (Paper #I, Suppl. 5). However, a weakness to our assessment of representativeness was that we did not investigate whether the EP/ELBW-born subjects included in each study were representative for the EP/ELBW who were born in the community from which the sample had been collected, and therefore generalisability was unknown and possibly threatened. In hindsight, representativeness could have been ensured by assigning a star if the individual study had been based on a large population of EP/ELBW subjects (i.e., not just a small geographic area or one private institution) and by demonstrating that eligible non-participating subjects were not different from those who did participate.

The $PEP_{99/00}$ cohort, which Study #II and #III are based on, involved all EP/ELBW births across all NICU`s in Norway during the period 19992000. As only parents of two EP/ELBW-born infants denied participation[173], the subjects in the original cohort were representative for EP/ELBWsubjects born in Norway in 1999–2000. As a general rule, the validity of the study requires that loss to follow-up does not exceed 20%[214,246]. With response rates around 60%, both our studies exceeded 20% loss to follow-up, which may have impacted the internal and external validity of the studies. We investigated representativeness of those included in the study by comparing neonatal background variables in participants versus eligible subjects who were lost to follow-up (Paper #II, Suppl. Table 2 and Paper #III Table 1).

In Study #II, we found that those who were lost to follow-up in the PDA surgery group were more immature (GA, BW) spent more days on IMV and had an increased rate of cerebral palsy, whereas those lost to follow-up in the no surgery group and in the no PDA group were similar to those participating, except for the lower rates of BPD. In Study #III, we found that those lost to follow-up in the PDA surgery group

had lower rates of normal neonatal cerebral ultrasound. Thus, our results from both studies may be skewed towards representing a less vulnerable part of the cohort.

However, comparison of neonatal background data is probably insufficient in regard to investigating representativeness at the ages of 11 and 19. For example, we did not compare the groups for potential confounding background variables such as smoking status at 19 years of age, and we do not know whether abnormal neonatal cerebral ultrsound may have affected these subjects into adulthood. Although one patient with known cerebral paresis did participate in the study, it is possible that other patients with cerebral paresis (or other neurodevelopmental impairments) did not accept the invitation to participate in Study #III as it involved incremental exercise testing on a threadmill. Further, we did not compare background variables for the caregivers who responded/did not respond to the questionnaires in Study #II.

When considering the impact of results from follow-up studies of adults born preterm, it is important to acknowledge that guidelines for newborn intensive care is constantly under development, and the outcomes of adults born EP twenty years ago may not be representative for the outcomes of infants born EP in 2022. In 1999, a consensus report from the Research Counsil of Norway recommended that the threshold of viability should be between 23 and 25 weeks of GA, i.e. futile before 23 weeks, optional (based on the infants vitality and the physicians judgement) at 23-24 weeks, and mandatory from week 25[247,248]. The average threshold for rescuscitation decreased subsequently from 23.6 to 23.0 weeks from 1999 to 2005[249]. Today, infants born at 23 weeks of gestation receives active life saving treatment in Norway, whereas infants born at week 22 are still rarely rescuscitated[248,250]. Comparing the guidelines for management of PDA used in the Western region of Norway in 1999–2000[172] with current guidelines developed by the University of Northern Norway[124], similarities were found in the conservative prophylactic approach (avoiding overhydration) and in contraindications for pharmacological closure (increased creatinine levels, increased risk of bleeding and NEC). In both periods, indications for active management included clinical findings compatible with PDA (1999–2000; La/Ao ratio >1.5 vs. current guidelines La/Ao ratio >1.6 and also PDA diameter >2.0

mm and reversed diastolic flow in the descending aorta), in combination with signs of hypotension/circulatory failure and problems weaning off mechanical ventilation. However, while first line causal treatment for PDA in the Western Region of Norway in 1999-2000 was surgical closure (probably reflecting fear of indomethacin induced NEC as described in Chapter 1.3.1), pharmacological closure of a PDA using ibuprofen is the current first line treatment. Moreover, while four regional hospitals (Ullevål, Rikshospitalet, Trondheim, Tromsø) performed PDA surgery in Norway in 1999–2000, the few surgical closures of PDA in 2022 are mainly performed at one institution in Norway (Oslo University Hospital), or a surgeon from Oslo University Hospital may travel to other institutions to perform the procedure (to the best of my knowledge).

5.1.4 Ethical considerations

Study #1: As systematic reviews do not directly collect sensitive or personal information about participants, conducting a systematic review does not normally require specific ethical approval.

Study #II: Information on voice and respiratory outcomes in EPB schoolchildren had been gathered trough comprehensive questionnaires in the follow-up of $PEP_{99/00}$ at 11 years of age (Appendix 3). As we were interested in the outcomes of PDA surgery, and our research questions could be answered with these previously collected data, we considered it unethical to collect new data. This choice is in line with the National strategy on access to and sharing of research data published in 2018, where The Norwegian Ministry of Education and Research encourages reuse of previously collected data and underlines that "*Research data should be managed and curated to take full advantage of their potential*"[251,p6].

Studie #III: Pulmonary function testing is commonly used and is not considered to represent any risk or discomfort to the participants. Cardiopulmonary testing with or without continuous laryngoscopy during testing is used on daily/weekly basis in our test laboratory. Participants were informed of any findings, such as asthma or laryngeal pathology, and referred for subsequent treatment in cases where the medical

assessment revealed a suspicion of any medical conditions. As we only had applied for, and received approval from, the ethical committee to perform laryngoscopy examinations and CLE testing in the subjects in the PDA surgery group, we could not determine the rate of LVCP in the groups not exposed to PDA surgery.

5.2 Discussion of the main findings

5.2.1 Incidence and prevalence of LVCP

Our systematic review revealed knowledge gaps in incidence and outcomes of LVCP in EPB subjects: Firstly, we found that only seven previously published studies had aimed to investigate the incidence of LVCP or outcomes of LVCP after PDA surgery in EPB subjects. Secondly, the rates of reported incidence of LVCP varied from 0–67%, and ten out of the 21 included studies did not report on how they had assessed for LVCP. None had performed preoperative laryngoscopy examinations, and only five studies performed postoperative laryngoscopy examinations of all subjects, not just those who had symptoms[15,153-155,158], and the pooled incidence of LVCP in these studies was 32%. Thus, with this systematic review, we have highlighted a clinical scenario that urgently needs more focus in the research community and by clinicians working with patients with voice and respiratory problems.

In Study #III, we reported an LVCP prevalence of 53% in EPB adults with a history of neonatal PDA surgery, and thus, higher than the pooled incidence (32%) of comparable studies in study #I, but within the range of the 95%CI (16; 50%). Interestingly, only one out of the 14 participants with isolated LVCP knew about their diagnosis in advance, whereas the two participants with LVCP who also had other laryngeal pathology were familiar with having laryngeal pathology in advance. This observation might indicate that most of the adults with isolated LVCP in our study were not severely impaired by their diagnosis, in contrast to adults with acute LVCP, who often struggle with dysphonia, swallowing difficulties, effort dyspnea, reduced exercise tolerance, and impaired health related quality of life[136,138,149,167,168]. Moreover, in investigating the incidence of LVCP, this underscores the importance of performing

laryngoscopy examinations of all subjects (not only those who are symptomatic) after PDA surgery.

Differences in study design increased heterogeneity

Including studies with diverse aims and study designs contributed to high heterogeneity in the overall pooled analysis, and may have led to invalid reports of the overall incidence of LVCP in Study #I. We considered whether the included studies were too different to be pooled, but chose to pool them and subsequently investigate the heterogeneity by stratifying the studies in sub-analyses based on study design. From previous studies, we were aware of the importance of investigating all of the participants post PDA surgery, not just symptomatic infants, in order to find the true incidence of LVCP, as some infants do not present with symptoms. Smith et al.[153] found that two out of 14 infants with LVCP did not have symptoms, whereas Pereira et al.[155] found that only two out of seven infants with LVCP were symptomatic (stridor, feeding difficulties). Reduced heterogeneity in subgroup analysis of studies where laryngoscopy examinations of all subjects were performed, confirmed that different methods of outcome assessment contributed to increased heterogeneity. Heterogeneity was further reduced when stratifying the group in which where all subjects exposed to PDA surgery were routinely assessed into two groups, based on whether they were retrospective or prospective studies. However, only five studies were included in this analysis (Paper #I, Figures 4–6).

Reporting of incidence and prevalence rates

Limitations may also be present for descriptions and calculations of incidence and prevalence. In Study #I, we described that the incidence was calculated by dividing the number of reported cases of LVCP by the total number of infants exposed to PDA surgery (subjects at risk) in each study; however, we actually reported the rate of EPB participants with LVCP divided by the number of cases examined by laryngoscopy. Thus, we did not comply to our own description of incidence calculation. Moreover, according to Greenland & Rothman 2008[169], this does not report incidence because the time aspect is left out. In Study #III, the number of cases with LVCP was also divided by the number of cases exposed to PDA surgery who had participated in the

study, but we referred to this number as prevalence, which is more in line with Rothman, 2008[217]. However, as we do not know how many subjects who had LVCP among the 18 young adults not participating in the study, the true prevalence in this cohort may range from 33.3% (16/48) if no additional subjects have LVCP to 70.8% (34/48) given that all the cases we did not examine had LVCP. Nonetheless, the reported overall incidence rate of 53% in Study #III was high compared to the pooled rate of 32% in prevoius studies aiming to investigate the incidence of LVCP after PDA surgery in EP/ELBW children reported in Study #I. Thus, aiming to examine all subjects postoperatively does not equal examining all subjects postoperatively, and loss to follow-up was a common limitation for the studies included in our systematic review as well. For example, Pereira et al. aimed to find the incidence of LVCP by investigating all PDA operated infants postoperatively but failed to examine 39 out of 100 subjects who either died, were lost to follow-up, or not extubated by the end of the study[155].

Other weaknesses to the incidence and prevalence estimates of LVCP in Study #I and #III is the lack of preoperative laryngoscopy examination, lack of routine postoperative laryngoscopy in all subjects exposed to PDA surgery, lack of postoperative laryngoscopy examination of the control group with PDA (who did not undergo surgery), and the long follow-up period between PDA surgery and diagnosis of LVCP. Thus, the estimates of incidence and prevalence of LVCP, with the assumption of LVCP beinga consequence of PDA surgery, did not account for the multifactorial causations of LVCP in neonates, children and adults[138,151], or the potential of recovery. Additional CT-examinations could possibly have contributed to resolve questions about differential diagnosis, assessing the entire course of the vagus and recurrent laryngeal nerve[252].

Recovery and compensation

The prevalence of a disease is increased when the disease has a high rate of occurrence and is prolonged, but reduced when the disease has high mortality or is of short duration[217]. Thus, the relatively high prevalence of LVCP among EPB adults in Study #III may be due to high occurrence of LVCP after PDA surgery combined with

low recovery rate of LVCP in EPB children[164], and possibly related to low mortality in critically ill EPB Norwegian neonates.

Nichols et al. retrospectively reviewed data from 66 EPB subjects diagnosed with left vocal fold immobility following isolated PDA ligation in order to identify laryngoscopic and functional outcomes and predictors of recovery[165]. Follow up at a median of 3.0 ±2.1 years after diagnosis revealed resolution of vocal fold immobility in only two out of 66 patients, but symptoms persisted to a lesser degree: respiratory symptoms (39% vs. 11%), dysphonia (78% vs. 47%) dysphagia (55% vs. 20%)[165], possibly indicating a functional compensation. No prognostic indicators of recovery were found, but symptoms at presentation were positively associated with similar symptoms at follow-up[165]. Other, smaller studies[154,155,158] including 5–12 patients with a follow-up period from 4.5 months to 9 months supports the observation of low rates of recovery, but some of them described laryngeal compensatory mechanisms[154,155]. Unfortunately, as we did not examine the participants immediately after surgery, we do not know the rate of recovery of LVCP in Study #III. However, at least one case of compensation was observed, where the left vocal cord crossed the midline.

Although the low recovery rates of LVCP after PDA surgery are unfortunate and inform us that LVCP may be a lifelong sequelae of PDA surgery, the potential of recovery through compensatory mechanisms is interesting, in particularly if we could figure out what facilitates compensation and thus improve follow-up in patients with LVCP, e.g. through voice therapy[253]. If compensation is not obtainable, vocal fold medialisation thyroplasty or injection medialisation may improve symptoms of glottic insufficiency (hoarseness, dysphagia or aspiration)[254], also in children with vocal fold immobility and a history of PDA surgery or prolonged intubation[255]. Moreover, advances in laryngeal reinnervation techniques may improve voice outcomes[256], and underlines the importance of postoperative laryngoscopy examinations.

5.2.2 Short-term outcomes associated with LVCP and PDA surgery

In the six studies comparing outcomes in groups with and without LVCP in Study #I, we reported a range of adverse outcomes associated with LVCP including: sepsis,

tube feeding/gastrostomy (due to aspiration or oral feeding problems), surgery for severe gastroesophageal reflux, stridor, dysphonia, BPD, reactive airway disease, asthma, prolonged need of IMV, and prolonged hospital stay[15,153,154,156,158,160]. In the quality assessment, only one of these studies[257] was assigned a star for comparability of cohorts on the basis of design or analysis, which apparently makes the studies reporting neonatal outcomes of LVCP in Study #I vulnerable to confounding and selection bias, as described under the methods discussion. This is supported by analyses (Paper#1, Figure 2&3), which showed that LVCP were associated with lower GA and BW.

However, as previously described, the NOS was adapted to assess the quality of studies reporting the incidence of LVCP after PDA surgery, not outcomes after LVCP, and therefore the item comparability was labelled as not applicable (N/A) for most of the studies reporting outcomes associated with LVCP (Paper #I, Suppl. 5 & 7). In fact, one of the studies reporting outcomes after LVCP did adjust for possible confounders (GA and severe IVH) and could have been assigned a star for comparability on the basis of the analysis[160], and another study adjusted for potential confounders, but did not report which[156], whereas the other four[15,35,154,158] would not earn a star for comparability. Thus, the complications associated with LVCP reported by studies that adjusted for potential confounders were BPD, reactive airway disease, gastroesophageal reflux disease and surgical interventions for feeding difficulties[156,160]. In accordance with these findings, the more recent study published by Pharande et al., in which groups with and without LVCP did not differ with respect to GA/BW or surgical age and weight, reported that the infants with LVCP needed more time to reach suck feeds, they stayed longer in hospital, and a higher proportion of them went home on oxygen. In addition, three subjects with LVCP underwent vocal cord medialisation because of aspiration[159].

Both in study #II and #III the PDA surgery group had lower GA, used more postnatal steroids, and spent more days on IMV compared to the EPB control groups, which is in line with results from previous observational studies on outcomes after PDA surgery[110,120,131]. In Study #III, however, GA and BW did not differ between groups

with and without LVCP, and a higher rate of postnatal steroids in the LVCP group was the only neonatal outcome variable that was different from that of the no LVCP group. As postnatal steroids are often used to prevent or manage BPD[258], an increased use may indicate that the infants in the LVCP group were in more difficult respiratory situations, although we found no between-group differences for BPD and days on IMV. As with days on IMV, we do not know if the postnatal steroids were distributed before or after the occurrence of LVCP, and thus the relationship between these variables is unclear.

PDA surgery was associated with BPD in study #III, but not in study #II, allthough the rates of BPD within the PDA surgery groups were almost the same (80% vs. 79%, respectively). Statistically significant differences in the rates of BPD only between those with and without PDA in study #II, may suggest that subjects with a PDA were more prone to develop BPD, independently of exposure to PDA surgery. Further, the lack of difference in rates of BPD between the PDA surgery vs. the PDA, no surgery group in Study #II may reflect comparison with an EPB control group where all had PDA (and thus, were more disposed for BPD), compared to the EPB control group used in Study #III where only 37% had PDA, close to the 35% prevalence of BPD reported in the general EPB population in the USA[40]. The possible causal relationship and eventual direction of causality between PDA/PDA surgery and BPD is unclear[86,131,228,259-261], but as this issue is discussed in Paper #III, it will not be repeated here.

5.2.3 Self-reported voice symptoms

Dysphonia (impaired voice production diagnosed by a clinician) is *characterized by altered vocal quality, pitch, loudness, or vocal effort that impairs communication and/or quality of life*[262p1]. A weakness to the studies included in this thesis is that the term dysphonia was used to describe self-reported symptoms or symptoms observed in neonates, but dysphonia was not objectively assessed by a clinician. Hoarseness is often used interchangeably with dysphonia but is often rather a symptom of altered voice quality as reported by patients[263], or by health care personnel caring for premature infants. PDA-surgery and LVCP are known risk factors associated with

dysphonia, and a hoarse cry/voice have been described as symptoms of LVCP or an indication for laryngoscopy examination after PDA surgery in numerous studies[158,160,165,166,264]. However, dysphonia is quite common in the EP population and also associated with other variables such as prolonged or repeated intubation[226,227].

In Study #I, four studies reported rates of dysphonia ranging from 20%–86% in those with LVCP compared to rates of 22–25% in those without LVCP[15,153,158,165]. In Study #II, we found associations between voice symptoms and PDA surgery, but these symptoms were also present in the no surgery and the no PDA group as well. Further, the associations between voice symptoms and PDA surgery may have been confounded by prolonged IMV and GA (Paper #II, Figure 3 & Table 3). In total, one or more symptoms related to respiration during physical exertion or voice were reported for 61% of the participants in the surgery group and 31% in the no-surgery group. In Study #III, 57% of the EP/ELBW-born who underwent PDA surgery as neonates and had LVCP as young adults reported having a hoarse voice and/or problems singing. Overall, only 14% of those with LVCP had no voice symptoms vs. 69% of those without LVCP, which is in concordance with the findings of Røksund et al., in which 86% of those in the LVCP group and 25% of those without LVCP reported trouble with their voice or hoarseness[15].

Although the rates of voice symptoms were increased in the PDA surgery and LVCP groups, the results from Study #I–III supports previous descriptions of dysphonia and hoarseness as relatively common symptoms which may be present due to a variety of laryngeal and extra laryngeal etiologies[265,266]. Dysphonia is a known complication of endotracheal intubation, and tube size, number of intubations, and length of intubation may all impact laryngeal injuries detected after extubation[267]. Possible etiologies in the EPB population may be an underdeveloped larynx, inappropriate use of voice, or lack of phonation[267]. Reynolds et al. reported that 61% out of 178 preterm-born children (GA 23–32 weeks) presented with dysphonia, which was associated with female gender, GA and duration of intubation[227]. Using an audtitory perceptual assessment scale French et al.[226] reported that 58% of 154 school aged children born at <25 weeks GA presented with moderate to severe hoarseness, which

was associated with repeated intubations (>5) and the female gender, but not duration of ventilation or tube size. Moreover, only 4/154 children had undergone PDA surgery, which was not associated with hoarseness[226]. Walz et al.[268] found that low GA and BW, prolonged use (≥4 weeks and ≥8 weeks) of mechanical ventilation, increased number of intubations, longer NICU stay, BPD, cardiac surgery, PDA, PDA surgery and intubation was associated with poorer parent perceived vocal quality among 69 preterm-born children (mean GA of 29, range 23–37 weeks) and mean age at follow-up was 28 (3–197 months). In multivariate analysis the most important factor associated with parent perceived voice quality was intubation ≥four weeks[268]. However, as children with a history of tracheostomy or known vocal fold pathology were excluded from the study, and multivariate analysis did not include PDA surgery, but rather the presence of a PDA, the results may not represent the full picture on risk factors of dysphonia in preterm-born children.

Although the prevalence of self-reported voice symptoms was high among EP/ELBW-born subjects with LVCP in Study #III as well, it is interesting that almost half of the subjects with LVCP did *not* report having a hoarse voice. In conversations with some of these young adults, we noticed a discrepancy between our perception of them having a hoarse voice, and the subjective reports of not having a hoarse voice. It is possible that some of the subjects did not perceive their voice as hoarse because of accommodation to their own voice from neonatal age. Some might also have succeeded at compensating with the right vocal cord as described above (Section 5.2.1 on recovery and compensation).

5.2.4 Self-reported breathing symptoms

In Study #II we found that PDA surgery was associated with an increased odds ratio of parent reported exercise related breathing symptoms (crude OR 3.4, 95%CI: 1.3; 9.2) but the difference in rates (39% vs. 16%) was not statistically significant after adjusting for days on IMV (adjusted OR: 2.6, 95%CI: 0.9;7.4). The rates of self reported breathing symptoms in Study #III, however, were high among both EPB subjects with and without PDA surgery (56% vs. 30%) and with and without LVCP (64% vs. 46%) and no between group differences were reported. The high rate of

symptoms in the LVCP group corroborates with results from a study by Brunner at al., who found that 75% of adults with unilateral vocal fold paralysis reported to have dyspnea during phonation and physical activity[269]. Moreover, we found that self-reported breathing symptoms were not associated with CLE score (Paper #III, Suppl. Figure 2), which is also supported by results of Brunner at al. who found no correlation between subjective breathing symptoms and position of the paralysed vocal fold or glottic width at rest[269].

A limitation of the question used for reporting of exercise related breathing problems is that it is not LVCP disease specific. Exercise related breathing symptoms are associated with a range of pulmonary or laryngeal conditions commonly reported in EPB infants, such as exercise induced bronchoconstriction or traumatic laryngeal injury (i.e. glottic or subglottic stenosis, arytenoid prolapse)[270-273] which may also lead to upper airway narrowing and increased resistance to airflow[145,274]. This may have contributed to a high rate of exercise related breathing symptoms across all EPB groups and reduced the potential impact of LVCP on the results. However, the custom-made question about 'scraping sounds' or abnormal sounds during physical exertion, developed by the research group to detect exercise laryngeal obstruction, and therefore putatively more disease specific, did not significantly differentiate between those with or without LVCP, even though the rate of reported symptoms was higher in the LVCP group (42% vs. 15%). This may indicate low validity and/or sensitivity of this custom-made question, or it may simply reflect that more than half of the LVCP participants did not have breathing symptoms during physical exertion.

Separately or combined, pulmonary and laryngeal conditions (and many other variables, e.g. poor physical contitioning[233]) may induce breathing problems during exercise[275]. It is therefore necessary to perform a proper medical work-up as the mechanisms behind the symptoms and the management of the individual diagnoses differ.

5.2.5 Lung function and exercise capacity

In Study #III we found that the mean z-score for FEV_1 (-1.76, 95%CI: -2.31; -1.21) in the PDA surgery group was below the lower limit of normal (-1.64) as defined by the GLI, representing the lower 5th percentile of a normal population[202], which may suggest an increased risk of future chronic obstructive pulmonary disorder[276]. However, PDA surgery was not found to be associated with impaired exercise capacity.

The association between PDA surgery and lung function may be related to numerous factors, including (as already alluded to) selection of the most vulnerable infants for PDA surgery[132], as implyed by the increased rate of BPD in the PDA surgery group compared to the EP-born controls. The mean difference in $zFEV_1$ between the PDA surgery group and the EPB controls were 1.08 (95%CI: 1.75; 0.42), and after adjustment for BPD, the difference was weaker, but still present (mean difference:0.89, 95%CI: 1.17; 1.61). The finding of reduced lung function in EPB subjects and the association with BPD are supported by results from Gough et al.[51] and the EPICure study, where $zFEV_1$ was reduced in EPB young adults (mean difference: 1.08 SD, 95%CI: 1.40; 0.77) compared to the term-born group, and most reduced in EPB subjects with a history of BPD[57].

Although mean FEV_1 was impaired below the 5th percentile, PDA surgery was not associated with reduced exercise capacity in Study #III. Our results therefore disagree with those of a study of preterm born (GA<29 weeks) young people born at the turn of the millennium, where abnormal lung function (FEF 75 <5th percentile) was associated with reduced sprint distance in a modified shuttle sprint test, and shorter duration of self-reported weekly exercise[277]. However, Welsh et al. reported that lung function and BPD were not associated with VO_2 in EPB children[47], which is in line with studies perfomed by our own research groups investigating exercise capacity in groups of EPB children and young adults, where no associations between lung function and exercise capacity could be observed[242,244,245]. Pianosi et al. reported that a mild airflow limitation in EPB children did not limit exercise performance, and that exercise capacity was best predicted by lean body mass[62]. In sum, one might argue

from the literature that achievement of an average (normal) exercise capacity does not seem to be limited by the level of airflow limitation associated with EP birth or BPD. In Study #III, we found that the EPB males had reduced weight, but not reduced BMI compared to the term born males. Moreover, although between group differences in peakVO_2 were only present for the male participants, our analysis showed no interaction between gender and group affiliation on peakVO_2 (Paper #III, Table 5).

Within the PDA surgery group, lung function measurements were not associated with LVCP, in contrast to reports from Røksund et al, in which the LVCP group had increased airway obstruction (FEV_1/FVC)/ compared to those without LVCP[15]. The lack of association between LVCP and exercise capacity, however, agreed with the findings reported by Røksund et al[15]. Similar to a recent study on breathing patterns in patients with EILO[278], we found prolonged inspiratiory time (Ti/Ttot) at peak exercise intensity, which may suggest increased airway resistance during inspiration in the subjects with LVCP. Unfortunately, the inspiratory curves from the spirometry assessments were not of good enough quality to further describe patterns of inspiratory flow rate at rest in our analyses.

Although we found higher CLE scores in the LVCP group (Paper #III, Figure 4), indicating increasing laryngeal obstruction during incremental exercise, the lack of association between LVCP and lung function or exercise capacity suggests that the glottic narrowing caused by the parlaysed left vocal cord did not increase airway resistance and/or decrease respiratory flow to the level where it impaired exercise capacity[142]. Measures of pressure and flow changes across cadaveric larynges have shown that reductions of the glottic cross-sectional area does not increase airway resistance to normal breathing significantly, until the area is narrowed to 0.5 cm^2 or less[279]. However, the impact of LVCP on airway resistance and ventilation may be more related to the dynamic narrowing of the glottic space during inspiration than the exact position (i.e. paramedian vs. intermediate position) of a paralysed left vocal cord[136]. Moreover, the exact degree of glottic narrowing which results in subjective breathing discomfort is unknown[150]. In Study #III, we did not measure the glottic

cross-sectional area as there currently is no available method to do that, and we do not know whether LVCP had an impact on airway resistance and/or exercise tolerance at an individual level. Individual variance in severity of laryngeal obstruction (expressd by the modified CLE score, range 4–16) within the LVCP group suggest individual differences and may have contributed to increased dispersion and inconclusive results (Paper #III, Figures 4 & 5).

Exercise capacity was reduced by 11% in the EPB groups combined compared to the term-born control group, a reduction similar to what is shown in previous studies[54]. Low levels of physical activity across the EPB groups may have contributed to increased differences in exercise capacity between EPB and term-born, whereas potential differences in exercise capacity between those with and without LVCP thereby may have been blurred or reduced (Paper #III, Figure 3): for example, if the level (and the intensity) of physical activity had been higher across all the EPB groups, it is possible that LVCP would have contributed to ventilatory impairment and poorer results in those affected. A range of variables may contribute to the reduced exercise capacity among EPB subjects, and these mechanisms are poorly understood[54]. Reduced levels of physical activity may contribute to reduced exercise capacity the same way it does in term-born subjects, but the pooled evidence that physical ativity improves cardiorespiratory function or body composition in the preterm population is inconclusive[280].

6. Conclusion

The reported incidence of LVCP after PDA surgery has a wide dispersion and LVCP is probably underreported in studies where only symptomatic EPB subjects undergoes laryngoscopy examination post-surgery. We found that LVCP was common after PDA surgery in EPB children and adults and associated with adverse neonatal outcomes such as BPD and feeding difficulties (study #I)

PDA surgery was associated with dysphonia and breathing problems during physical exertion (Study #II), whereas LVCP was associated with dysphonia and exercise induced laryngeal obstruction, but not breathing problems during physical exertion (Study #III). PDA surgery, but not LVCP, was associated with reduced lung function compared to other EPB adults or term-born adults. Exercise capacity was reduced among EPB adults compared to term-born adults, but it was not further impaired in subjects who underwent PDA surgery or had LVCP (Study #III).

Thus, although associated with adverse outcomes at neonatal age and voice symptoms in children and adults, LVCP does not seem to have an impact on exercise capacity and lung function in adults with a history of PDA surgery. With the exception of one patient with LVCP, only the three patients with other severe laryngeal pathology were aware of their laryngeal condition before participating in Study #III, which may suggest that most of the participants with LVCP had adapted well to the laryngeal condition and that they were less affected by LVCP than those who aquire LVCP as adults. Still, subjects with LVCP, and in particular those with symptoms, may benefit from closer follow up by the health care system.

Our results may have been inconclusive due to the small sample size and wide distributions liked to individual differences within those in the LVCP group, possibly due to compensatory mechanisms or comorbidities among some subjects. Thus, relatively rare conditions like LVCP, that nevertheless are important on individual levels, need to be studied within the context of international consortia.

Answers to research questions

Research question #1: What is the reported incidence of LVCP after surgical PDA ligation in extremely premature born infants?

The pooled proportion of reported incidence of LVCP was 9% overall, but increased to 32% in the subgroup analysis of studies that performed laryngoscopy examinations in all infants exposed to PDA surgery.

Research question #2: Which study level characteristics may explain the wide incidence variation reported by different studies?

One study level characteristic that may partially explain the wide dispersion in reported incidence of LVCP after PDA surgery may be whether laryngoscopy has been performed in all subjects exposed to PDA surgery vs. only in subjects with symptoms. Another being whether the study design was retrospective or prospective.

Research question #3: What are the short and long-term consequences of LVCP in extremely preterm born infants/children with a history of PDA surgery?

The systematic review found that LVCP was associated with the following short-term outcomes: Stridor, dysphonia, sepsis, BPD, tube feeding/gastrostomy/Nissen fundoplication, prolonged duration of IMV, prolonged hospital stay. Long-term outcomes associated with LVCP were reactive airways disease, asthma and increased pulmonary obstruction (FEV_1/FVC, % of predicted). However, only two of the studies reporting outcomes of LVCP adjusted for potential confounding. In study #III, LVCP was associated with more use of postnatal steroids in study #III.

Research question #4: Is the odds ratio of having exercise related respiratory symptoms increased among EPB schoolchildren who underwent PDAsurgery as neonates compared to EPB schoolchildren who received pharmacological or conservative PDA management?

The crude odds ratio of having exercise related respiratory symptoms was increased in EPB schoolchildren who underwent PDA surgery compared to EPB schoolchildren who received pharmacological or conservative PDA management.

Research question #5: Is the odds ratio of having voice related symptoms increased among EPB schoolchildren who underwent PDA surgery as neonates compared to EPB schoolchildren who received pharmacological or conservative PDA management?

The odds ratio of having voice related symptoms was increased when comparing EPB schoolchildren who underwent PDAsurgery with EPB schoolchildren who received pharmacological or conservative PDA management

Research question #6: What is the prevalence of LVCP in this national cohort of EP/ELBW adults who underwent PDA surgery as neonates?

Laryngoscopy examinations of 30/48 eligible EPB adults who underwent PDA surgery as neonates in 1999–2000 identified LVCP in 16/30 (53%) of the subjects.

Research question #7: Does lung function and exercise capacity differ between adults presenting with and without LVCP after PDA surgery?

Lung function and exercise capacity was not associated with LVCP.

Research question #8: Does lung function and exercise capacity differ between EPB adults who underwent neonatal PDA surgery compared to EPB controls and term born controls?

The PDA surgery group had reduced lung function, but not reduced exercise capacity compared to the EPB control group. Both EPB groups presented with reduced lung function and exercise capacity compared to term-born adults.

7. Future perspectives

Allthough LVCP is a known postoperative complication following surgical ligation of a PDA in EPB neonates, and the use of PDA surgery has decreased, surgical ligation is still a treatment option for the smallest EPB infanst with a symptomatic hsPDA. Furthermore, an unknown number of EPB children and adults live with LVCP as a consequence of neonatal PDA surgery today. It is therefore still relevant to investigate the outcomes of PDA surgery and of LVCP after PDA surgery, including the possibilities of compensation and recovery of LVCP or the effects of treatment. Moreover, EPB patients with history of neonatal PDA surgery should be considered for laryngoscopy examination, in particular if presenting with voice symptoms.

To find the true incidence of LVCP after PDA surgery in EPB infants, a prospective poplulation-based study including pre- and postoperative laryngoscopy examinations of all surgically treated infants should be performed. However, preoperative examinations of EPB infants introduces practical and ethical concerns. As many of the infants are already intubated before surgery, extubation, examination and reintubation may impose unnessesary discomfort to the infant[156], and may also impose an additional risk of laryngeal injury. In addition, it is important to figure out how to protect the LRLN from injury during PDA surgery. Better equipment for transcathether closure of PDA also in EPB infants[281] may contribute to a future reduction in the rate of LVCP.

Upper airway resistance in patients with LRLN paralysis is higher in women compared to men, possibly due to smaller dimensions of the female airways[143,282]. We do not know whether LVCP affects children differently compared to adults as their laryngeal dimensions are narrower and the laryngeal cartilages are softer compared to that of adults. Thus, although LVCP was not associated with impaired lung function or exercise capacity in adults, it is still possible that increased upper airway resistance due to LVCP may result in impaired lung function or exercise capacity in children,

who are more vulnerable to reduction in airway diameters (i.e., acute subglottic laryngitis). Future studies should address this issue as well.

8. References

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9. Appendices and Papers

APPENDIX

Appendix 1

Database:

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 20, 2022>

#	Query	Results from 21 Jan 2022
1	ductus arteriosus, patent.mp. or ductus arteriosus, patent/	9,441
2	(persistent ductus arteriosus or patent ductus arteriosus).mp.	9,419
3	1 or 2	13,179
4	infant, low birth weight/ or infant, very low birthweight/ or infant, extremely low birthweight/ or infant, premature/ or infant, extremely premature/	75,685
5	(preterm infant* or premature infant* or low birth weight infant*).mp.	53,699
6	(preterm neonate* or premature neonate* or low birth weight neonate*).mp.	9,039
7	4 or 5 or 6	98,894
8	ligation/	24,178
9	(ligation or ligature or surgical clip or clipping or closure or surgery or surgical or suture).mp.	3,424,674
10	8 or 9	3,424,674
11	3 and 7 and 10	1,666
12	(left vocal cord paresis* or left vocal cord paralysis* or vocal cord paresis* or vocal cord paralysis* or vocal fold paresis* or vocal fold paralysis* or unilateralo paresis* or unilateral paralysis*).mp.	8,205
13	limit 12 to humans	7,107
14	11 and 13	25
15	3 and 13	62
16	(exercise capacity* or aerobic capacity* or exercise* or VO2*).mp.	432,028
17	14 and 16	1
18	(lung function* or spirometry* or FEV1*).mp.	79,092
19	14 and 18	1

Appendix 2

Database:

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 01, 2022>

#	Query	Results from 2 Feb 2022
1	ductus arteriosus, patent.mp. or ductus arteriosus, patent/	9,453
2	(persistent ductus arteriosus or patent ductus arteriosus).mp.	9,436
3	1 or 2	13,198
4	infant, low birth weight/ or infant, very low birthweight/ or infant, extremely low birthweight/ or infant, premature/ or infant, extremely premature/	75,840
5	(preterm infant* or premature infant* or low birth weight infant*).mp.	53,787
6	(preterm neonate* or premature neonate* or low birth weight neonate*).mp.	9,055
7	4 or 5 or 6	99,048
8	ligation/	24,196
9	(ligation or ligature or surgical clip or clipping or closure or surgery or surgical or suture).mp.	3,430,956
10	8 or 9	3,430,956
11	3 and 7 and 10	1,668
12	(left vocal cord paresis* or left vocal cord paralysis* or vocal cord paresis* or vocal cord paralysis* or vocal fold paresis* or vocal fold paralysis* or unilateralo paresis* or unilateral paralysis*).mp.	8,216
13	limit 12 to humans	7,118
14	11 and 13	25
15	3 and 13	62
16	dysphonia/	1,958
17	14 and 16	0
18	15 and 16	2
19	(respiratory symptoms* or breathing symptoms*).mp.	18,379
20	14 and 19	1
21	15 and 19	2
22	18 and 21	1
23	(hoarse* and voice*).mp.	2,170
24	14 and 23	1
25	15 and 23	4
26	dyspnea/	23,246
27	14 and 26	1
28	15 and 26	1

Appendix 3

Prosjekt Ekstrem Prematuritet

Barneklinikken, Haukeland universitetssykehus,
Universitetet i Bergen, Seksjon for pediatri

Skjemaet fylles ut av pårørende og bes sendt tilbake til Barneklinikken, Haukeland universitetsklinikk i vedlagte frankerte returkonvolutt
(Barneklinikken, Haukeland universitetssykehus, v/Trond Markestad, 5021 Bergen)

Barnets navn: _____

Fødselsdato: ☐☐ ☐☐ ☐☐

Mors navn:_____

Adresse:_____

Postnummer: ☐☐☐ Sted: _____

Mors fødselsnummer: ☐☐ ☐☐ ☐☐ ☐☐☐☐☐

Nærmeste pårørendes navn (hvis forskjellig fra mor):

_____ Evnt. slektskap til barnet:_____

1. **Vennligst oppgi barnets høyde og vekt sist det ble målt <u>samtidig</u>**
   Dersom det skjedde mer enn for <u>1 år</u> siden, setter vi pris på å få nytt mål

Dato for måling: ☐☐ ☐☐ ☐☐ Høyde: ☐☐☐ cm, Vekt: ☐☐☐ kg
(dag, måned, år)

2. **Har barnet vært innlagt i sykehus siden 5 års alder?**

   ☐ Nei
   ☐ Ja; i så fall: Hvor mange ganger ? ☐☐ ganger

3. **Hvis barnet har vært innlagt i sykehus <u>etter 5 års alder</u>, skriv *årsaken* til at barnet har vært innlagt og *hvor gammelt barnet da var*:**

Opphold Nummer	**Årsak til innleggelse**	**Alder i hele år**	Ikke skriv her ICP
1			
2			
3			
4			
5			

Spørsmål om lungefunksjonen

4. **Har barnet <u>noen gang</u> (etter nyfødtperioden) hatt tung pust piping/surkling/tetthet i brystet?**
Kryss av for det alternativet du mener passer best.

☐ Ja, før 5 års alder, men ikke etter 5 års alder
☐ Ja, både før og etter 5 års alder
☐ Ja, ikke før, men etter 5 års alder
☐ Nei, aldri ; *hvis nei, gå til spørsmål 9*

5. Har barnet hatt tung pust eller piping/surkling/tetthet i brystet i løpet av <u>de siste 12 månedene</u>?

☐ Ja
☐ Nei; *hvis nei gå til spørsmål 9*

6. **Hvor mange anfall med tung pust eller piping/surkling/tetthet i brystet har barnet hatt i løpet av de <u>siste 12 månedene</u>?**

☐ Ingen
☐ 1 til 3
☐ 4 til 12
☐ mer enn 12
☐ har slike plager hele tiden

7. Hvor ofte har barnets søvn i gjennomsnitt blitt forstyrret på grunn av tung pust eller piping/surkling/tetthet i brystet <u>de siste 12 månedene</u> ?

☐ aldri våknet
☐ mindre enn 1 natt pr uke
☐ 1 eller flere netter pr uke

8. Har piping/surkling/tetthet i brystet eller tung pust noen gang vært så alvorlig <u>de siste 12 måneder</u> at barnet har hatt problemer med å snakke slik at han/hun bare kunne si ett eller to ord mellom hvert pust?

☐ Ja
☐ nei

9. Har barnet <u>noen gang</u> hatt astma?

☐ Ja
☐ nei

10. Har barnet i løpet av <u>de siste 12 måneder</u> hatt tung pust eller piping/surkling/tetthet i brystet under eller etter fysisk trening, aktiv lek eller mosjonering?

☐ Ja
☐ nei

11. Har barnet i løpet av de siste 12 måneder hatt tørr hoste om natten, utenom hoste i forbindelse med forkjølelse eller andre luftveisinfeksjoner?

☐ Ja
☐ nei

12. Har barnet brukt oksygen (surstoff) hjemme etter at han/hun kom hjem fra nyfødtavdelingen?

☐ Nei
☐ Ja, men sluttet da han/hun var ☐☐ år og ☐☐ måneder gammel
☐ Ja, bruker det fortsatt, i alle fall i perioder

13. Har barnet brukt astmamedisiner etter at han/hun kom hjem fra nyfødtavdelingen?
Antibiotika/penicillin ved lungebetennelse og bronkitt regnes ikke med.

☐ Nei, barnet har ikke brukt slike medisiner
☐ Ja, tidligere men sluttet med
- ☐ Inhalasjonssteroider *(Flutide, Pulmicort, Becotide, Seretide, Symbicort)*

  da han/hun var ☐☐ år og ☐☐ måneder gammel

- ☐ Andre astmamedisiner *(Singulair, Ventolin, Bricanyl, Airomir, Oxis, Serevent, Atrovent. o.l)*

  da han/hun var ☐☐ år og ☐☐ måneder gammel

☐ Ja, barnet bruker fortsatt medisiner, i så fall hvilke:
- ☐ Inhalasjonssteroider *(Flutide, Pulmicort, Becotide, Seretide, Symbicort);*
  i så fall brukes disse fast eller i perioder?
  ☐ fast daglig ☐ bare i perioder med forkjølelse eller tung pust
- ☐ Anfallsmedisiner *(Efedrin, Ventolin, Bricanyl, Airomir, Oxis, Serevent, Atrovent.o.l)*
  i så fall brukes disse fast eller i perioder?
  ☐ fast daglig ☐ bare ved tung pust eller før anstrengelse
- ☐ Singulair
- ☐ Andre lungemedisiner, skriv ned hvilke: _____

14. Har barnet hatt episoder med lungebetennelse eller bronkitt som har blitt behandlet med penicillin eller andre antibiotika etter 5 års alder?

☐ Nei
☐ Ja. I så fall; Omtrent hvor mange ganger fram til for 1 år siden?: ☐☐ ganger
Omtrent hvor mange ganger siste 1 år (*sett 0 for ingen*) ☐☐ ganger

15. Hvor mange ganger har barnet fått penicillin eller andre antibiotika for andre sykdommer enn lungesykdommer etter 5 år? *(sett 0 for ingen)* ☐☐ ganger

16. Har barnet pusteproblemer ut over det normale ved vanlig fysisk anstrengelse?

☐ Nei ☐ Litt mer enn normalt ☐ Mye mer enn normalt

17. Lager barnet "skrapelyder" eller andre unormale lyder fra strupen ved fysisk anstrengelse?

☐ Nei ☐ Litt ☐ Mye

Spørsmål om barnets stemme

18. Hvordan vil du beskrive barnets talestemme?

☐ Utmerket ☐ God ☐ Litt svak/utydelig ☐ Meget svak/utydelig ☐ Har ikke stemme

19. Er barnets stemme så svak eller utydelig at den begrenser muligheten for å bli hørt i et støyende miljø?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

20. Er barnets stemme slik at den påvirker deltagelse i skolearbeid eller vanlige sosiale aktiviteter?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

21. Har barnet problemer med å rope eller snakke med høy stemme?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

22. "Sprekker" stemmen når barnet roper?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

23. Er stemmen mer hes enn hos andre barn på samme alder?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye mer ☐ Ekstremt

24. Er stemmen slik at det har påvirket barnet deltagelse i sang?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

Spørsmål om andre sykdommer

Har, eller har barnet hatt:

25. atopisk *(kløende)* eksem? ☐ Nei ☐ Ja, tidligere ☐ Ja, fortsatt
26. høysnue? ☐ Nei ☐ Ja, tidligere ☐ Ja, fortsatt
27. andre allergiske sykdommer? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
    Beskriv i så fall:_____
28. epilepsi? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
29. dren i ørene? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
30. nedsatt hørsel ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
    Hvis fortsatt, kryss av behandling: ☐ Ingen ☐ Høreapparat ☐ Cochleaimplantat ☐ Døv, ingen apparater

31. skjeling ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
32. svekket syn ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt;
    Hvis fortsatt; ☐ Nærsynt ☐ Langsynt ☐ Blind ett øye ☐ Blind begge øyne ☐ Annet, beskriv;_____
33. Bruker barnet briller? ☐ Nei ☐ Ja, hvilken styrke? _____

Har barnet

34. fjernet falsk mandel (polypp, adenoid) ☐ Nei ☐ Ja
35. fjernet mandlene? ☐ Nei ☐ Ja
36. hatt feberkramper? ☐ Nei ☐ Ja, sist ☐☐ år gammel
37. hatt hjernehinnebetennelse? ☐ Nei ☐ Ja
38. hatt hodeskade med tap av bevissthet og innleggelse i sykehus? ☐ Nei ☐ Ja
39. Nedsatt førlighet i armer og/eller ben? ☐ Nei ☐ Ja, Beskriv i så fall:_____

40. Har, eller har barnet hatt, andre sykdommer som ikke er nevnt ovenfor? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
    Beskriv i så fall:_____
    _____

41. Bruker barnet i dag andre medisiner enn de som er nevnt i pkt 13 og 15?

☐ Nei ☐ Ja. Hvis ja, beskriv hvilke_____

Spørsmål om ernæring

42. Hvordan vil du beskrive hvor flink barnet er til å spise?

☐ Aldri hatt spisevansker av betydning

☐ Hadde spisevansker de første ☐☐ årene, men ikke nå lenger

☐ Har spisevansker nå, men bare de siste ☐☐ årene
☐ Har hele tiden hatt spisevansker, også nå

43. Hvis barnet har eller har hatt spisevansker etter <u>5 års</u> alder; hvordan har disse artet seg *(kryss av for <u>alle</u> aktuelle)**?***

☐ Spiser lite, vanskelig å få til å spise (småspist)
☐ Vansker med å spise/svelge klumper og fast mat
☐ Liker bare enkelte ting; i så fall: hva vil han/hun ikke spise? _____
_____
☐ Andre spisevansker; beskriv:_____
☐ Bruker PEG eller sonde; beskriv i så fall:_____

44. Går barnet på en diett som er anbefalt av lege?

☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt, beskriv nærmere:_____

Vekt og pubertet

Hva synes du om barnets vekt?

Svært undervektig ☐ Litt undervektig ☐ Passelig ☐ Litt overvektig ☐ Svært overvektig ☐

Sammenlignet med jevnaldrende - hvordan vurderer du hans/hennes kroppslige utvikling?

Mye tidligere ☐ Litt tidligere ☐ Omtrent som andre ☐ Litt senere ☐ Mye senere ☐

Spørsmål om aktivitet, ferdigheter og utvikling

45. Hvor utholdende er barnet i lek og idrettsaktivitet?

☐ Holder følge med jevnaldrende barn i lek og idrettsaktivitet
☐ Litt mindre utholdende enn jevnaldrende barn
☐ Mye mindre utholdende enn jevnaldrende barn

46. Hvor fysisk aktiv i lek, sport og lignende vil dere si at barnet er?

☐ Mer aktiv enn gjennomsnitt for jevnaldrende
☐ Omtrent like aktiv som gjennomsnitt for jevnaldrende
☐ Mindre aktiv enn gjennomsnitt for jevnaldrende

47. Hvordan oppfatter du barnets fysiske ferdigheter (grovmotorikk)
(F.eks. løpe, hoppe, sparke ball, sykle o.s.v.?)

☐ Lik jevnaldrende
☐ Mer "kløne te" eller umoden i sine ferdigheter
☐ Flinkere enn de fleste jevnaldrende

48. Hvordan oppfatter du barnets ferdigheter med hendene
(F.eks. tegne, skrive, klippe, bygge med Lego o.s.v.?)

☐ Lik jevnaldrende
☐ Mer "kløne te" eller umoden i sine ferdigheter
☐ Flinkere enn de fleste jevnaldrende

49. Hvordan vil du beskrive barnets språk i dag?
Velg det alternativet du synes passer best.

☐ Snakker minst like godt som andre jevnaldrende barn
☐ Har samme eller bedre ordforråd som andre, men dårligere uttale
☐ Har mindre ordforråd, men god uttale
☐ Har både mindre ordforråd og dårligere uttale
☐ Har ikke, eller svært lite, språk

50. Deltar barnet i <u>organisert</u> og eller <u>uorganisert</u> aktivitet?
Kryss av <u>alle</u> aktuelle

☐ Deltar i lagidretter/sport (fotball o.l), beskriv hva:_____
☐ Deltar i idrettslag, men ikke lagsport (ski, løping o.l), beskriv hva:_____
☐ Deltar i annen organisert aktivitet (kor, speider o.l): beskriv hva: _____
☐ Fysisk aktivitet alene eller med familie/venner (ski, o.l), beskriv hva:_____
☐ Annen aktivitet med familie/venner(spille instrument o.l), beskriv hva:_____

51. Hvor mange dager i uken <u>utenom skolen</u> driver barnet fysisk aktivitet slik at det blir andpusten og/eller svett? *(kryss bare av <u>ett</u> alternativ)*

☐ Hver dag
☐ 4-6 ganger i uken
☐ 2-3 ganger i uken
☐ 1 gang i uken
☐ Sjeldnere enn 1 gang uken
☐ Aldri

52. Hvordan vurderer du barnets kompetanse i sportslige aktiviteter?

☐ Svært høy
☐ Litt høy
☐ Middels
☐ Litt lav
☐ Svært lav

53. Får, eller har barnet fått, spesielle hjelpetiltak? *(Kryss av for alle aktuelle faggrupper).*

Fysioterapeut	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Logoped	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Ekstra støttetiltak i barnehage	☐ Nei	☐ ja, beskriv;_____			
Ekstra støttetiltak i skolen	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Hvis ja; ☐ Assistent i vanlig klasse	☐ Spesialklasse	☐ Annet, beskriv ressurser:			
_____					
PPT (Pedagogisk psykologisk tjeneste)	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Psykolog/barnepsykiater	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Barne- og ungdomspsykiatrisk (BUP)	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Fylkets habiliteringstjeneste	☐ Nei	☐ ja, inntil alder		år	☐ ja, fortsatt
Er det etablert ansvarsgruppe?	☐ Nei	☐ nei, men planlagt,			☐ ja
Etablert individuell opplæringsplan?	☐ Nei	☐ nei, men planlagt			☐ ja

54. Får dere annen støtte fra det offentlige for barnet?

☐ Ingen
☐ Hjelpestønad
☐ Grunnstønad
☐ Omsorgspenger/pleiepenger, beskriv:_____
☐ Støttekontakt
☐ Andre avlastningstiltak; beskriv:_____

55. Har barnet gått i barnehage?

☐ Nei
☐ Ja, gikk i barnehage i år og måneder

56. Hvordan fungerer barnet sammen med andre barn, for eksempel på skolen

☐ Barnet skiller seg ikke fra andre jevnaldrende barn
☐ Barnet har samspillvansker med andre barn
Hvis samspillvansker, angi hvordan (flere rubrikker kan krysses av):
- ☐ Barnet plages av andre barn, føler seg utenfor, sky og isolert
- ☐ Barnet er sint, urolig og plager andre barn
- ☐ Barnet faller utenfor og er isolert, men uten å mistrives eller bli plaget
- ☐ Andre vansker i samspill med andre; vennligst beskriv disse:_____

_____

_____

57. Hvordan vurderer dere barnets sosiale kompetanse?

☐ Svært høy
☐ Litt høy
☐ Middels
☐ Litt lav
☐ Svært lav

58. Hvordan vurderer dere barnets skolefaglige kompetanse?

☐ Svært høy
☐ Litt høy
☐ Middels
☐ Litt lav
☐ Svært lav

Hvordan vil dere beskrive barnets selvbilde, trivsel og krav til dere?

Når dere sammenligner med det dere tror er gjennomsnitt for jevngamle barn, hvordan opplever dere

59. Barnets selvbilde

☐ Mye bedre ☐ Noe bedre ☐ Middels ☐ Noe lavere ☐ Mye lavere

60. Barnets trivsel

☐ Mye bedre ☐ Noe bedre ☐ Middels ☐ Noe lavere ☐ Mye lavere

61. Hvor krevende barnet er <u>nå</u> med hensyn til behov fra dere foreldre

☐ Mye mer ☐ Litt mer ☐ Middels ☐ Noe mindre ☐ Mye mindre

62. Hvor krevende barnet har vært <u>tidligere</u> med hensyn til behov fra dere foreldre

☐ Mye mer ☐ Litt mer ☐ Middels ☐ Noe mindre ☐ Mye mindre

Avføring og vannlatning

63. Tisser barnet på seg om dagen?	☐ Nei	☐ Av og til	☐ Ofte	
64. Tisser barnet på seg om natten?	☐ Nei	☐ Av og til	☐ Ofte	
65. Får barnet avføring i bukse/bleie om dagen?	☐ Nei	☐ Av og til	☐ Ofte	
66. Får barnet avføring i bukse/bleie om natten?	☐ Nei	☐ Av og til	☐ Ofte	
67. Hvor ofte har barnet avføring?	☐ Flere ganger pr dag	☐ 1-2 ggr/d	☐ Sjeldnere	
68. Hvordan er avføringen?	☐ Normalt formet	☐ Løs	☐ Hard	

Spørsmål om søvn

69. Har, eller har barnet hatt søvnvansker?

☐ Aldri hatt søvnvansker av betydning

☐ Hadde søvnvansker de første ☐☐ årene, men ikke nå lenger

☐ Har søvnvansker nå, men bare de siste ☐☐ årene

☐ Har hele tiden hatt søvnvansker, også nå

70- Hvis barnet <u>har</u> eller <u>har hatt</u> søvnvansker, hvordan vil du beskrive disse
Kryss av <u>alle</u> aktuelle

☐ Vansker med å legge seg til å sove om kvelden *(innsovningsvansker)*
☐ Hyppige oppvåkninger i løpet av natten
☐ Våkner uvanlig tidlig
☐ Våkner uvanlig sent

71. Her er noen utsagn om vanlige søvnproblemer. Kryss av for hvordan barnet har det <u>nå</u>

	Stemmer ikke	**Stemmer delvis**	**Stemmer helt**
Hun/han gisper etter luft eller får ikke puste når det sover	☐	☐	☐
Hun/han har problemer med å puste om natten	☐	☐	☐
Hun/han snorker	☐	☐	☐
Hun/han opplever søvnighet på dagtid	☐	☐	☐
Hun/han har problemer med innsovning eller hyppige oppvåkninger	☐	☐	☐

72. På hverdager: Når legger hun/han seg vanligvis?

kl ☐☐:☐☐ Når står hun/han vanligvis opp? kl ☐☐:☐☐

73. Hvor lang tid går det vanligvis fra hun/han legger seg til hun/han sovner inn?

☐ **timer :** ☐☐ **minutter**

74. Hvor lang tid er hun/han våken om natten etter at hun/han først har sovnet?

☐ **timer :** ☐☐ **minutter**

75. Synes du barnet får nok søvn?

☐ **Ikke nok** ☐ **Litt lite** ☐ **Passe** ☐ **Litt mye** ☐ **For mye**

Litt om familien

76. Hvor mange søsken eller halvsøsken har barnet?

☐☐ søsken/halvsøsken

For **helsøsken** : Oppgi alder, kjønn, høyde og vekt:

Søsken nr. 1: ☐☐ år og ☐☐ mndr: ☐ gutt ☐ jente Høyde __ __ __ cm Vekt __ __ kg

Søsken nr. 2: ☐☐ år og ☐☐ mndr: ☐ gutt ☐ jente Høyde __ __ __ cm Vekt __ __ kg

Søsken nr. 3: ☐☐ år og ☐☐ mndr: ☐ gutt ☐ jente Høyde __ __ __ cm Vekt __ __ kg

Søsken nr. 4: ☐☐ år og ☐☐ mndr: ☐ gutt ☐ jente Høyde __ __ __ cm Vekt __ __ kg

Søsken nr. 5: ☐☐ år og ☐☐ mndr: ☐ gutt ☐ jente Høyde __ __ __ cm Vekt __ __ kg

77. Hva er foreldrenes (biologiske) høyde og vekt:

Mors høyde __ __ __ cm Mors vekt __ __ __ kg

Fars høyde __ __ __ cm Fars vekt __ __ __ kg

78. Hvem bor barnet sammen med til daglig?

☐ Mor og far
☐ Bare mor
☐ Bare far
☐ Både mor og far, men hver for seg (for eksempel en uke hos hver)
☐ Mor og ny partner (stefar)
☐ Far og ny partner (stemor)
☐ Fosterforeldre
☐ Andre, hvem:_____

79. Spørsmål om spesielle sykdommer i familien

Har, eller har noen hatt, astma?	☐ Ingen	☐ Ja, mor	☐ Ja, far	☐ Ja, søsken
Har, eller har noen hatt, høysnue?	☐ Ingen	☐ Ja, mor	☐ Ja, far	☐ Ja, søsken
Har, eller har noen hatt, atopisk eksem	☐ Ingen	☐ Ja, mor	☐ Ja, far	☐ Ja, søsken
Har, eller har noen hatt atferdsvansker vansker med konsentrasjon, lærevansker (ADHD o.l)	☐ Ingen	☐ Ja, mor	☐ Ja, far	☐ Ja, søsken

I så fall; hvem, og hvilke vansker:_____

80. Hvordan vil du beskrive helsen til familiemedlemmene?

	Svært god	God	Middels	Dårlig	Svært dårlig
Barnet	☐	☐	☐	☐	☐
Mor	☐	☐	☐	☐	☐
Far	☐	☐	☐	☐	☐
Søsken	☐	☐	☐	☐	☐

81. Røyker foreldre eller andre omsorgspersoner *(fyll ut alle aktuelle)***?**

☐ Nei, verken mor eller far
☐ Ja, mor
☐ Ja, far
☐ Ja, samboer av mor eller far
☐ Ja, andre som bor i huset

82. Røykes det *inne* i huset?

☐Nei ☐Ja

83. Hva er <u>høyeste</u> fullførte utdannelse for mor og far?

MOR:
☐ 9-/-10årig grunnskole
☐ 1-2 års videregående skole
☐ Videregående yrkesfaglig
☐ 3-årig videregående allmennfaglig (inkl. gymnas**)**
☐ Høgskole, universitet inntil 4 år (cand.mag, sykepleier, lærer, ingeniør eller lignende
☐ Høgskole, universitet mer enn 4 år (hovedfag, master, embetseksamen)
☐ Annen utdannelse; beskriv:_____

Har mor norsk som morsmål? ☐ ja ☐ nei; hvis nei: hvilket språk?_____

FAR:
☐ 9-/-10årig grunnskole
☐ 1-2 års videregående skole
☐ Videregående yrkesfaglig
☐ 3-årig videregående allmennfaglig (inkl. gymnas**)**
☐ Høgskole, universitet inntil 4 år (cand.mag, bachelor, sykepleier, lærer, ingeniør e.l.)
☐ Høgskole, universitet mer enn 4 år (hovedfag, master, embetseksamen)
☐ Annen utdannelse; beskriv:_____

Har far norsk som morsmål? ☐ ja ☐ nei; hvis nei: hvilket språk?_____

84. Hva er mors og fars yrkesmessige situasjon?

MOR:
☐ Fulltidsarbeidende (minst 30 t/u)
☐ Deltidsarbeidende (under 30 t/u)
☐ Arbeidsledig/på tiltak/arbeidssøkende

☐ Student/elev
☐ Hjemmearbeidende
☐ Trygdet/under attføring
☐ Annet

Mors yrke: _____

FAR:

☐ Fulltidsarbeidende (minst 30 t/u)
☐ Deltidsarbeidende (under 30 t/u)
☐ Arbeidsledig/på tiltak/arbeidssøkende
☐ Student/elev
☐ Hjemmearbeidende
☐ Trygdet/under attføring
☐ Annet

Fars yrke: _____

Vennligst fyll også ut de neste sidene som er internasjonale standardiserte spørsmål om atferd, psykisk helse og sosial fungering.

Fylles ut av foreldre

Barnets navn: ----------, f.dato:

Bruk blyant eller kulepenn ved utfylling. Kryss av inne i boksen - slik: ☐

Barnets klassetrinn: . klassetrinn

Utfylt av: Mor ☐ Far ☐ Begge ☐

Andre ☐ (evt. hvem ?) :……

Kryss av i en rubrikk for hvert utsagn nedenfor: **Stemmer ikke**, **Stemmer delvis** eller **Stemmer helt**.
Det er veldig viktig at du svarer på alle spørsmålene, selv om du ikke er sikker eller synes utsagnet virker rart. Om rubrikkene ikke passer helt ber vi deg likevel om å velge ett av alternativene.
Svar ut fra barnets oppførsel de siste 6 månedene eller dette skoleåret.
Dere vil kanskje reagere på at noen utsagn delvis gjentas og at rekkefølgen kan virke ulogisk. Det skyldes at dette er satt sammen av spørreskjemaer som brukes vitenskapelig i internasjonale undersøkelser

		Stemmer ikke	Stemmer delvis	Stemmer helt
1	Omtenksom, tar hensyn til andre menneskers følelser	☐	☐	☐
2	Rastløs, overaktiv, kan ikke være lenge i ro	☐	☐	☐
3	Klager ofte over hodepine, vondt i magen eller kvalme	☐	☐	☐
4	Deler gjerne med andre barn (godter, leker, andre ting)	☐	☐	☐
5	Har ofte raserianfall eller dårlig humør	☐	☐	☐
6	Ganske ensom, leker ofte alene	☐	☐	☐
7	Som regel lydig, gjør vanligvis det voksne ber om	☐	☐	☐
8	Mange bekymringer, virker ofte bekymret	☐	☐	☐
9	Hjelpsom hvis noen er såret, lei seg eller føler seg dårlig	☐	☐	☐
10	Stadig urolig eller i bevegelse	☐	☐	☐
11	Har minst en god venn	☐	☐	☐
12	Slåss ofte med andre barn eller mobber dem	☐	☐	☐
13	Ofte lei seg, nedfor eller på gråten	☐	☐	☐
14	Vanligvis likt av andre barn	☐	☐	☐
15	Lett avledet, mister lett konsentrasjonen	☐	☐	☐
16	Nervøs eller klengete i nye situasjoner, lett utrygg	☐	☐	☐
17	Snill mot yngre barn	☐	☐	☐
18	Lyver eller jukser ofte	☐	☐	☐
19	Plaget eller mobbet av andre barn	☐	☐	☐
20	Tilbyr seg ofte å hjelpe andre (foreldre, lærere, andre barn)	☐	☐	☐
21	Tenker seg om før han / hun gjør noe	☐	☐	☐
22	Stjeler hjemme, på skolen eller andre steder	☐	☐	☐
23	Kommer bedre overens med voksne enn med barn	☐	☐	☐
24	Redd for mye, lett skremt	☐	☐	☐
25	Fullfører oppgaver, god konsentrasjonsevne	☐	☐	☐

Samlet, synes du at barnet ditt har vansker med et eller flere av følgende områder: med følelser, konsentrasjon, oppførsel eller med å komme overens med andre mennesker?

☐ Nei ☐ Ja – små vansker ☐ Ja – tydelige vansker ☐ Ja - alvorlige vansker

Hvis du har svart "Ja", vennligst svar på følgende spørsmål:

Hvor lenge har disse vanskene vært tilstede?

Mindre enn 1 måned ☐ **1-5 måneder** ☐ **6-12 måneder** ☐ **Mer enn ett år** ☐

Blir barnet selv forstyrret eller plaget av vanskene?

Ikke i det hele tatt ☐ **Bare litt** ☐ **En god del** ☐ **Mye** ☐

Påvirker vanskene barnets dagligliv på noen av de følgende områder? (kryss av)

	Ikke i det hele tatt	**Bare litt**	**En god del**	**Mye**
Hjemme / i familien	☐	☐	☐	☐
Forhold til venner	☐	☐	☐	☐
Læring på skolen	☐	☐	☐	☐
Fritidsaktiviteter	☐	☐	☐	☐
Er vanskene en belastning for deg eller familien som helhet ?	☐	☐	☐	☐

Noen spørsmål til fra et annet internasjonalt spørreskjema:

		Stemmer ikke	Stemmer delvis	Stemmer helt
26	Gir et veslevoksent inntrykk	☐	☐	☐
27	Ses på som en "liten professor" av andre barn	☐	☐	☐
28	Lever delvis i sin egen verden med begrensede, spesielle interesser	☐	☐	☐
29	Har svært lett for å lære seg store mengder fakta utenat, men vanskeligere for å forklare mening og sammenheng	☐	☐	☐
30	Tolker alt som sies bokstavelig, selv uttrykk som "hoppe over middagen"	☐	☐	☐
31	Språket er formelt, omstendelig, gammeldags eller "robotlignende"	☐	☐	☐
32	Lager egne ord og uttrykk	☐	☐	☐
33	Har en stemme eller et tonefall som er annerledes enn vanlig	☐	☐	☐
34	Er overraskende dyktig på enkelte områder og svak på andre områder	☐	☐	☐
35	Snakker uten problemer, men tilpasser seg ikke situasjonen eller andres behov i en samtale	☐	☐	☐
36	Mangler empati (innlevelsesevne)	☐	☐	☐
37	Kommer med naive og pinlige bemerkninger	☐	☐	☐
38	Har avvikende blikkontakt	☐	☐	☐
39	Vil omgås klassekamerater, men vet ikke hvordan det gjøres	☐	☐	☐
40	Kan bare være sammen med andre på egne premisser	☐	☐	☐
41	Har ingen "bestevenn"	☐	☐	☐
42	Mangler "sunn fornuft"	☐	☐	☐
43	Er dårlig i lagspill eller gruppearbeid, har egne regler	☐	☐	☐
44	Har klossete, dårlig koordinerte, rare, spesielle bevegelser eller fakter	☐	☐	☐
45	Har ufrivillige ansikts- eller kroppsbevegelser	☐	☐	☐
46	Har problemer med å fullføre dagligdagse aktiviteter på grunn av tvangsmessige gjentakelser av visse handlinger	☐	☐	☐
47	Har spesielle rutiner som ikke kan endres	☐	☐	☐
48	Opptatt av eller knytter seg til ting/gjenstander på en særegen måte	☐	☐	☐
49	Mobbes av andre barn	☐	☐	☐
50	Har påfallende uvanlige ansiktsutrykk	☐	☐	☐
51	Har påfallende uvanlig kroppsholdning	☐	☐	☐
52	Kan ikke uttale enkelte ord eller lyder	☐	☐	☐
53	Greier ikke fortelle, forklare, eller uttrykke seg	☐	☐	☐
54	Har vanskelig for å forstå eller oppfatte ting som blir sagt	☐	☐	☐
55	Har vanskelig for å føre en samtale med andre	☐	☐	☐
56	Har problemer med å lese og skrive	☐	☐	☐
57	Har problemer med tallbegrep, matematikk	☐	☐	☐
58	Har ansiktstics (grimaser), rykninger i andre deler av kroppen, eller andre uvanlige bevegelser eller vaner	☐	☐	☐
59	Har ufrivillige ord eller lyder, f. eks. grynt, kremt, harking, banning	☐	☐	☐
60	Vasker seg mer enn normalt, er redd for smitte	☐	☐	☐
61	Må ofte sjekke eller kontrollere ting	☐	☐	☐
62	Er overdrevent opptatt av orden og symmetri	☐	☐	☐
63	Må ha gjentatte forsikringer og svar på spørsmål	☐	☐	☐

		Stemmer ikke	Stemmer delvis	Stemmer Helt
64	Forteller om plagsomme eller forstyrrende tanker	☐	☐	☐
65	Gjør alt for å ikke skuffe oss	☐	☐	☐
66	Hater å ikke være best	☐	☐	☐
67	Har veldig høye mål for seg selv	☐	☐	☐
68	Mister besinnelsen eller kontrollen	☐	☐	☐
69	Krangler med voksne	☐	☐	☐
70	Nekter å adlyde voksnes krav eller regler	☐	☐	☐
71	Irriterer andre med vilje	☐	☐	☐
72	Bebreider andre for egne feil eller dårlig oppførsel	☐	☐	☐
73	Er nærtagende eller blir lett irritert	☐	☐	☐
74	Er sint eller blir lett fornærmet	☐	☐	☐
75	Er slem eller hevnlysten	☐	☐	☐
76	Er ikke nøye med detaljer eller gjør slurvefeil i skolearbeidet	☐	☐	☐
77	Har vanskelig for å holde på oppmerksomheten i oppgaver eller lek	☐	☐	☐
78	Synes ikke å høre etter når han/hun snakkes direkte til	☐	☐	☐
79	Følger ikke instruksjoner eller fullfører ikke ting på skolen eller hjemme	☐	☐	☐
80	Har vanskelig for å organisere oppgaver og aktiviteter	☐	☐	☐
81	Unnviker, misliker eller er uvillig til å utføre oppgaver som krever vedvarende psykisk anstrengelse (f.eks. skolearbeid, lekser)	☐	☐	☐
82	Mister ting som er nødvendige for oppgaver eller aktiviteter	☐	☐	☐
83	Blir distrahert (forstyrret) av tilfeldige stimuli (ting rundt seg)	☐	☐	☐
84	Er glemsk i dagliglivet	☐	☐	☐
85	Har vanskelig for å sitte stille eller å holde hender eller føtter i ro	☐	☐	☐
86	Går fra plassen sin i klasserommet eller i andre situasjoner der det forventes at en sitter i ro	☐	☐	☐
87	Springer ofte omkring eller klatrer mye i situasjoner der dette ikke passer seg	☐	☐	☐
88	Har vanskelig med å leke eller holde på med fritidsaktiviteter på en rolig måte	☐	☐	☐
89	Er ”på farten” eller handler som ”drevet av en motor”	☐	☐	☐
90	Snakker veldig mye (”i ett kjør”)	☐	☐	☐
91	Buser ut med svar før spørsmålene er ferdig stilt	☐	☐	☐
92	Har problemer med å vente på sin tur	☐	☐	☐
93	Avbryter eller trenger seg på andre (f.eks. andres lek eller samtale)	☐	☐	☐
94	Snakker hjemme men ikke på skolen	☐	☐	☐
95	Blir ordentlig redd uten grunn	☐	☐	☐
96	Er redd for å være alene hjemme	☐	☐	☐
97	Andre sier at hun/han bekymrer seg for mye	☐	☐	☐
98	Er redd for å gå på skolen	☐	☐	☐
99	Er sjenert	☐	☐	☐
100	Har bevisst gått ned i vekt	☐	☐	☐

		Stemmer ikke	Stemmer delvis	Stemmer Helt
101	Har unormale tanker om vekt og kroppsform	☐	☐	☐
102	Unngår bestemte matsorter fordi de er fetende	☐	☐	☐
103	Driver fysisk trening på en overdreven måte	☐	☐	☐
104	Fremkaller selv oppkast eller brekninger	☐	☐	☐
105	Trøstespiser	☐	☐	☐
106	Har skyldfølelse i forbindelse med spising	☐	☐	☐
107	Følger strenge dietter eller ritualer for å kontrollere matinntaket	☐	☐	☐
108	Er vegetarianer	☐	☐	☐
109	Er fornøyd med utseendet sitt	☐	☐	☐
110	Er fornøyd med kroppen sin	☐	☐	☐
111	Forteller at hun/han føler seg for tykk	☐	☐	☐
112	Er fornøyd med spisevanene sine	☐	☐	☐
113	Har selv valgt en egen diett/kost som er forskjellig fra familiens	☐	☐	☐

Vi takker for at du/dere har vært villige til å delta i undersøkelsen om små for tidlig fødte barns helse og utvikling så langt. Undersøkelsen er viktig for å se om det er ting vi bør endre i den tidlige behandlingen av barna og for å forstå hva barna og dere som familie trenger av oppfølging og støtte i oppveksten. Vi vil gi tilbakemelding om resultatene fra studien.

Kan vi få lov å kontakte dere dersom vi har behov for å få tilleggsopplysninger?

☐ Ja ☐ Nei

Hvis **ja,** ber vi om å få oppgitt måter å kontakte dere på:

Navn: _____

Adresse: _____

Postnummer: ☐☐☐☐ Poststed: _____

Telefonnummer: Hjemme:_____ Mobil: _____

Sted:_____ **Dato:** _____ _____

Underskrift pårørende

Dere kan lese mer om undersøkelsen på Prosjekt Ekstrem Prematuritets hjemmeside på internett:
http://www.uib.no/mfr/prosjekter/ekstremprematuritet

VENNLIGST SE OVER AT DU HAR SVART PÅ ALLE SPØRSMÅLENE
Tusen takk for hjelpen !

Appendix 4

PREMATURSTUDIEN VED BARNEKLINIKKEN I BERGEN

UNDERSØKELSE AV LUNGEFUNKSJON, ARBEIDSKAPASITET OG LIVSKVALITET HOS BARN SOM ER FØDT FOR TIDLIG

Spørreskjema for ungdom

Løpenummer (fylles ut på Barneklinikken): ☐☐ - ☐☐☐

Kjære deltaker

Takk for at du vil være med i denne undersøkelsen igjen. I tillegg til lungeundersøkelsen, ønsker vi at du skal fylle ut noen spørreskjemaer som kan fortelle oss hvordan du har det. Det finnes ikke riktige eller gale svar. Det er viktig at du finner det alternativet som passer best for deg.

Du synes kanskje det er mange spørsmål, og at noen kan være vanskelig å svare på. Gjør så godt du kan og ta den tiden du trenger! Prøv å svare i den rekkefølgen spørsmålene står. Les spørsmål og forklaringer nøye.

Selv om noen av spørsmålene kan se like ut, er det viktig at du svarer på alle. Når du er ferdig, ber vi deg se etter om du har svart på alle spørsmålene.

Du svarer ved å krysse av i rutene. Hvis det er aktuelt å sette flere enn ett kryss, vil det stå i parentes etter spørsmålet.

Dine svar vil ikke bli vist til noen.

Takk for at du tar deg tid til å fylle ut spørreskjemaene !

Om deg selv

1. Kjønn
☐ Mann ☐ Kvinne

2. Alder
☐☐ år

3. Hvem bor du sammen med? *(Sett ett eller flere kryss)*
☐ Ingen
☐ Ektefelle /samboer
☐ Foreldre
☐ Andre personer over 18 år
☐ Personer under 18 år
☐ Institusjon / bofellesskap med tilsyn
☐ Egne barn

Om utdanning og arbeid

4.

	Elev med klasseromsbasert utdanning	Lærling	Er ikke i skolen
Velg det som best beskriver din hverdag	❍	❍	❍

5. Hvilken klasse går du i?

	Allmenfaglig	Yrkesfaglig
•1. videregående	☐	☐
•2. videregående	☐	☐
•3. videregående	☐	☐
•Folkehøgskole	☐	

•Annet (*spesifiser)*……..

6. Hvilke planer for videre utdanning har du? *(sett ett eller flere kryss)*
☐ Høgskole eller universitet i 4 år eller mer
☐ Høgskole eller universitet mindre enn 4 år
☐ Annen yrkesutdanning
☐ Ingen planer
☐ Vet ikke

Dersom du er elev eller lærling:

7. Hvor mange dager har du hatt fravær siste måneden?

8. Hvor mange enkelttimer (i tillegg til hele dager) fravær har du hatt siste måneden? _____

OM FORELDRE

9. Hvilken utdannelse har dine foreldre fullført?

Mor	❍ Grunnskole, ungdomsskole eller lign. ❍ Videregående skole med yrkesfag, yrkesskole, realskole ❍ Videregående skole med allmennfag, gymnas/artium ❍ Høgskole eller universitet, mindre enn 4 år ❍ Høgskole eller universitet, 4 år eller mer ❍ Vet ikke
Far	❍ Grunnskole, ungdomsskole eller lign. ❍ Videregående skole med yrkesfag, yrkesskole, realskole ❍ Videregående skole med allmennfag, gymnas/artium ❍ Høgskole eller universitet, mindre enn 4 år ❍ Høgskole eller universitet, 4 år eller mer ❍ Vet ikke

10. Hva er mors og fars yrkesmessige situasjon?

MOR:

☐ Fulltidsarbeidende (minst 30 t/u)
☐ Deltidsarbeidende (under 30 t/u)
☐ Arbeidsledig/på tiltak/arbeidssøkende
☐ Student/elev
☐ Hjemmearbeidende
☐ Trygdet/under attføring
☐ **Annet**

Mors yrke: _____

FAR:

☐ Fulltidsarbeidende (minst 30 t/u)
☐ Deltidsarbeidende (under 30 t/u)
☐ Arbeidsledig/på tiltak/arbeidssøkende
☐ Student/elev
☐ Hjemmearbeidende
☐ Trygdet/under attføring
☐ **Annet**

Fars yrke: _____

11. Bor dine (biologiske/adoptiv) foreldre sammen? ❍ Ja ❍ Nei

12. Hvor god råd synes du familien din har i forhold til de fleste andre?	Omtrent som de fleste andre	Bedre råd	Dårligere råd
	❍	❍	❍

Om fritid/aktivitet

13. *Utenom skoletiden:* **Hvor mange dager i uken driver du idrett, eller mosjonerer du så mye at du blir andpusten og/eller svett?** *(sett bare ett kryss)*

☐ Hver dag
☐ 4-6 ganger i uken
☐ 2-3 ganger i uken
☐ En gang i uken
☐ Mindre enn en gang i uken
☐ Aldri

14. *Utenom skoletiden*: **Til sammen hvor mange timer i uken driver du idrett eller mosjonerer du så mye at du blir andpusten og/eller svett:** *(sett bare ett kryss)*

☐ Ingen
☐ Omtrent 1/2 time
☐ Omtrent 1 time
☐ Omtrent 2-3 timer
☐ Omtrent 4-6 timer
☐ 7 timer eller mer

15. Er du aktivt medlem av et idrettslag?

Ja☐ Nei☐

16. Hvor lenge pleier du å holde på hver gang med disse aktivitetene? *(sett ett kryss for hver linje)*

	Mindre enn ½ time	½-1 time	Mer enn 1 time
•Ser på TV/DVD	☐	☐	☐
•Spiller PC/TV spill	☐	☐	☐
•Spiller, chatter eller surfer på nettet	☐	☐	☐

Om helse/helsetjenester

17. Har du funksjonsnedsettelse på noen av disse områdene??

	Nei	Litt	Middels	Mye
•Er bevegelseshemmet	☐	☐	☐	☐
•Har nedsatt syn	☐	☐	☐	☐
•Har nedsatt hørsel	☐	☐	☐	☐
•Hemmet på grunn av kroppslig sykdom	☐	☐	☐	☐
•Hemmet på grunn av psykiske plager	☐	☐	☐	☐

•Bruker du rullestol: ☐Ja ☐Nei

18. Har du hatt kontakt med følgende hjelpetilbud SISTE SKOLEÅR? Hvis ja, kryss av for hvor ofte.

❑ **Skolehelsetjeneste**
❍ Hver uke ❍ Hver måned ❍ Hver tredje måned ❍ Hvert halvår ❍ Sjeldnere

❑ **Spesialpedagogiske tiltak/spesialundervisning**
❍ Hver uke ❍ Hver måned ❍ Hver tredje måned ❍ Hvert halvår ❍ Sjeldnere

❑ **Pedagogisk psykologisk tjeneste (OT/PPT)**
❍ Hver uke ❍ Hver måned ❍ Hver tredje måned ❍ Hvert halvår ❍ Sjeldnere

❑ **Psykisk helsevern for barn og unge (BUP)**
❍ Hver uke ❍ Hver måned ❍ Hver tredje måned ❍ Hvert halvår ❍ Sjeldnere

❑ **Psykisk helsevern for voksne (VOP)**
❍ Hver uke ❍ Hver måned ❍ Hver tredje måned ❍ Hvert halvår ❍ Sjeldnere

❑ **Barnevernet**
❍ Hver uke ❍ Hver måned ❍ Hver tredje måned ❍ Hvert halvår ❍ Sjeldnere

Spørsmål om andre sykdommer

19. Har, eller har du hatt:

Atopisk *(kløende)* eksem? ☐ Nei ☐ Ja, tidligere ☐ Ja, fortsatt
Høysnue? ☐ Nei ☐ Ja, tidligere ☐ Ja, fortsatt
Andre allergiske sykdommer? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
Beskriv i så all:_____
Epilepsi? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
Dren i ørene? ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
Nedsatt hørsel ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
Hvis fortsatt, kryss av behandling: ☐ Ingen ☐ Høreapparat ☐ Cochleaimplantat ☐ Døv, ingen apparater

Skjeling ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
Svekket syn ☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt;
Hvis fortsatt; ☐ Nærsynt ☐ Langsynt ☐ Blind ett øye ☐ Blind begge øyne ☐ Annet, beskriv;_____
Bruker briller? ☐ Nei ☐ Ja, hvilken styrke? _____

20. Har du

Fjernet falsk mandel (polypp, adenoid) ☐ Nei ☐ Ja
Fjernet mandlene? ☐ Nei ☐ Ja
Hatt feberkramper? ☐ Nei ☐ Ja, sist år gammel
Hatt hjernehinnebetennelse? ☐ Nei ☐ Ja
Hatt hodeskade med tap av bevissthet og innleggelse i sykehus? ☐ Nei ☐ Ja
Nedsatt førlighet i armer og/eller ben? ☐ Nei ☐ Ja, Beskriv i så fall:_____

21. Har, eller har du hatt, andre sykdommer som ikke er nevnt ovenfor?

☐ Nei ☐ Ja; tidligere ☐ Ja, fortsatt
Beskriv i så fall:_____
_____
_____

22. Hvor ofte har du vært borte fra skolen pga sykdom de siste 12 månedene?

Mindre enn en uke☐ 1-2 uker☐ Mer enn 2 uker☐

Om luftveiene (fra ISAAC)

23. Har du noen gang hatt tung pust eller piping/surkling/tetthet i brystet?

Ja ☐ Nei ☐

*Hvis du har svart **nei**, gå til spørsmål* **28**

24. Har du hatt tung pust eller piping/surkling/tetthet i brystet i løpet av de siste 12 månedene?

Ja ☐ Nei ☐

*Hvis du har svart **nei**, gå til spørsmål* **28**

25. Hvor mange anfall av tung pust eller piping/surkling/tetthet i brystet har du hatt i løpet av de siste 12 månedene?

☐ Ingen
☐ 1 til 3
☐ 4 til 12
☐ Mer enn 12
☐ Har slike plager hele tiden

26. Hvor ofte har din søvn i gjennomsnitt blitt forstyrret på grunn av tung pust eller piping/surkling/tetthet i brystet de siste 12 månedene?

☐ Aldri våknet
☐ Mindre enn 1 natt pr. uke
☐ 1 eller flere netter pr. uke

27. Har piping/surkling/tetthet i brystet eller tung pust vært så alvorlig de siste 12 månedene at du har hatt problemer med å snakke slik at du bare kunne si ett eller to ord mellom hvert pust? Ja ☐ Nei ☐

28. Har du noen gang hatt astma? Ja ☐ Nei ☐

29. Har du i løpet av de siste 12 månedene hatt tung pust eller piping/surkling/tetthet i brystet under eller etter fysisk trening, aktiv lek eller mosjonering?

Ja ☐ Nei ☐

30. Har du i løpet av de siste 12 månedene hatt tørr hoste om natten, utenom hoste i forbindelse med en forkjølelse eller andre luftveisinfeksjoner?

Ja ☐ Nei ☐

31. Har du hatt lungebetennelser siden sist du var her?

☐ Nei
☐ Ja, 1-3 ganger

☐ Ja, 4-10 ganger
☐ Ja, flere enn 10 ganger

32. Opplever du pustebesvær utover normal andpustethet i forbindelse med anstrengelse?

Ja ☐ Nei ☐

Dersom ja:

Er pustebesværet verst *under* anstrengelse eller *rett etter* anstrengelse:
☐ under ☐ rett etter ☐ vet ikke

Er pustebesværet verst på *ut-pust* eller *inn-pust*:
☐ ut-pust ☐ inn-pust ☐ vet ikke

Er pustebesværet ledsaget av *smerter i brystet*:
☐ nei ☐ ja

33. Er hoste eller tung pust *etter* anstrengelse/trening et problem for deg?

Ja ☐ Nei ☐

Dersom ja:

Hvor mye plages du?:
☐ Ikke noe
☐ Litt
☐ Ganske mye
☐ Veldig mye

34. Har du diagnosen anstrengelses-utløst astma?

Ja ☐ Nei ☐

35. Har du pusteproblemer ut over det normale ved vanlig fysisk anstrengelse?

☐ Nei ☐ Litt mer enn normalt ☐ Mye mer enn normalt

36. Lager du "skrapelyder" eller andre unormale lyder fra strupen ved fysisk anstrengelse?

☐ Nei ☐ Litt ☐ Mye

Spørsmål om stemmen din

37. Er stemmen din mer hes enn hos andre på samme alder?

☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye mer ☐ Ekstremt

Om bruk av medisiner

38. Har du brukt astma-medisin i forbindelse med trening eller anstrengelse i løpet av de siste 12 månedene?

Ja ☐ Nei ☐

39. Har du brukt medisiner mot astma i løpet av de siste 12 månedene?

☐ Nei
☐ Ja, av og til
☐ Ja, regelmessig i mer enn 3 måneder

40. Dersom du har brukt medisiner mot astma i løpet av de siste 12 månedene, angi type medisiner: *(Kryss for de typene du har brukt - du kan krysse flere steder. De mest brukte angis med navn i parentes)*

☐ Medisiner som åpner luftrørene *(Bricanyl, Ventoline, Airomir, Oxis, Serevent)*
☐ Kortison til inhalasjon *(Pulmicort, Becotide, Aerobec, Flutide, Alvesco)*
☐ Medisin som både åpner og forebygger *(Symbicort , Seretide, Relvar)*
☐ Singulair tabletter *(Montelukast)*
☐ Lomudal til inhalasjon

41. Hvor ofte de siste 3 månedene har du brukt reseptfrie medisiner mot noen av plagene nedenfor? ***(medisiner ikke foreskrevet av lege, for eksempel kjøpt på butikk eller apotek. Sett ett kryss pr. linje)***

	Aldri	1 dag i uken eller sjeldnere	2 dager i uken	3 dager i uken	4 dager i i uken eller mer
•Hodepine	☐	☐	☐	☐	☐
•Muskel-/leddsmerter	☐	☐	☐	☐	☐
•Magesmerter	☐	☐	☐	☐	☐
•Ryggsmerter	☐	☐	☐	☐	☐
•Andre plager	☐	☐	☐	☐	☐

42. Bruker du medisiner som du har fått av lege på resept?

Ja ☐ Nei ☐

Om kosthold og spisevaner

43. Står du på diett/kosthold ordinert av lege?

Ja ☐ Nei ☐

Hvis Ja, spesifiser:_____

44. Hvor ofte spiser du til vanlig følgende måltider? *(Sett ett kryss for hver linje)*

	Hver dag	4-6 dager i uken	1-3 dager i uken	Sjelden eller aldri
•Frokost	☐	☐	☐	☐
•Matpakke/formiddagsmat	☐	☐	☐	☐
•Middag	☐	☐	☐	☐
•Kveldsmat	☐	☐	☐	☐

45. Nedenfor er en liste over ting som gjelder spisevaner. Opplever du noe av dette? *(Sett ett kryss for hver linje)*

	Aldri	Sjelden	Ofte	Alltid
•Når jeg først har begynt å spise, kan det være vanskelig å stoppe	☐	☐	☐	☐
•Jeg kaster opp etter at jeg har spist	☐	☐	☐	☐
•Jeg bruker for mye tid til å tenke på mat	☐	☐	☐	☐
•Jeg føler at maten kontrollerer livet mitt	☐	☐	☐	☐
•Når jeg spiser, skjærer jeg maten opp i små biter	☐	☐	☐	☐
•Jeg bruker lengre tid enn andre på et måltid	☐	☐	☐	☐
•Eldre mennesker synes at jeg er for tynn	☐	☐	☐	☐
•Jeg føler at andre presser meg til å spise	☐	☐	☐	☐

46. Hvor ofte spiser/drikker du vanligvis noe av følgende? *(Sett ett kryss for hver linje)*

	Hver dag	Oftere enn 3 dager i uken	Sjeldnere enn 3 dager i uken	Aldri
•Grønnsaker	☐	☐	☐	☐
•Frukt	☐	☐	☐	☐
•Brødmat	☐	☐	☐	☐
•Melk	☐	☐	☐	☐
•Kjøtt	☐	☐	☐	☐
•Fisk	☐	☐	☐	☐
•Godteri	☐	☐	☐	☐
•Cola/brus/saft med sukker	☐	☐	☐	☐
•Cola/brus/saft uten sukker	☐	☐	☐	☐
•Fastfood (*hamburger, pizza, pølser, o l)*	☐	☐	☐	☐

Om tobakk og alkohol

47. Har du prøvd å røyke? *(minst en sigarett)* Ja ☐ Nei ☐

*Hvis du har svart "**nei**", gå til spørsmål* **50**

48. Røyker du? *(sett ett kryss og oppgi evt. antall sigaretter)*

☐ Ja, jeg røyker ca _____ sigaretter daglig
☐ Ja, jeg røyker av og til, men ikke daglig
☐ Nei, ikke nå, men tidligere røykte jeg av og til
☐ Nei, ikke nå lenger, men tidligere røykte jeg ca. _____sigaretter daglig
☐ Nei, jeg røyker ikke

49. Hvis du røyker eller har røykt daglig, hvor gammel var du da du begynte å røyke?
_____år gammel

50. Bruker du eller har du brukt snus eller lignende? *(sett ett kryss)*

☐ Nei, aldri ☐Ja, men jeg har sluttet ☐Ja, av og til ☐Ja, hver dag

51. Hvis du bruker eller har brukt snus, hvor gammel var du da du begynte med snus?
_____år gammel

52.

	Ja	Nei	Vet ikke
Har du noen gang prøvd å drikke alkohol? (Dvs. alkoholholdig øl, vin, brennevin eller hjemmebrent)	❍	❍	❍

*Hvis du har svart "**nei**" gå til spørsmål* **60**

53. Hvor gammel var du da du begynte å drikke alkohol? _____år gammel

	Nei, aldri	Ja, en gang	Ja, 2-3 ganger	Ja, 4-10 ganger	Ja, mer enn 10 ganger
54. Har du noen gang drukket sa mye alkohol at du har vært tydelig beruset (full) ?	❍	❍	❍	❍	❍

55. Omtrent hvor mye øl, cider, rusbrus, vin eller brennevin drikker du vanligvis i løpet avto uker? Regn ikke med alkoholfritt øl.

	antall
Øl - flasker (0,33 dl):	
Cider/ Rusbrus (ca 0,33 dl):	
Vin - antall glass (ca 1,5 dl):	
Brennevin - antall glass (ca 0,4 dl):	
Hjemmebrent - antall glass (ca 0,4 dl):	

56. På hvilke ukedager drikker du som oftest alkoholholdige drikker? (Sett ett eller flere kryss)

❍ Fredager ❍ Lørdager ❍ Andre dager i uken

57.

	Ja	Nei
Har du noen gang prøvd hasj, marihuana eller andre narkotiske stoffer?	❍	❍
Har du noen gang brukt anabole steroider?	❍	❍

58.

	Ja	Nei
Har du noen gang vært med i bil kjørt av noen (inkludert deg selv) som var høy, eller hadde brukt alkohol eller andre rusmiddel?	❍	❍
Bruker du noen gang alkohol eller rusmiddel for å slappe av, tro bedre om deg selv eller passe inn?	❍	❍
Bruker du noen gang alkohol eller rusmiddel alene?	❍	❍
Glemmer du noen gang ting du har gjort når du var påvirket av alkohol eller rusmiddel?	❍	❍
Sier familie eller venner at du bør kutte ned på alkohol eller rusmiddelbruk?	❍	❍
Har du kommet i vansker når du har brukt alkohol eller rusmiddel?	❍	❍

Om smerter

59. I løpet av de siste 6 månedene: Hvor ofte har du hatt følgende plager? (Sett ett kryss for hver linje)

	Omtrent hver dag	Mer enn én gang i uken	Omtrent hver uke	Omtrent hver måned	Sjelden eller aldri
Hodepine	❍	❍	❍	❍	❍
Vondt i magen	❍	❍	❍	❍	❍
Vondt i ryggen	❍	❍	❍	❍	❍
Svimmel	❍	❍	❍	❍	❍
Vondt i nakke og skuldre	❍	❍	❍	❍	❍

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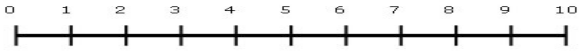
60. Hvor sterk er denne smerten som har plaget deg mest, vanligvis? *(Fint om du setter ring rundt det tallet på linjen som passer best for deg - fra ingen smerte til den verst tenkelige smerte)*



Ingen smerte — Verst tenkelige smerte

61. Stemmer noe av det som står nedenfor for deg? *(sett ett kryss for hver linje)*

	Stemmer	Stemmer ikke
•Smerter gjør det vanskelig for meg å sovne	☐	☐
•Smerter forstyrrer den gode nattesøvnen min	☐	☐
•Smerter gjør det vanskelig å sitte i skoletimen	☐	☐
•Smerter gjør det vanskelig for meg å gå merr enn en kilometer	☐	☐
•På grunn av smerter har jeg problemer i gymtimen	☐	☐

62. Har smertene alt i alt hindret deg i å utføre daglige aktiviteter? *(ett kryss pr. linje)*

	Nei	Ja, av og til	Ja, ofte
•På skolen	☐	☐	☐
•I fritiden	☐	☐	☐

Hvis ja, **hva slags smerter hindret deg i å utføre daglige aktiviteter?** *(sett eller flere kryss)*

Hodepine/migrene☐ Magesmerter☐ Muskel-/leddsmerter☐ Andre smerter☐

Om hvordan du har det

63. Vennligst kryss av for hvert utsagn: Stemmer ikke, Stemmer delvis eller Stemmer helt. Prøv å svare på alt selv om du ikke er helt sikker eller synes utsagnet virker rart. Svar på grunnlag av hvordan du har hatt det de siste 6 månedene.

	Stemmer ikke	Stemmer delvis	Stemmer helt
Jeg prøver å være hyggelig mot andre. Jeg bryr meg om hva de føler	❍	❍	❍
Jeg er rastløs. Jeg kan ikke være lenge i ro	❍	❍	❍
Jeg har ofte hodepine, vondt i magen eller kvalme	❍	❍	❍
Jeg deler gjerne med andre (mat, spill, andre ting)	❍	❍	❍
Jeg blir ofte sint og har kort lunte	❍	❍	❍
Jeg er ofte for meg selv. Jeg gjør som regel ting alene	❍	❍	❍
Jeg gjør som regel det jeg får beskjed om	❍	❍	❍
Jeg bekymrer meg mye	❍	❍	❍
Jeg stiller opp hvis noen er såret, lei seg eller føler seg dårlig	❍	❍	❍
Jeg er stadig urolig eller i bevegelse	❍	❍	❍
Jeg har en eller flere gode venner	❍	❍	❍
Jeg slåss mye. Jeg kan få andre til å gjøre det jeg vil	❍	❍	❍
Jeg er ofte lei meg, nedfor eller på gråten	❍	❍	❍
Jeg blir som regel likt av andre på min alder	❍	❍	❍
Jeg blir lett distrahert, jeg synes det er vanskelig å konsentrere meg	❍	❍	❍
Jeg blir nervøs i nye situasjoner. Jeg blir lett usikker	❍	❍	❍
Jeg er snill mot de som er yngre enn meg	❍	❍	❍
Jeg blir ofte beskyldt for å lyve eller jukse	❍	❍	❍
Andre barn eller unge plager eller mobber meg	❍	❍	❍
Jeg tilbyr meg ofte å hjelpe andre (foreldre, lærere, andre barn/unge)	❍	❍	❍
Jeg tenker meg om før jeg handler (gjør noe)	❍	❍	❍
Jeg tar ting som ikke er mine hjemme, på skolen eller andre steder	❍	❍	❍
Jeg kommer bedre overens med voksne enn de på min egen alder	❍	❍	❍
Jeg er redd for mye, jeg blir lett skremt	❍	❍	❍
Jeg fullfører oppgaver. Jeg er god til å konsentrere meg	❍	❍	❍

	Nei	Ja - små vansker	Ja - tydelige vansker	Ja - alvorlige vansker
64. Samlet, synes du at du har vansker på ett eller flere av følgende områder: med følelser, konsentrasjon, oppførsel eller med å komme overens med andre mennesker?	❍	❍	❍	❍

65. *Hvis noen form for ja, kryss av:*

	Mindre enn en måned	1-5 måneder	6-12 måneder	Mer enn ett år
Hvor lenge har disse vanskene vært tilstede?	❍	❍	❍	❍

	Ikke i det hele tatt	Bare litt	En god del	Mye
Forstyrrer eller plager vanskene deg?	❍	❍	❍	❍

66. Virker vanskene inn på livet ditt på noen av disse områdene?

	Ikke i det hele tatt	Bare litt	En god del	Mye
HJEMME / I FAMILIEN	❍	❍	❍	❍
FORHOLD TIL VENNER	❍	❍	❍	❍
LÆRING PÅ SKOLEN	❍	❍	❍	❍
FRITIDSAKTIVITETER	❍	❍	❍	❍

	Ikke i det hele tatt	Bare litt	En god del	Mye
67. Er vanskene en belastning for de rundt deg (familie, venner, lærere osv.) ?	❍	❍	❍	❍

68.

	Stemmer ikke	Stemmer delvis	Stemmer helt
Synes du det er vanskelig å omgås med eller å få kontakt med mennesker, spesielt personer på din egen alder?	❍	❍	❍
Foretrekker du å være alene heller enn å være sammen med andre mennesker?	❍	❍	❍
Har du problemer med å oppfatte sosiale signaler?	❍	❍	❍
Hender det at andre mennesker påpeker at din oppførsel eller dine følelsesmessige reaksjoner er upassende eller sårende?	❍	❍	❍
Har du en sterk interesse eller hobby som opptar så mye av tiden din at det går utover andre aktiviteter?	❍	❍	❍
Synes du eller andre at du har svært faste rutiner eller at du er svært opptatt av dine interesser?	❍	❍	❍
Synes du eller andre mennesker at du påtvinger andre dine rutiner eller interesser?	❍	❍	❍

69. Her blir du spurt om ting du kan ha gjort i løpet av det siste året som har forårsaket problemer for deg selv eller andre.

	Stemmer helt	Stemmer delvis	Stemmer ikke
Jeg blir ordentlig redd uten grunn	❍	❍	❍
Jeg er redd for å være alene hjemme	❍	❍	❍
Folk sier til meg at jeg bekymrer meg for mye	❍	❍	❍
Jeg er redd for å gå på skolen	❍	❍	❍
Jeg er sjenert	❍	❍	❍

	Stemmer helt	Stemmer delvis	Stemmer ikke
Jeg vasker meg mer enn normalt. Jeg er redd for smitte.	❍	❍	❍
Jeg må ofte sjekke eller kontrollere ting.	❍	❍	❍
Jeg er opptatt av orden og symmetri.	❍	❍	❍
Jeg må ofte ha gjentatte forsikringer og svar på spørsmål.	❍	❍	❍
Jeg har plagsomme eller forstyrrende tanker.	❍	❍	❍

	Stemmer helt	Stemmer delvis	Stemmer ikke
Jeg gjør alt jeg kan for ikke å skuffe foreldrene mine	❍	❍	❍
Jeg hater å ikke være best	❍	❍	❍
Mine foreldre forventer at jeg skal gjøre ting perfekt	❍	❍	❍
Dersom jeg ikke kan gjøre ting perfekt kan jeg like gjerne la være	❍	❍	❍
Jeg har veldig høye mål for meg selv	❍	❍	❍
Bare de beste resultater er gode nok	❍	❍	❍

	Stemmer helt	Stemmer delvis	Stemmer ikke
Jeg er fornøyd med spisevanene mine	❍	❍	❍
Jeg trøstespiser	❍	❍	❍
Jeg har skyldfølelse i forbindelse med spising	❍	❍	❍
Jeg må ha strenge dietter for å kontrollere hvor mye jeg spiser	❍	❍	❍
Jeg synes jeg er for tykk	❍	❍	❍

70. Hvor høy er du (cm) ?

71. Hvor mye veier du (kg) ?

72. Hvordan vurderer du din egen vekt?

❍ Svært undervektig	❍ Svært undervektig	❍ Litt undervektig	❍ Passelig	❍ Litt overvektig	❍ Svært overvektig

73.	Aldri	Sjelden	I blant	Ofte	Svært ofte
Hvor ofte har du problemer med å fullføre en oppgave etter at de interessante delene er unnagjort?	❍	❍	❍	❍	❍
Hvor ofte er det vanskelig for deg å få orden på ting når du skal utføre en oppgave som krever organisering?	❍	❍	❍	❍	❍
Hvor ofte har du problemer med å huske avtaler eller forpliktelser?	❍	❍	❍	❍	❍
Når du har en oppgave som krever at du tenker nøye igjennom det du skal gjøre, hvor ofte unngår eller utsetter du å begynne på den?	❍	❍	❍	❍	❍
Hvor ofte sitter du og fikler med noe når du må sitte lenge i ro?	❍	❍	❍	❍	❍
Hvor ofte føler du deg overdrevet aktiv og tvunget til å gjøre noe, som om du var drevet av en indre motor?	❍	❍	❍	❍	❍
Hvor ofte gjør du slurvefeil når du må jobbe med en kjedelig eller vanskelig oppgave?	❍	❍	❍	❍	❍
Hvor ofte har du problemer med å holde oppmerksomheten oppe når du gjør kjedelig eller ensformig arbeid?	❍	❍	❍	❍	❍
Hvor ofte har du vansker med å konsentrere deg om hva folk sier, selv når de snakker direkte til deg	❍	❍	❍	❍	❍
Hvor ofte har du vanskeligheter med å finne igjen ting hjemme eller på jobb?	❍	❍	❍	❍	❍
Hvor ofte blir du distrahert av aktiviteter eller lyder rundt deg?	❍	❍	❍	❍	❍
Hvor ofte forlater du plassen din på møter eller i andre situasjoner der det forventes at du blir sittende?	❍	❍	❍	❍	❍
Hvor ofte føler du deg rastløs eller urolig i kroppen?	❍	❍	❍	❍	❍
Hvor ofte har du vanskelig for å ta det med ro og slappe av når du har tid for deg selv?	❍	❍	❍	❍	❍
Hvor ofte opplever du å snakke for mye i sosiale sammenhenger?	❍	❍	❍	❍	❍
Hvor ofte opplever du at du fullfører setninger for andre før de rekker å fullføre dem selv?	❍	❍	❍	❍	❍
Hvor ofte har du problemer med å vente på tur i situasjoner der dette er nødvendig?	❍	❍	❍	❍	❍
Hvor ofte avbryter du andre når de holder på med noe?	❍	❍	❍	❍	❍
Hvor ofte synes du det er vanskelig å fullføre oppgaver tilfredsstillende innenfor en gitt tidsramme?	❍	❍	❍	❍	❍
Hvor ofte synes du det er vanskelig å prioritere arbeidsoppgaver i situasjoner hvor dette er nødvendig?	❍	❍	❍	❍	❍

73.	Aldri	Sjelden	I blant	Ofte	Svært ofte
Hvor ofte har du tatt impulsive beslutninger uten å tenke gjennom konsekvensene?	❍	❍	❍	❍	❍
Hvor ofte har du hatt vansker med å begrense deg selv (f.eks fra å drikke for mye eller bruke mer penger enn vanlig)?	❍	❍	❍	❍	❍
Hvor ofte har du kjørt fortere enn andre?	❍	❍	❍	❍	❍
Hvor ofte kjører du uforsvarlig?	❍	❍	❍	❍	❍

74. De følgende spørsmålene handler om hva du har følt og gjort de siste to ukene. Hvis en setning stemte om deg mesteparten av tiden, kryss av "riktig". Hvis den bare stemte noen ganger, kryss av "noen ganger riktig". Hvis en setning ikke stemte om deg, kryss av "ikke riktig".

	Riktig	Noen ganger riktig	Ikke riktig
Jeg var lei meg eller ulykkelig	❍	❍	❍
Jeg var ikke glad for noe	❍	❍	❍
Jeg følte meg så trøtt at jeg bare ble sittende uten å gjøre noen ting	❍	❍	❍
Jeg var veldig rastløs	❍	❍	❍
Jeg følte meg lite verdt	❍	❍	❍
Jeg gråt mye	❍	❍	❍
Jeg syntes det var vanskelig å tenke klart eller konsentrere meg	❍	❍	❍
Jeg hatet meg selv	❍	❍	❍
Jeg følte meg som et dårlig menneske	❍	❍	❍
Jeg følte meg ensom	❍	❍	❍
Jeg tenkte at ingen egentlig var glad i meg	❍	❍	❍
Jeg tenkte at jeg aldri kunne bli så god som andre barn/ungdommer	❍	❍	❍
Jeg gjorde alt galt	❍	❍	❍

75. Tenk på hvordan du har hatt det den siste måneden. Hvordan du har tenkt og følt om deg selv, og om viktige mennesker omkring deg. Vennligst kryss av i boksen som er nærmest det som passer for deg. Det er ingen riktige eller gale svar.

	Helt enig	Litt enig	Middels	Litt uenig	Helt uenig
Jeg kommer i mål dersom jeg står på	❍	❍	❍	❍	❍
Jeg fungerer best når jeg lager meg klare mål	❍	❍	❍	❍	❍
Jeg har noen venner/familiemedlemmer som pleier å oppmuntre meg	❍	❍	❍	❍	❍
Jeg er fornøyd med livet mitt til nå	❍	❍	❍	❍	❍

	Helt enig	Litt enig	Middels	Litt uenig	Helt uenig
I familien min er vi enige om hva som er viktig i livet	❍	❍	❍	❍	❍
Jeg får lett andre til å trives sammen med meg	❍	❍	❍	❍	❍
Jeg vet hvordan jeg skal nå målene mine	❍	❍	❍	❍	❍
Jeg legger alltid en plan før jeg begynner med noe nytt	❍	❍	❍	❍	❍
Vennene mine holder alltid sammen	❍	❍	❍	❍	❍
Jeg trives godt i familien min	❍	❍	❍	❍	❍
Jeg har lett for å finne nye venner	❍	❍	❍	❍	❍
Når det er umulig for meg å forandre på ting slutter jeg å gruble på dem	❍	❍	❍	❍	❍
Jeg er flink til å organisere tiden min	❍	❍	❍	❍	❍
Jeg har noen nære venner/familiemedlemmer som virkelig bryr seg om meg	❍	❍	❍	❍	❍
I familien min er vi enig om det meste	❍	❍	❍	❍	❍
Jeg er flink til å snakke med nye folk	❍	❍	❍	❍	❍
Jeg føler jeg er dyktig	❍	❍	❍	❍	❍
I familien min har vi regler som forenkler hverdagen	❍	❍	❍	❍	❍
Jeg har alltid noen som kan hjelpe meg når jeg trenger det	❍	❍	❍	❍	❍
Når jeg skal velge noe vet jeg oftest hva som blir riktig for meg	❍	❍	❍	❍	❍
Familien min ser positivt på tiden framover selv om det skjer noe veldig leit	❍	❍	❍	❍	❍
Jeg finner alltid noe artig å snakke om	❍	❍	❍	❍	❍
Min tro på meg selv får meg gjennom vanskelige perioder	❍	❍	❍	❍	❍
I familien min støtter vi opp om hverandre	❍	❍	❍	❍	❍
Jeg finner alltid på noe trøstende å si til andre som er lei seg	❍	❍	❍	❍	❍
I motgang har jeg en tendens til finne noe bra jeg kan vokse på	❍	❍	❍	❍	❍

Om søvn

	Stemmer helt	Stemmer delvis	Stemmer ikke
76. Jeg har problemer med innsovning og/eller våkner ofte	❍	❍	❍

Dersom stemmer helt/ stemmer delvis:

77. Hvor lenge har du hatt disse vanskene?

78. Hvor mange netter i uken har du:

	0	1	2	3	4	5	6	7
- innsovningsvansker.	❍	❍	❍	❍	❍	❍	❍	❍
- våkner ofte.	❍	❍	❍	❍	❍	❍	❍	❍

	Stemmer helt	Stemmer delvis	Stemmer ikke
79. Jeg snorker (eller andre sier jeg snorker)	❍	❍	❍

	Stemmer helt	Stemmer delvis	Stemmer ikke
80. Kjenner du deg søvnig eller trøtt om dagen?	❍	❍	❍

Dersom stemmer helt/stemmer delvis:

81. Hvor mange dager i uken opplever du

	0	1	2	3	4	5	6	7
- søvnig (jeg dupper lett av).	❍	❍	❍	❍	❍	❍	❍	❍
- trøtt (er sliten/uopplagt).	❍	❍	❍	❍	❍	❍	❍	❍

82.

	Hverdager	Helg
Når legger du deg vanligvis?		
Når står du vanligvis opp?		

83.

	Timer	Minutter
Hvor lang tid går det vanligvis fra du legger deg til du sovner?		
Hvor lenge er du våken i løpet av natten (etter at du først har sovnet)?		
Hvor mye søvn trenger du for å føle deg uthvilt?		

84.

	Aldri	Sjeldent (noen ganger per år)	Iblandt (noen ganger per måned)	For det meste (flere ganger i uken)	Alltid (hver dag)
Hvor ofte tar du deg en blund på dagtid?	❍	❍	❍	❍	❍
Hvor ofte forsover du deg til skolen?	❍	❍	❍	❍	❍

85.

	Timer	Minutter
Hvor lang tid går det vanligvis fra du legger deg til du sovner?		
Hvor lenge er du våken i løpet av natten (etter at du først har sovnet)?		
Hvor mye søvn trenger du for å føle deg uthvilt?		

86. Hvor mange av de viste elektroniske gjenstandene benytter du på soverommet den siste timen før du sovner? Sett kryss.

___ PC
___ Mobiltelefon
___ MP3-spiller
___ Nettbrett
___ Spillekonsoll (Playstation, Xbox, WII etc)
___ TV

Takk for din deltakelse!

ID. NR____

KIDSCREEN SPØRRESKJEMA

BARNE/UNGDOMSVERSJONEN

Dato: _____ _____
Måned *År*

Hei,

Hvordan har du det? Hvordan føler du deg? Dette er det vi ønsker at du skal fortelle oss. Les alle spørsmålene nøye. Hvilket svar tenker du først på? Velg det svaret som passer best til svaret ditt og kryss av.

Husk:

Dette er ikke en prøve, så det er ikke noe galt eller riktig svar. Det er viktig at du svarer på alle spørsmålene og at du krysser av tydelig. Når du skal svare er det fint om du prøver å huske den siste uka. Du trenger ikke vise svarene dine til noen. Ingen som kjenner deg vil se på skjemaet når du har fylt det ut.

Er du gutt eller jente?

○ Jente ○ Gutt

Hvor gammel er du?

_____ år

Når er du født

Dato___.____.___

Har du en langvarig funksjonshemming, sykdom eller medisinsk tilstand?

○ Nei

○ Ja Hvilken _____

1. Fysisk aktivitet og helse

1. Til vanlig, hvordan vil du si at helsen din er?

- ○ utmerket
- ○ veldig bra
- ○ bra
- ○ ganske bra
- ○ dårlig

	Når du tenker på den siste uka…	Ikke I det hele tatt	litt	ganske	veldig	I høy grad
2.	Har du følt deg frisk og sprek?	○	○	○	○	○
3.	Har du vært fysisk aktiv (for eksempel løpt, klatret, syklet)?	○	○	○	○	○
4.	Har du kunnet løpe bra?	○	○	○	○	○

	Når du tenker på den siste uka..	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
5.	Har du følt deg full av energi?	○	○	○	○	○

2. Følelser

	Når du tenker på den siste uka...	Ikke i det hele tatt	Litt	Ganske	Veldig	I høy grad
1.	Har livet ditt vært bra?	○	○	○	○	○
2.	Har du vært glad for at du lever?	○	○	○	○	○
3.	Har du følt deg fornøyd med livet ditt?	○	○	○	○	○

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
4.	Har du vært i godt humør?	○	○	○	○	○
5.	Har du følt deg glad?	○	○	○	○	○
6.	Har du hatt det gøy?	○	○	○	○	○

3. Humør

	Når du tenker på den siste uka ...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
1.	Har du følt at alt du gjør blir feil?	○	○	○	○	○
2.	Har du følt deg trist?	○	○	○	○	○
3.	Har du følt deg så ille/elendig at du ikke har villet gjøre noe?	○	○	○	○	○
4.	Har du følt at alt i livet ditt går galt?	○	○	○	○	○
5.	Har du vært skikkelig lei?	○	○	○	○	○
6.	Har du følt deg ensom?	○	○	○	○	○
7.	Har du følt deg presset?	○	○	○	○	○

4. Om deg selv

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
1.	Har du vært fornøyd med deg selv slik du er?	○	○	○	○	○
2.	Har du vært fornøyd med klærne dine?	○	○	○	○	○
3.	Har du vært bekymret for utseendet ditt?	○	○	○	○	○
4.	Har du vært sjalu på andre jenters eller gutters utseende?	○	○	○	○	○
5.	Ville du gjerne forandre noe ved kroppen din?	○	○	○	○	○

5. Fritid

	Når du tenker på den siste uka ...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
1.	Har du hatt nok tid for deg selv?	○	○	○	○	○
2.	Har du kunnet gjøre de tingene du ønsker i fritiden din?	○	○	○	○	○
3.	Har du hatt nok muligheter til å være ute?	○	○	○	○	○
4.	Har du hatt nok tid til å være sammen med venner?	○	○	○	○	○
5.	Har du kunnet velge hva du vil gjøre i fritiden din?	○	○	○	○	○

6. Familie og hjemmeliv

	Når du tenker på den siste uka...	Ikke i det hele tatt	Litt	Ganske	Veldig	I høy grad
1.	Har moren/faren din forstått deg?	○	○	○	○	○
2.	Har du følt at moren/faren din er glad I deg?	○	○	○	○	○

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
3.	Har du vært glad hjemme?	○	○	○	○	○
4.	Har moren/faren din hatt nok tid til deg?	○	○	○	○	○
5.	Har moren/faren din behandlet deg rettferdig?	○	○	○	○	○
6.	Har du kunnet snakke med moren/faren din når du har lyst?	○	○	○	○	○

7. Økonomi

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
1.	Har du hatt nok penger til å gjøre de samme tingene som vennene dine?	○	○	○	○	○
2.	Har du hatt nok penger til det du trenger?	○	○	○	○	○

	Når du tenker på den siste uka...	Ikke I det hele tatt	litt	ganske	veldig	I høy grad
3.	Har du hatt nok penger til å gjøre ting sammen med vennene dine?	○	○	○	○	○

8. Venner

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
1.	Har du vært sammen med vennene dine?	○	○	○	○	○
2.	Har du gjort ting sammen med andre jenter og gutter?	○	○	○	○	○
3.	Har du hatt det gøy sammen med vennene dine?	○	○	○	○	○
4.	Har du og vennene dine hjulpet hverandre?	○	○	○	○	○
5.	Har du kunnet snakke med vennene dine om alt?	○	○	○	○	○
6.	Har du kunnet stole på vennene dine?	○	○	○	○	○

9. Skole

	Når du tenker på den siste uka...	Ikke i det hele tatt	Litt	Ganske	Veldig	I høy grad
1.	Har du vært glad på skolen?	○	○	○	○	○
2.	Har du klart deg bra på skolen?	○	○	○	○	○
3.	Har du vært fornøyd med lærerne dine?	○	○	○	○	○

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
4.	Har du klart å følge med på skolen?	○	○	○	○	○
5.	Har du likt å være på skolen?	○	○	○	○	○
6.	Har du kommet godt ut av det med lærerne dine?	○	○	○	○	○

10. Mobbing

	Når du tenker på den siste uka...	Aldri	Sjelden	Ganske ofte	Veldig ofte	Alltid
1.	Har du vært redd for andre jenter og gutter?	○	○	○	○	○
2.	Har du blitt ertet av andre jenter og gutter?	○	○	○	○	○
3.	Har du blitt mobbet av andre jenter og gutter?	○	○	○	○	○

Appendix 5

Prosjekt Ekstrem Prematuritet

Et nasjonalt samarbeidsprosjekt ledet av Medisinsk fødselsregister, Barneklinikken, Haukeland universitetssykehus og Universitetet i Bergen

Vekst, helse og utvikling hos barn født ekstremt for tidlig

Navn:…….. **Dato:**……

Studie ID:……

DEL A

1. **Hvordan vil du beskrive stemmen din ved vanlig tale?**

   ☐ Utmerket ☐ God ☐ Litt svak/utydelig ☐ Meget svak/utydelig

   ☐ Har ikke stemme

2. **Er stemmen din svak eller utydelig slik at den begrenser muligheten for å bli hørt i et støyende miljø?**

   ☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

3. **Er stemmen slik at den påvirker deltagelse i skolearbeid eller vanlige sosiale aktiviteter?**

   ☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

4. **"Sprekker" stemmen når du roper?**

   ☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

5. **Er stemmen mer hes enn hos andre på din alder?**

   ☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

6. **Er stemmen slik at det har påvirket din deltagelse i sang?**

   ☐ Ikke i det hele tatt ☐ Litt ☐ Moderat ☐ Mye ☐ Ekstremt

7. **Har du pusteproblemer ut over det normale ved fysisk anstrengelse?**

   ☐ Nei ☐ Litt mer enn normalt ☐ Mye mer enn normalt

(Dersom du krysser for *litt mer* eller *mye mer* enn normalt: Fyll ut DEL B)

8. Lager du "skrapelyder" eller andre unormale lyder fra strupen ved fysisk anstrengelse?

□ Nei □ Litt □ Mye

9. Hvor mange GANGER i uken driver du med idrett, eller mosjonerer du så mye at du blir andpusten og/ eller svett?

□ Hver dag □ 4-6 ganger i uken □ 2-3 ganger i uken □ En gang i uken
□ En gang i mnd □ Mindre enn en gang i mnd □ Aldri

10. Hvor mange TIMER i uken driver du med idrett, eller mosjonerer du så mye at du blir andpusten og/eller svett?

□ Ingen □ omtrent ½ time □ omtrent 1 time □ omtrent 2-3 timer
□ omtrent 4-6 timer □ 7 timer eller mer

11. Har du noen sykdommer/diagnoser?

Allergi □ Ja □ Nei Beskriv hvilke:……

Astma □ Ja □ Nei (Dersom ja, fyll ut DEL B)

Sure oppstøt/gastroøsofagal refluks □ Ja □ Nei

Andre sykdommer/diagnoser/plager:……...

……

12. Bruker du noen medisiner nå?

□ JA □ NEI

Hvis Ja, Hvilke medisiner bruker du daglig eller ved behov?

……

……

Synes du medisinene virker/har effekt?

……..

……..

DEL B UTFYLLENDE OM PUSTEBESVÆR OG SYMPTOMER FRA LUFTVEIENE

1B Har du blitt operert/vært i narkose?

□ Ja □ Nei

Hvis Ja, hva slags kirurgi? _____

3B Hvor mange øvre luftveisinfeksjoner (forkjølelser) har du hatt siste 12 mnd?

□ Ofte (>10 ganger) □ Av og til (4-10 ganger) □ Sjeldent (0-3 ganger) □ Aldri hatt

4B I hvilke situasjoner opplever du pusteproblemer?

□ Opplever ikke dette
□ Ved luftveisinfeksjoner/forkjølelser
□ I hvile
□ Ved lett anstrengelse (gange)
□ Ved moderat anstrengelse/trening (eks. jogging)
□ Ved kraftig anstrengelse (hard trening / konkurranse)
□ Annet

4B.2 Er det noe som gjør at du lettere får slike pusteproblemer?

□ Anstrengelse	□ Sigarettrøyk	□ Røykos
□ Sterke lukter/parfyme	□ Kulde	□ Fuktig/rått vær (tåke)
□ Psykisk belastning/stress	□ Støv	□ Varme (Syden)
□ Trestøv/kjemikalier	□ Reflux	□ Søvn
□ Nesetetthet		

□Annet:_____

5B.1 Dersom du har pustevansker ved anstrengelse eller fysisk aktivitet, kryss av hva som passer.

□ Jeg har problemer med innpust
□ Jeg har problemer med utpust
□ Jeg hører unormal lyd/piping i pusten
□ Jeg følger tetthet/smerte i hals
□ Jeg føler tetthet/smerte i bryst

5B.2 Dersom du har pustevansker ved anstrengelse eller fysisk aktiv, hvor lang tid tar det før pustevanskene forsvinner etter at du har stoppet aktiviteten.

□ 0-5 min. □ 5-15 min. □ 15-45 min. □ 45 min. eller mer

6B Dersom du har astma: Hvor ofte har du hatt astmaanfall siste 12 mnd?

□ INGEN □ 1-3 GANGER □ 4-12 GANGER □ > 12 GANGER

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Review

Left vocal cord paralysis after patent ductus arteriosus ligation: A systematic review

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Educational aims

The reader will be able to

- Appreciate that left vocal cord paresis (LVCP) is a significant side-effect of surgical closure of PDA in neonates born preterm.
- Appreciate the clinical importance of performing postoperative laryngoscopy in all infants born preterm exposed to surgical closure of PDA.
- Understand that LVCP can present with a wide variety of clinical symptoms in the neonatal period and later in life.
- Understand the risks of misdiagnosing LVCP.

ARTICLE INFO

Keywords:
Infant, extremely low birth weight
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Recurrent laryngeal nerve
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Laryngoscopy

ABSTRACT

Context: Extremely premature (EP) infants are at increased risk of left vocal cord paralysis (LVCP) following surgery for patent ductus arteriosus (PDA).
Objective: A Systematical Review was conducted to investigate the incidence and outcomes of LVCP after PDA ligation in EP born infants.
Data sources: Searches were performed in Cochrane, Medline, Embase, Cinahl and PsycInfo.
Study selection: Studies describing EP infants undergoing PDA surgery and reporting incidence of LVCP were included.
Data extraction and synthesis: Study details, demographics, incidence of LVCP, diagnostic method and reported outcomes were extracted. DerSimonian and Laird random effect models with inverse variance weighting were used for all analyses.
Study appraisal: The Newcastle-Ottawa scale for observational studies was used for quality assessment.
Results: 21 publications including 2067 infants were studied. The overall pooled summary estimate of LVCP incidence was 9.0% (95% CI 5.0, 15.0). However, the pooled incidence increased to 32% when only infants examined with laryngoscopy were included. The overall risk ratio for negative outcomes was higher in the LVCP group (2.20, 95% CI 1.69, 2.88, $p = 0.01$) compared to the non-LVCP-group.
Conclusions: Reported incidence of LVCP varies widely. This may be explained by differences in study designs and lack of routine vocal cords postoperative assessment. LVCP is associated with negative outcomes in EP infants. The understanding of long-term outcomes is scarce. Routine laryngoscopy may be necessary to identify all cases of LVCP, and to provide correct handling for infants with LVCP.

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence interval; CLD, chronic lung disease; EP, extremely premature; GA, gestational age; LVCP, left vocal cord paralysis; NOS, Newcastle-Ottawa Quality Assessment Scale; PDA, patent ductus arteriosus; SA, surgical age; SW, surgical weight.

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Introduction

The ductus arteriosus fails to close spontaneously in up to 40–65% of extremely premature infants [1,2]. A patent ductus arteriosus (PDA) shunts blood back from the descending aorta into the pulmonary artery, potentially causing systemic hypoperfusion and pulmonary over circulation [3].

PDA surgical ligation is currently the second-line of treatment, and it is used when the medical treatment has failed or is contra-indicated [4,5]. Up to 20–30% of extremely premature infants with a clinically significant PDA undergo surgical PDA ligation [1,6,7]. This can be done by applying a small metal clip or by using a suture. Because of its close proximity to the ductus arteriosus [8], the left recurrent laryngeal nerve may be injured during surgery, causing both left vocal cord paresis or paralysis (LVCP). Early symptoms of LVCP are stridor, hoarseness, weak cry and feeding difficulties [9,10]. However, symptoms can be weak or even absent. In fact, LVCP can be unnoticed unless specifically looked for postoperatively for example via [11] flexible nasolaryngoscopy. This procedure allows visualization of the larynx without the use of anaestetics [12] and is the recommended diagnostic method for LVCP in infants [13,14]. Known risk factors for LVCP after surgical PDA ligation are low gestational age at birth (GA) [11], low birth weight (BW) [15] and low weight at surgery [11,16]. Thus, extremely premature infants undergoing surgical PDA ligation have an increased risk of iatrogenic nerve damage compared to other premature infants [17]. A recent metaanalysis reported large discrepancies between studies regarding the incidence of LVCP in infants and children undergoing cardiothoracic surgery for congenital heart disease [16]. Some of this variability could potentially be explained by inconsistencies regarding postoperative vocal cord evaluation between studies [16].

The objectives of this study are to (1) determine the incidence of LVCP after surgical PDA ligation in extremely premature infants, (2) determine study level characteristics that may explain the wide incidence variation reported by different studies and (3) explore short- and long-term consequences and/or associated comorbidities of LVCP in extremely premature born infants.

Methods

Protocol and registration

We registered the review protocol in the PROSPERO International prospective register of systematic reviews under the identification number CRD42016029921 (Supplemental File 1) and followed the checklist for Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA, Supplemental File 2) [18].

Eligibility criteria

We included studies of extremely premature infants born at gestational age $\leq$28 weeks and/or $\leq$1000 g birthweight diagnosed with PDA, and reported cases of LVCP following surgical PDA ligation. We excluded studies with less than 80% of extremely premature infants or lacking a description of a subpopulation of extremely premature infants. Eligible study designs were cohort or case-control. Case reports, case series, narrative reviews, letters, editorials, commentaries and abstracts were excluded. Outlined in Supplemental File 3.

Literature search strategy

We searched the following databases from their inception through December 19, 2015: MEDLINE, Embase, PsycINFO, Cinahl and the Cochrane Library. The search was updated on December 20th, 2016 without additional included citations. In collaboration with a librarian (G.A), M.S.E. developed a highly sensitive search strategy for MEDLINE, using search terms relevant to the population and intervention (e.g., extremely premature infants, patent ductus arteriosus ligation). To identify grey literature, we searched Open Grey and Google Scholar. We searched Prospero and Clinical trials.gov for ongoing studies, and reference lists of relevant reviews and citations of included studies to identify other potentially relevant references. The search strategy was modified for the other databases. No restrictions were placed on publication date, study design or language. We describe the complete search strategy in Supplemental File 4.

Study selection

Two investigators (M.S.E. and S.M.) independently conducted the initial screening of references identified by the search strategy. Titles and abstracts were retained for full-text review if one of the investigators identified the study as being potentially eligible. Two investigators (M.S.E. and O.D.R.) independently screened the remaining full text references. Any disagreements were resolved by consensus, and a third investigator (S.M.) was consulted if consensus was not met.

Data abstraction

One investigator (M.S.E.) abstracted data from the selected studies, while another investigator (O.D.R.) over-read the abstracted data for inconsistencies. Disagreements regarding data abstracted were resolved by consensus between the two authors. The following data were extracted: Author details, year of publication, study methods, key characteristics of participants, intervention details, control conditions, incidence LVCP, diagnostic method and outcomes.

In addition, study authors were contacted for additional information if needed. They were asked about full text versions of abstracts, assessment method for LVCP, or information about number of extremely premature infants in the cohort, potentially allowing us to perform sub-analysis of incidence of LVCP in extremely premature infants.

Quality assessment of individual studies

Two investigators (M.S.E. and N.R.O.) independently assessed methodological quality of identified studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) [19]. This is a quality measure tool for observational studies recommended by Cochrane [20] that assesses methodological quality by assigning points up to a maximum of nine points for the least risk of bias in three domains: (1) selection of study groups (four points); (2) comparability of groups (two points); and (3) ascertainment of exposure and outcomes (three points). We provide further details on the use of NOS for this Systematic Review in Supplemental File 5. Disagreements were resolved by consensus or through a third investigator (O.D.R).

Synthesis of results

We statistically pooled results when $\geq$2 studies were present for the same outcome. A pooled proportion of the incidence of LVCP including 95% confidence intervals (CIs) was calculated. Incidence was calculated by dividing the number of reported cases of LVCP by the total number of PDA ligated infants in each study, not

divided by the number of cases examined by laryngoscopy. DerSimonian and Laird random effect model with inverse variance weighting was used for all analyses. A Freeman–Tukey Double Arcsine Transformation was used to stabilize the variances prior to pooling for incidence estimates. For the analysis of and/or associated co-morbidities, we pooled studies using random effects models estimating risk ratios and 95% confidence intervals. Due to the small number of studies reporting consequences and/or associated co-morbidities, we did not attempt to stratify when significant heterogeneity was present. Heterogeneity between studies was tested for both incidence proportion and consequences with Cochrane's Q and I-squared. High heterogeneity was indicated by a Q p-value <0.10 or I-squared >50%. When substantial heterogeneity was present, we attempted to explain heterogeneity by stratifying by a priori covariates. Publication bias was assessed by visual inspection of the funnel plot and an Egger's test for the main analysis of occurrence of LVCP. All analyses were conducted using Stata 14.0 (College Station, TX).

Results were synthesized descriptively if a quantitative synthesis was not feasible. We placed greater emphasis on the evidence coming from studies with more precise estimates of effect. We also focused on documenting and identifying patterns of the intervention across outcome categories. We analyzed potential reasons for inconsistencies in treatment effects across studies by evaluating differences in method of assessment, intervention and study design.

Results

Study selection

The literature search identified 1985 unique records. Many of these (1815 or 91.4%) were excluded by title and abstract screen. In addition, we were not able to retrieve the full texts of 37 abstracts. Full-texts of 133 publications were reviewed of which, 112 were excluded resulting in 21 studies included in the review [11,15,17,21–40]. The selection process is outlined in Fig. 1. Reasons for exclusions of publications were: No description of LVCP after PDA surgery (n = 84), and/or less than 80% extremely premature infants or no subgroup of extremely premature infants described (n = 22), no PDA surgery (n = 2), not appropriate study design (n = 2), duplicate (n = 1) or chapter in book (n = 1). Reasons for exclusions are detailed in Supplemental File 6.

Study characteristics

Descriptions of study characteristics including study-population, exposure, diagnostic method and outcomes are provided in Table 1. The majority of study designs were cohort studies (n = 20), and one [23] was a case–control study.REF 23 here 17 studies were retrospective and four were prospective. Seven studies [11,15,17,23,33,35,37] aimed at measuring the incidence of LVCP following PDA ligation, and seven studies [15,22,23,32,33,35,37] at detecting risk-factors/co-morbidities or outcomes following LVCP after PDA ligation. Half of the included studies [21,24,25,27–30,34,39,40] did not report or reported unclearly how LVCP was assessed. Specifically, six studies [15,17,22,32,36,41] assessed via laryngoscopy only symptomatic infants, examining laryngoscopically all infants after PDA ligation [11,23,33,35,37].

The pooled mean GA at birth between the 21 included studies was 25.6 (range of means 24.5–27.1) weeks and the pooled mean BW was 816.5 (range of means 679–1040) g. The pooled mean surgical age of the 12 studies reporting this was 22.0 (range of means 12–57) days. The pooled mean surgical weight of the 8 studies reporting it was 933.1 (range of means 722–1404) g. There were 8 studies that included a higher maximum GA/BW range. However, all of these included more than 90% extremely premature infants [24,29,34,41] and/or a described subgroup of extremely premature infants [11,17,23,36] and therefore, were used in our analyses.

Six studies [11,15,17,22,23,35] compared GA and BW in children with and without LVCP. Only five of these [11,15,22,23,35] were included in this meta-analysis (Figs. 2 and 3), as one study [17] did not report variations from the mean. Infants with LVCP had 1.2 weeks (95% CI −2.01, −0.39, I^2: 70.4%, p = 0.009) lower GA, and 175.5 g (95% CI −321.5, −29.6; I^2: 82.7%, p < 0.001) lower BW.

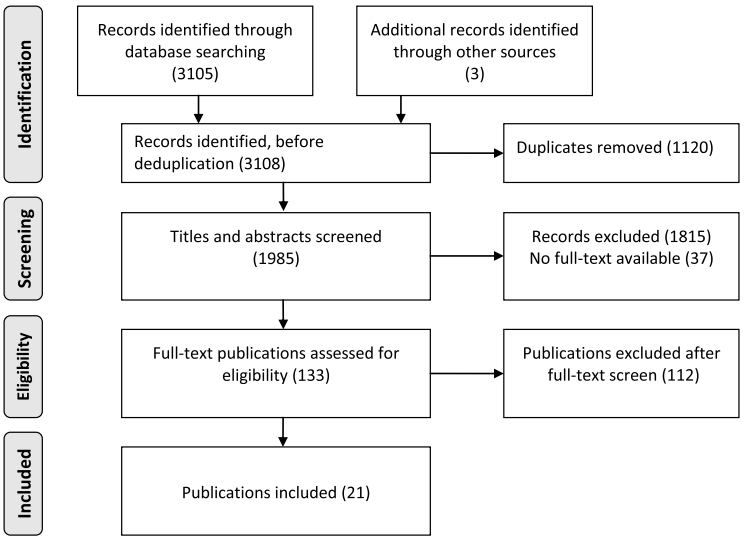

Fig. 1. Flow diagram of study selection.

Table 1
Characteristics of studies and participants included in the analyses.

Author, year, study design	Population demographics	Diagnostic method (LVCP)	Incidence of LVCP, cases/total (%)	Outcomes following LVCP
Alexander, 2009 Retrospective 1996–2005	All ELBW infants with PDA. 1: No treatment (N = 54): GA, 25.7 ± 1.9 wk; BW, 729.6 ± 169.6 g 2: Indomethacin (N = 82): GA, 26.3 ± 1.9 wk; BW, 758.2 ± 139.4 g 3: Primary surgery (N = 46): GA, 24.8 ± 1.5 wk; BW 678.7 ± 153.5 g 4: Indomethacin + surgery (N = 58): GA: 25.7 ± 1.8 wk; BW, 724.4 ± 139.7 g	NR	0/104 (0%)	NR
Benjamin, 2010 Retrospective 2004–2006	All ELBW infants, all PDA ligated. +LVCP (N = 22): GA, 24.5 ± 1 wk; BW, 722 ± 122 g; SA, 17 ± 8.7 d; SW, 722 ± 140 g. −LVCP (N = 33): GA, 24.8 ± 1.3 wk; BW, 728 ± 132 g; SA, 22 ± 14.5 d; SW, 798 ± 219 g	Laryngoscopy if symptoms (N = 25/55)	22/55 (40%)	Days of mechanical ventilation, bronchopulmonary dysplasia, reactive airway disease, gastrostomy tube, Nissen fundoplication, neurodevelopmental impairment, IVH
Clement, 2008[5] Retrospective 2003–2005	ELBW (N = 18) and VLBW (N = 5) infants, all PDA ligated. All LVCP was EP. +LVCP (N = 12): GA, 24.8 (24–26 wk); BW 725 (580–887 g); SA, 14.5 (6–31 d) −LVCP (N = 11): GA, 27 (25–31 wk); BW, 1040 (700–1540 g); SA, 13.8 (4–53 d)	Laryngoscopy (N = 20/23)	12/18 (67%)	Tube feeding, gastrostomy, hospital stay, readmission, ventilator support, supplemental oxygen, chronic lung disease
Ghosh, 1985 Retrospective 1979–1983	ELBW infants (N = 27/30). All infants (N = 30) were PDA ligated. GA, 27 (23–34 wk); BW, 811 (650–1620 g)	NR	1/30 (3.33%)	NR
Heuchan, 2012 Retrospective, 2001–2007	ELBW infants (N = 125), all PDA ligated. GA, 26 (IQR 25–27 wk); BW, 840 (IQR 730–1035 g)	NR	6/125 (4.8%)	NR
Hines, 2003[3] Retrospective, 1996–2002	EP infants (N = 94/100), 99/100 PDA ligated. GA: 25.6 (23–31 wk); BW, 859 (420–1500 g); SA, 16 (3–51 d)	Bronchoscopy if symptoms	5/94 (5.3%)	NR
Hutchings, 2013 Retrospective, 2005–2009	ELBW infants (N = 95/98)[†], all PDA ligated. GA, 26 ± 2wk; BW, 923 ± 394 g; SA, 29 ± 3 wk; SW, 1222 ± 506 g	NR	10/95 (10.5%)	NR
Ibrahim, 2015 Retrospective 2010–2014	ELBW infants (N = 120), all PDA ligated. Early ligation (N = 75): GA, 25 (22–28 wk); BW, 765 (607–923 g); SA, 12 (6–20 d); SW, 756 (646–900 g) Late ligation (N = 45): GA, 24.6 (22–27 wk); BW, 773 (620–901 g); SA, 30 (24–30 d); SW, 833 (690–990 g)	NR	1/120 (0.83%)	NR
Kang, 2013 Prospective 2004–2009	EP infants (N = 85/92), all PDA ligated. GA, 25 (23–36 wk); BW, 721 (462–2420 g); SA, 34 (10–94 d); SW, 1005 (627–3080 g)	NR	2/85 (2.4%)	NR
Lee, 2008 Retrospective 1994–2006	VLBW/ELBW infants (N = 94), all PDA ligated. GA, 26wk^{+3d} ± 2 wk^{+1} d; BW: 869 ± 223 g	NR	0/94 (0%)	NR
Mandhan, 2009 Retrospective 1987–2005	ELBW infants (N = 145), all PDA ligated. GA, 25.5 ± 2.3 (24–36 wk); BW, 837.7 ± 277.2 (450–1000 g) SA, 14.1 ± 1.8 d; SW, 881.3 ± 338.1 g	NR	1/145 (0.7%)	NR
Natarajan, 2010 Retrospective 2004–2006	EP infants (N = 82), all PDA ligated. GA, 25.5 (23–28 wk); BW, 765 (484–1150 g); SA, 21 (5–58 d)	NR	0/82 (0%)	NR
Nichols, 2014 Retrospective 2001–2012	532 infants were PDA ligated. 66 were included in further analysis. +LVCP (N = 66): GA, 24.75 ± 1.6 wk; BW, 704.2 ± 185.6 g; SA, 18.4 ± 13.9 d	Laryngoscopy (N = 66/532)	66/532 (12.4%)	Stridor, dysphonia, tube feeding, bronchopulmonary dysplasia, IVH, retinopathy of prematurity, laryngomalacia, subglottic stenosis
Pereira, 2006 Prospective 2001–2004	Premature infants (N = 100), all PDA ligated. GA, 25 wk; BW, 740 g; SA, 23 d; SW, 914 g	Laryngoscopy (N = 61/100)	7/61 (11.5%)	Stridor, feeding difficulty, feeding tubes, weak cry
Robie, 1996 Retrospective 1990–1992	ELBW infants (N = 82), all PDA ligated. GA, 2.7 ± 1.74 (23–32 wk); BW, 756 ± 135 (420–1000 g)	NR	2/82 (2.4%)	NR
Røksund, 2010 Retrospective 1982–1985/ 2008–2009	EP infants with PDA. PDA-ligated (N = 13): SA, 12 (4–29 d) +LVCP (N = 7): GA, 27.1 ± 1.5 wk; BW, 874 ± 138 g −LVCP (N = 4): GA, 27.0 ± 2.9 wk; BW, 982 ± 283 g No surgery (N = 33): GA, 27.5 ± 1.4 wk; BW, 1051 ± 178 g	Laryngoscopy (N = 11/13)	7/11 (64%)	Ventilator treatment, oxygen treatment, measures of lung function, peak heart frequency, blood pressure, wheezing, severe stridor during heavy exercise
Rukholm, 2012 Retrospective 2003–2010	EP infants (N = 111), all PDA ligated. Results presented as mean (95% CI) +LVCP (N = 19): GA, 25.4 (24.8–26.0 wk); BW, 743.8 (665.4–822.1 g); SA, 22.7 (16.3–29.1 d); SW, 845.8 (766.5–925.2 g) −LVCP (N = 92): GA, 26.7 (26.0–27.5 wk); BW, 990 (858.4–1121.5 g); SA, 52.7 (23.8–81.6 d); SW, 1404 (966.3–1843.4 g)	Laryngoscopy (31/111)	19/111 (17.1%)	Gastroesophageal reflux syndrome, sepsis, bronchopulmonary dysplasia, gastric feeding tube, pneumonia, anemia of prematurity

(*continued on next page*)

Table 1 (*continued*)

Author, year, study design	Population demographics	Diagnostic method (LVCP)	Incidence of LVCP, cases/total (%)	Outcomes following LVCP
Smith, 2009[§] Prospective 2004–2007	EP infants (*N* = 60/86), all PDA ligated. All LVCP were <28 wk GA. +LVCP (*N* = 14): GA, 25.4 ± 1.2 wk; BW, 829 ± 205 g; SA, 27 ± 1.3 wk; SW, 911 ± 181 g −LVCP (*N* = 72): GA, 26. 9 ± 2.6 wk; BW, 1033 ± 414 g; SA, 29 ± 3.3 wk; SW, 1211 ± 449 g	Laryngoscopy (*N* = 86/89)	14/60 (23.3%)	Stridor, dysphonia
Spanos, 2009[§] Prospective 1995–2005	ELBW infants (*N* = 55/105), all PDA ligated. All cases of LVCP were EP. Results presented in median (mean absolute deviation) Suture: GA, 25.0 ± 2.0 wk; BW, 740 ± 288 g; SW, 1054 ± 626 g Clip: GA, 24.7 ± 1.3 wk; BW, 561 ± 169 g; SW, 762 ± 210 g	Laryngoscopy (*N* = 68/105)	13/55 (23.6%)	Hoarseness/stridor, aspiration, episodes of decreased oxygen saturation
Sørensen, 2010§ Retrospective 1998–2007	EP infants (*N* = 31/46), all PDA ligated. [*] 3/3 infants with LVCP was EP Total: GA, 26 $wk^{+6,5d}$ (23^{+6}–34 $wk^{+0\ d}$); BW, 943.5 (535–1793 g) <28 wk: (*N* = 31) GA, 25$wk^{+4,2d}$ BW, 788 g	NR Laryngoscopy if clinical suspicion	3/31 (9.7%)	NR
Zbar, 1996[§] Retrospective 1991–1994	ELBW infants (*N* = 22/68), all PDA ligated. 5/22 with LVCP was EP. +LVCP (*N* = 6): GA, 26.3 wk; BW, 900 g −LVCP (*N* = 62): GA, 33.8 wk; BW, 2300 g	Laryngoscopy if symptoms	5/22 (22.7%)	NR

Results given in mean ± standard deviation and/or range unless other is specified. GA; gestational age, BW; birth weight, SA; age at surgery, SW; weight at surgery. LVCP; left vocal cord paralysis, EP; extremely premature (≤1000 g/≤28 weeks), ELBW; extremely low birth weight (<1000 g), VLBW; very low birth weight (<1500 g), LBW: Low birth weight (<2500 g), Wk; weeks, g; gram, IVH; intraventricular hemorrhage, NR; not reported.

§ Analysis of incidence of LVCP was performed based on a described subgroup of extremely premature children.

[*] Additional information provided by author of the publication.

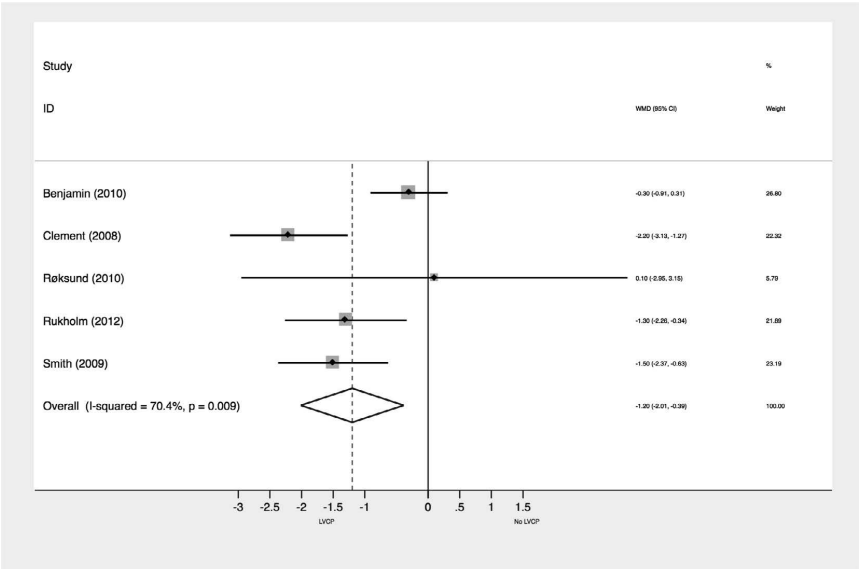

Fig. 2. Gestational age (weeks), weighted mean difference between infants with and without LVCP.

Analysis of reported incidence of left vocal fold paralysis

Twenty-one studies involving 2067 infants were included in analysis of the incidence of LVCP after PDA surgery (Fig. 4). Five studies [11,17,23,36,37], calculated the incidence of LVCP in a subgroup of extremely premature infants, not among all infants who underwent PDA ligation in the study. Reported incidence of LVCP ranged from 0% to 67% in the individual studies. The overall pooled incidence summary estimate was 9.0% (95% CI 5.0, 15.0%). However, significant heterogeneity was present with an I^2 of 91.9% and Q *p*-value <0.01. No visual evidence was noted by visual inspection of the funnel plot, and the Egger's test ($p = 0.26$) also suggested that no publication bias was present.

Subgroup analyses

As shown in Fig. 5, heterogeneity decreased, and pooled reports of LVCP were impacted after stratifying by type of LVCP identification method The weighted pooled proportion of LVCP incidence was 2% (95% CI 0, 4%, $I^2 = 72.2\%$, Q-$p < 0.01$) in studies not reporting or reporting unclearly how infants with LVCP after PDA ligation were evaluated [21,24,25,27–30,34,39,40]. The pooled incidence

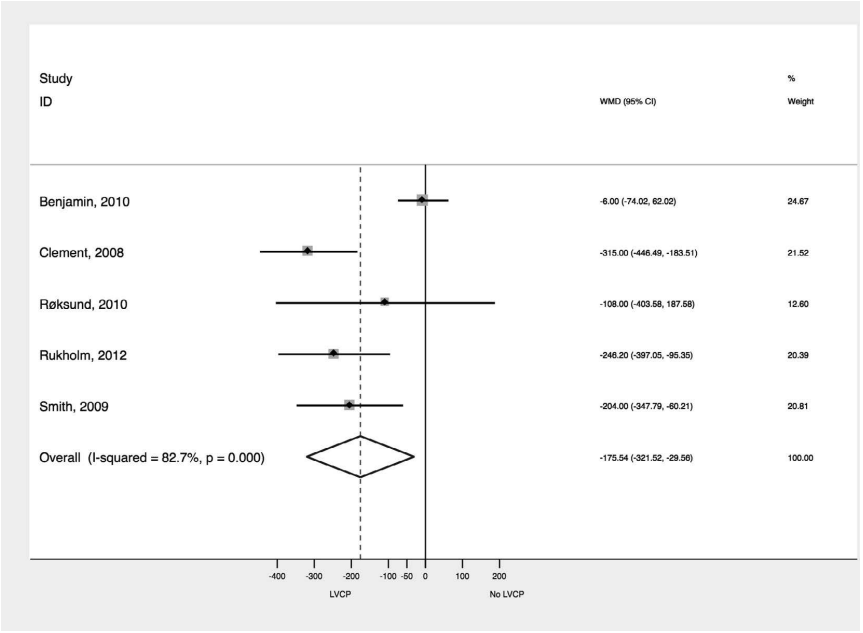

Fig. 3. Birth weight (g), weighted mean difference between infants with and without LVCP.

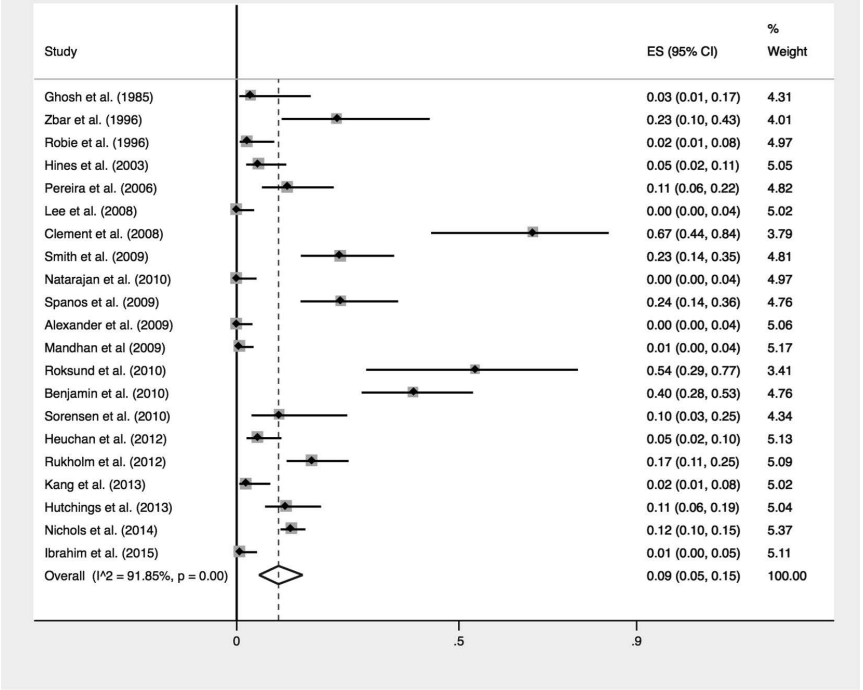

Fig. 4. Individual study and overall incidence of LVCP following patent ductus arteriosus surgery. ES; effect size.

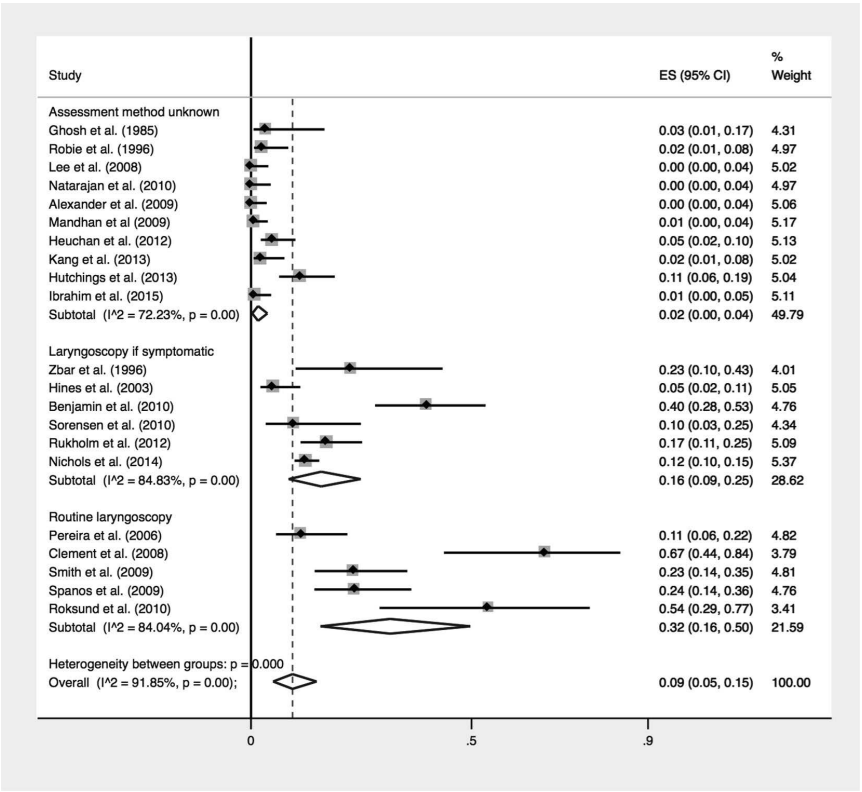

Fig. 5. Overall Incidence of LVCP, stratified by type of assessment method. ES; effect size.

was 16% (95% CI 9, 25%, I^2: 84.83%, Q-p < 0.01) in studies assessing symptomatic infants via laryngoscopy [15,17,22,32,36,41], and 32% (95% CI 16, 50%, I^2: 84.04%, Q-p < 0.01) in studies assessing all infants via laryngoscopy [11,23,33,35,37]. After the latter were stratified by retrospective (n = 31) [23,35] vs. prospective design (n = 215) [11,33,37] (Fig. 6), the heterogeneity decreased substantially in the retrospective studies (I^2: 48.94%, Q-p = 0.14; prospective studies I^2 was 74.47%, Q-p = 0.05). Retrospective studies had a higher pooled incidence of LVCP of 61.0% (95% CI 43, 78%) compared to prospective studies (19.0%, 95% CI 11, 28%). Heterogeneity was not reduced by stratification based on PDA surgical closure method (clip or suture, I^2 > 88%).

Analysis of reported comorbidities and/or consequences of LVCP

Eight of the 21 included studies reported consequences and/or comorbidities following LVCP after PDA ligation in extremely premature infants [11,15,17,22,23,33,35,37]. Six of these studies [11,15,22,23,35,37] were included in the meta-analysis because two lacked comparison group. Fig. 7 illustrates the consequences and/or comorbidities of LVCP following PDA ligation reported by two or more studies. Bronchopulmonary dysplasia (BPD) was reported by four studies [15,22,23,35] including 235 infants. The risk for BPD among premature infants with LVCP was increased; risk ratio (RR) = 1.60 (95% CI 1.29, 1.99, I^2: 0.0%, Q-p = 0.58). The need of enteral feeding via nasogastric tube or gastrostomy was reported in three studies [15,22,23] including 189 patients. This risk was strong in premature infants with LVCP although imprecise due to small sample sizes (RR = 5.76 (95% CI 2.15, 15.46, I^2 = 0.0%, Q-p = 0.40). Two studies [11,37] including 115 patients reported stridor, and this risk was elevated (RR = 5.22 (95% CI 1.97, 13.86, I^2 = 20.2%, Q-p = 0.26) but imprecise. Asthma or reactive airway disease was reported by two studies [22,35] including 99 patients, and the risk of asthma was strong (RR = 2.45 (95% CI 1.52, 3.92, I^2 = 0.0%, Q-p = 0.58) and precise. The risk of aspiration, gastroesophageal reflux/gastroesophageal reflux syndrome or intraventricular hemorrhage were all reported by two or three studies [15,22,23] and included in the meta-analysis, but the pooled risks between individual studies were not statistically significant. Three studies [22,23,35] including 89 infants reported differences in total days spent on mechanical ventilation between infants with and without LVCP (Fig. 8). Infants with LVCP spent on average 16.5 days (95% CI: 8.57, 24.07, I^2 = 58.6%, p = 0.089) longer on mechanical ventilation.

Additional analysis

Additional pooling of data was not performed because of the 21 included studies had non-uniform reporting of data among or less than two studies reported a given outcome. For example, only one study followed children beyond the age of ten years. Data from additional analyses are presented in Table 2. Significant differences between subjects with and without LVCP as regards neonatal outcomes were reported for neonatal sepsis [15], initial length of hos-

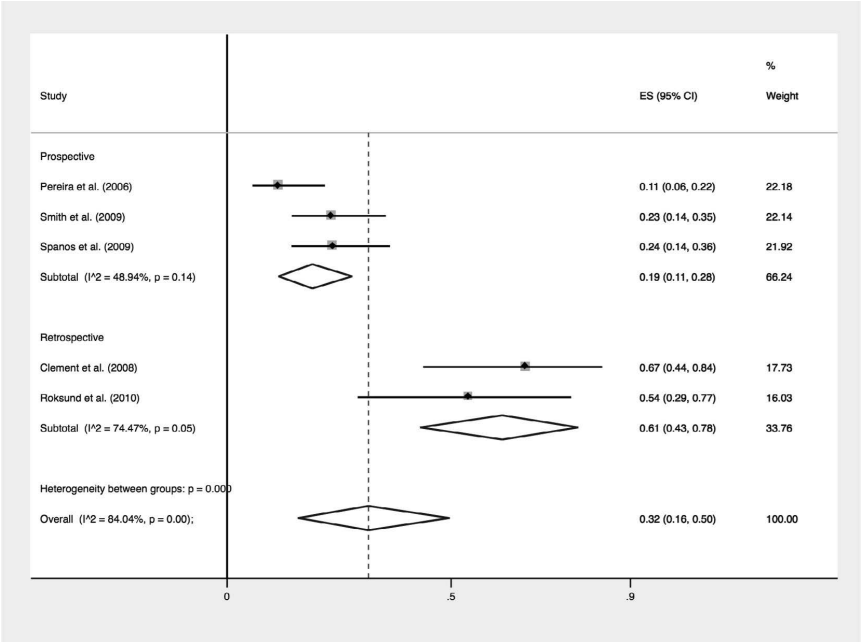

Fig. 6. Overall incidence of LVCP among studies routinely assessing patients with laryngoscopy. ES; effect size.

pital stay [23], dysphonia [11,37] and subjects undergoing gastroesophageal reflux disease surgery [22]. One study [35] reported follow-up data after discharge and found significantly more airway obstruction as measured by spirometry in the LVCP group.

Quality assessment

Assessment of quality in the included studies is summarized in Supplemental File 7. Seventeen studies (81%) scored 4 out of 9 possible stars. Two studies [21,35] had a control group of extremely premature infants with PDA who did not undergo PDA ligation, and scored three additional stars (7/9) for selection and comparability. The only study [11] earning a star for assessment of outcome examined 97% of infants with laryngoscopy postoperatively. One study [37] scored only three stars, because 35% of patients were lost to follow-up and not accounted for. No studies examined infants for LVCP preoperatively and therefore, all studies missed a potential star for demonstrating that the outcome of interest was not present at the start of the study.

Discussion

The overall pooled incidence of LVCP after PDA ligation in extremely premature children was 9.0%. However, the incidence varied widely (0–67%) between studies. Higher incidence was seen in studies that examined *all* children with laryngoscopy after ligation (32%), and in studies with a retrospective design (61%) compared to those with a prospective design (19%). Results revealed a scarcity of follow-up studies that could provide further knowledge on short- and long-term outcomes. However, based on analyses of the available outcome data, we found that infants with LVCP, overall, had a significantly higher risk of negative outcomes. Further prospective research analyzing confounding factors is needed.

To our knowledge, this is the first systematic review that focused on identifying the incidence of LVCP after PDA ligation in extremely premature infants. A strength of this study is that the aim and search strategy were restricted to one type of cardiothoracic surgery and we only included studies describing extremely premature infants. Thus, our search strategy was more specific compared to a previous systematic review [16] on LVCP that included various types of cardiothoracic surgery in infants and children. In addition, we had no language restrictions, and our search identified new research on the topic.

Low gestational age, low birth weight and low weight at surgery are known risk factors for LVCP [11,15,17]. Therefore, we expected a high LVCP pooled incidence in this research as we only included studies describing extremely premature infants. However, our overall LVCP pooled incidence is similar (9.0% vs 8.7%) to that reported by Strychowsky et al. [16], in a sub-analysis of 21 studies investigating incidence of LVCP after PDA ligation in infants and children. Congruent results between these two meta-analyses could be due to the expectedly high proportion of extremely premature infants in studies investigating consequences of surgical PDA ligation. Of note, about half of the studies included by Strychowsky et al. [16,11,15,17,22,23,25,33,35–37,40] ($n = 11$) were also included in our meta-analysis.

LVCP assessment methods could partly explain the large between-studies variability in the reported incidence of LVCP [16]. For example, our results showed that the incidence of LVCP was substantially higher in studies routinely assessing all infants postoperatively via laryngoscopy (32%), compared to those that performed laryngoscopy only in symptomatic infants (16%). The pooled incidence of LVCP was only 1% in studies with unclear or unreported vocal cord assessment method. Strychowsky et al. [16] found a weighted pooled proportion for LVCP of 39% in studies that assessed infants and children by laryngoscopy after PDA liga-

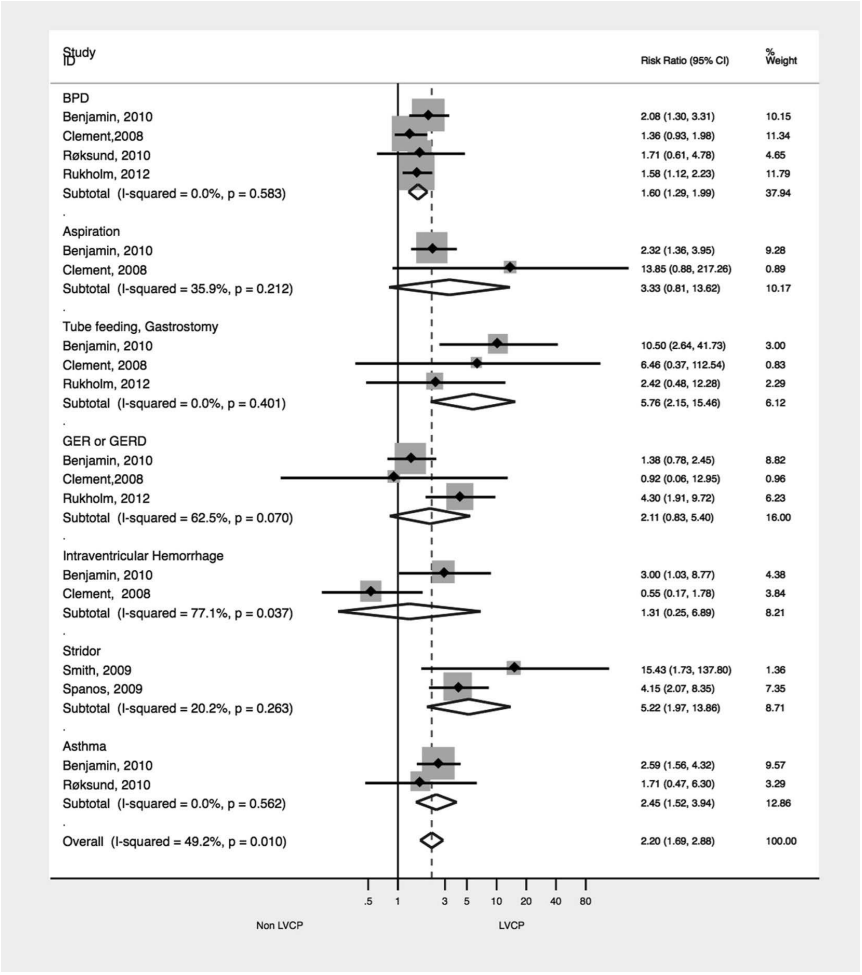

Fig. 7. Individual studies and overall risk of consequences and/or comorbidities of LVCP.

tion. As five of six studies [11,17,22,23,35,37] used in Strychowsky's analysis were included in our analysis, congruent results are not surprising. We chose to exclude one study [22] from our sub analysis because only symptomatic infants were examined via laryngoscopy. This exclusion contributed to a slightly lower weighted pooled proportion of LVCP in our study (32% vs. 39%). This variability in reported incidence may be due to the transient nature of LVCP symptoms in infants. It seems clear that the methods of assessment significantly impact incidence reports, and that LVCP may be undetected unless routinely looked for via laryngoscopy [11,32,33,38,42]. In addition, some infants presenting with typical symptoms of LVCP, such as stridor and dysphonia, may not have LVCP when examined via laryngoscopy [11,22,37]. This stresses the point that symptom-based diagnosis of LVCP is not reliable, may cause misleading rates of postoperative LVCP incidence and also may lead to misdiagnoses and erroneous management of these infants.

Preoperative laryngoscopy was not performed in all but one study [15]. Considering that extremely premature infants referred to PDA surgery are critically ill and may require intubation before surgery [15,43,44], preoperative laryngoscopy may be difficult and unethical to perform [43,44]. Lack of preoperative assessment of the vocal cords may confuse the postoperative LVCP incidence rates, as other potential causes of LVCP among infants exists. For example, cases of idiopathic or neurological causes of LVCP have been reported among neonates [9,10,44]. Moreover, a large PDA can possibly compress the left recurrent laryngeal nerve and lead to injury [45]. In addition, findings of vocal cord paralysis would have been equally distributed between the right and left side should intubation have caused direct injury to the vocal cord. However, this was not the case in any of the included studies. Theoretically, one may speculate that a partial preoperative paralysis of the left recurrent laryngeal nerve due to a large pulsating PDA, or a partial paralysis of the left recurrent laryngeal nerve due to perioperative traction on the nerve, may lead to a transient immobilization of the left side of the larynx, and thus predispose the left side of the larynx to postoperative intubation trauma. However, this needs to be addressed in properly designed studies.

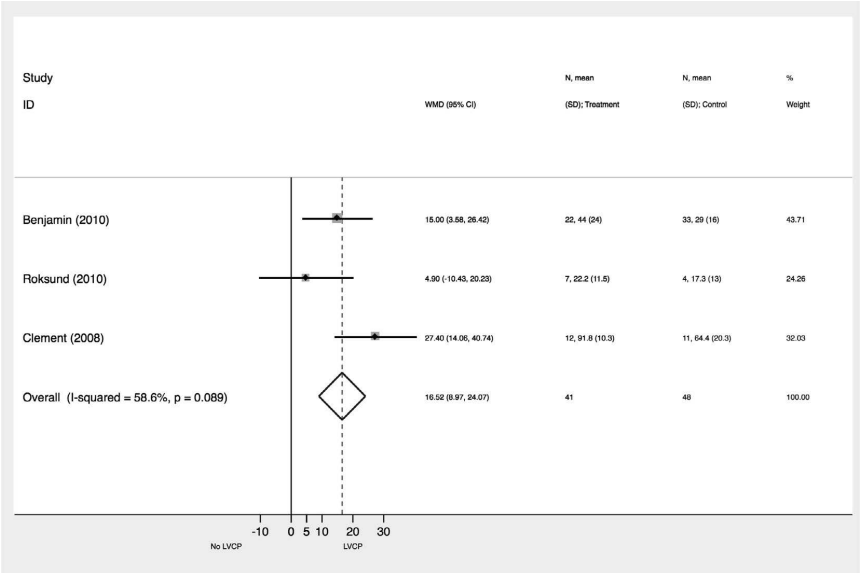

Fig. 8. Duration of ventilation (total number of days). Weighted mean difference between infants with and without LVCP.

Table 2
Additional analysis.

Study	Outcomes	LVCP	No LVCP	*p*-Value
Respiratory outcomes				
Spanos, 2009	Episodes of decreased O_2-saturation, *N* (%)	2/13 (15)	4/54 (7)	0.48
Roksund, 2010	Forced expiratory volume (FEV1), % of predicted	71.9%	83.3%	<0.05*
Roksund, 2010	Flow through middle half of forced vital capacity, % of predicted	51%	83%	<0.05
Roksund, 2010	Peak expiratory flow, % of predicted, mean (95% CI)	76.4 (63–90)	102.5 (92–113)	>0.05
Roksund, 2010	Forced vital capacity, % of predicted, mean (95% CI)	99.1 (85–113)	98.0 (83–113)	>0.05
Roksund, 2010	Maximal oxygen uptake, % of reference, mean (95% CI)	96.2 (83–110)	96.3 (72–121)	>0.05
Laryngeal outcomes				
Roksund, 2010	Dysphonia, *N* (%)	6/7 (85.7)	1/4 (25.0)	*0.07*
Smith, 2009	Dysphonia, *N* (%)	9/14 (20.5)	8/72 (11)	*<0.001**
Spanos, 2009	Dysphonia, *N* (%)	9/13 (69)	9/54 (17)	<0.001*
Nichols, 2014	Dysphonia, *N* (%)	51/66 (77.3)	–	
Nichols, 2014	Laryngomalacia, *N* (%)	26/66 (38)	–	
Nichols, 2014	Subglottic stenosis, *N* (%)	3/66 (5)	–	
Feeding outcomes				
Benjamin, 2010	Nissen fundoplication, *N* (%)	9/22 (41)	1/33 (3)	0.001*
Other outcomes				
Benjamin, 2010	Hospital stay (total days)	148.2	96.8	<0.001*
Benjamin, 2010	Neurodevelopmental IMPAIRMENT (18–22 months)	10/22 (56)	8/11 (36)	0.34
Benjamin, 2010	Intraventricular hemorrhage (grade 3 or 4), *N* (%)	8/22 (36)	4/33 (12)	0.05
Clement, 2008	Readmission within 12 months, *N* (%)	6/12 (50)	2/11 (18)	0.19
Nichols, 2014	Retinopathy of prematurity, *N* (%)	50/62 (81)	–	
Rukholm, 2012	Retinopathy of prematurity, *N* (%)	8/19 (42.1)	22/92 (23.3)	0.154
Rukholm, 2012	Sepsis, *N* (%)	14/19 (73.7)	36/92 (39.1)	0.010
Roksund, 2010	Peak heart rate, beats per minute, mean (95% CI)	185.0 (178–183)	196.3 (188–206)	>0.05

* Marks significant difference ($p < 0.05$) between groups as reported in individual publications. Two exceptions are *p*-values for Dysphonia from Smith et al. (2009) and Roksund et al. (2010), as these values were calculated based on Odds Ratios by authors of this Systematical Review.

Differences in study design could also have impacted the between study variability in reported LVCP incidence. The three prospective studies [11,33,37] included in our analysis had a substantially lower incidence of LVCP compared to the two retrospective studies [23,35]. A possible explanation for this could be due to the fact that surgeons participating in prospective studies may be more cognizant of the risk of recurrent laryngeal nerve damage and therefore, more cautious during surgery. However, Carpes

et al. [44] described a *higher* odd of damaging the recurrent laryngeal nerve upon visualization of the nerve during surgery. This observation could imply that the laryngeal nerve is vulnerable to low impact trauma such as traction, and that efforts made to avoid damaging to the nerve could actually be harmful.

We found that a range of adverse outcomes or comorbidities were associated with LVCP. As several studies [23,32,33,37,38] have reported low rates (0–33%) of recovery, infants are thus left with a potential for life-long sequelae. Undetected LVCP that is confused with other medical conditions could theoretically lead to inappropriate and potentially harmful treatment choices. Infants with LVCP can present with symptoms such as apneas or increased work of breathing associated with stridor. Such symptoms might leave infants susceptible for prolonged hospital stay, and prolonged and possibly unnecessary mechanical ventilation in the misbelief that they suffer from lung disease [22,23,33,35]. In turn, such unnecessary treatment can complicate subsequent handling of the baby and also lead to acute and chronic pulmonary problems, e.g., BPD [43,46]. Early LVCP detection could theoretically allow use of less invasive ventilatory support, such as CPAP, and thus facilitate better airflow despite laryngeal obstruction.

In older children symptoms of LVCP have been confused with symptoms of asthma [35]. These children have been treated with medications instead of receiving treatment for their actual condition. Therefore, we propose that laryngoscopy should be performed before hospital discharge in infants who have undergone surgical PDA ligation.

Benefits versus disadvantages of surgical ligation of PDA have been debated in recent years [6,47–50]. Surgical ligation has been associated with a range of morbidities [11,23,51–54]. Extremely premature infants undergoing surgical PDA ligation are often the most vulnerable and at risk of a range of morbidities [55]. We can hardly study the consequences of PDA surgery and LVCP without facing the problem of selection bias or confounding by surgical indication as infants selected for surgical ligation may have a higher baseline risk for comorbidities [50]. We suggest that future studies prospectively enroll extremely premature infants undergoing PDA ligation and explore possible short and long-term consequences of LVCP. Future studies should also perform routinely pre- and postoperative laryngoscopy examinations, use matched controls, and try to control for selection bias.

Study limitations

Our study has several strengths including an exhaustive search, a rigorous protocol driven approach, and meta-analytical analyses of potentially important subgroups. The major limitation of this study, similar to many meta-analyses, lies in the data on which it was based; i.e., the wide heterogeneity and the varying approach between the included studies. However, we were able to explain some of this heterogeneity that could also be utilized to speculate over issues of clinical interest.

Conclusion

The pooled incidence of LVCP after PDA ligation in extremely premature infants was 9%, with a wide heterogeneity depending on the method used for LVCP assessment and study design. Unfortunately, routine laryngoscopy is rarely performed in relation to PDA ligation, preventing identification of all cases of PDA-related LVCP. A range of adverse outcomes and/or comorbidities were found to be associated with LVCP; however, the full picture of this still remains unknown due to lack of systematic follow-up studies. Early recognition of LVCP seems to be of significant clinical value, which supports routine laryngoscopy performed after PDA ligation.

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Contributors' statements

All authors contributed to conceptualization and design of the study, reviewed and revised the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ms. Engeseth performed the search, screening of titles, abstracts and full-text records, data abstraction, quality assessment, contributed to meta-analysis and drafted the initial manuscript.

Dr. Maeland performed titles and abstract screen of records.

Professor Røksund performed full-text screen of articles and contributed to data abstraction.

Dr. Olsen performed quality-assessment of articles.

Dr. Goode performed the meta-analysis and contributed to draft of the original manuscript.

Professor Halvorsen participated in quality assessment and as a clinical neonatologist he secured clinical relevance and interpretation of the findings.

Directions for future research

- Prospective multi-center cohort study including all infant born preterm undergoing PDA surgical closure to determine the incidence and risk factors of LVCP.
- Investigate the mechanisms of injury that leads to LVCP in infants born preterm exposed to surgical closure of PDA.
- Investigate clinical symptoms and outcomes of LVCP after surgical closure of PDA in infants born preterm with, both during their NICU hospitalization and later in life.
- Develop therapies aimed at alleviating symptoms and restoring laryngeal function in ex-preterm children with LVCP after surgical closure of PDA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.prrv.2017.11.001.

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Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

A Systematic Review and Meta-Analysis: Incidence and consequences of left recurrent laryngeal nerve paralysis following surgical ligation of patent ductus arteriosus in extremely premature infants.

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

04/01/2016

4 Anticipated completion date

Give the date by which the review is expected to be completed.

31/12/2016

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ✖

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Ms Merete S. Engeseth

7 Named contact email

Enter the electronic mail address of the named contact.

msen@hvl.no

8 Named contact address

Enter the full postal address for the named contact.

The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Inndalsveien 28, 5063 Bergen, Norway

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

0047 41566026

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, University of Bergen, Uni research Health, Bergen, Duke University, North Carolina

Website address:

www.hvl.no. www.uib.no, www.duke.edu

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Ms	Merete Salveson	Engeseth	1. The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences. 2. Department of Clinical Science, Section for Paediatrics, University of Bergen, Norway
Professor	Ola Drange	Røksund	1. The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway
Dr	Silje	Mæland	1.The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, 2.Uni research Health.
Dr	Nina Rydland	Olsen	1. The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences
Dr	Adam	Goode	1. Department of Orthopaedic surgery, Duke University, Durham, NC

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

The Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, are funding the PhD-student (Merete S. Engeseth).

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Professor	Thomas	Halvorsen	University of Bergen

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

What is the incidence of left vocal fold paresis after surgical ligation of patent ductus arteriosus among children born extremely premature?

What are the short- and long term consequences of left recurrent laryngeal nerve paresis following patent ductus arteriosus ligation among children born extremely premature?

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We will perform searches in MEDLINE, EMBASE, Cochrane and PsycINFO. We will search for population specific keywords like premature children and patent ductus arteriosus, and intervention specific keywords like surgical ligation. No limitations on Language or publication period in the search.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Condition: A significant and isolated patent ductus arteriosus. Outcome: Left recurrent laryngeal nerve paresis or left vocal fold/cord paresis/paralysis.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

We will include studies describing a main population or a sub-population of extremely premature children (< 28 weeks/< 1000g) who had a clinically significant patent ductus arteriosus.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Isolated surgical ligation of a patent ductus arteriosus, with and without preceding pharmacotherapy, with and without examination by laryngoscope. Operation performed in the neonatal intensive care unit bedside or in a standard operating room. We include different methods for ligation: suture, clip, and video-assisted surgery. Infants who have undergone surgery for other congenital anomalies or congenital heart disease as well will be excluded.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

Extremely premature infants who have had a significant and isolated patent ductus arteriosus, but have received pharmacotherapy (non-steroidal anti-inflammatory drugs like ibuprofen, indomethacin or acetaminophen) or conservative management (diuretics, fluid restriction, digoxin, mechanical ventilation) instead of surgery.

22 Types of study to be included

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

We will include prospective and retrospective observational studies (cohort-studies, cross-sectional studies, case-series, case-control studies). Case-series, case- control and case-report studies will be excluded from the meta-analysis. Editorials, reviews, summaries and comments will be excluded from the meta-analysis.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

Studies must have taken place in a neonatal intensive care unit.

24 Primary outcome(s)

Give the most important outcomes.

Prevalence of left recurrent laryngeal nerve palsy/paresis or vocal cord paresis or vocal fold paresis or vocal cord paralysis or vocal fold paralysis

Give information on timing and effect measures, as appropriate.

Diagnosis of left recurrent laryngeal nerve paresis made With- or without laryngoscopic examination. Outcomes reported both immediately (before 24 months of corrected gestational age) and/or at long term follow-up after surgical ligation of a patent ductus arteriosus.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Prevalence of any comorbidity and /or complication in the population such as chronic lung disease, bronchopulmonal dysplasia, mortality, sepsis, intraventricular haemorrhage, neurodevelopmental impairment, cognitive function, stridor, voice impairment, necrotizing enterecolitis, tube feeding, retinopathy of prematurity, lung function, exercise capacity, physical activity level.

Give information on timing and effect measures, as appropriate.

Bronchopulmonal dysplasia is defined as the need for supplemantal oxygen at 36 weeks corrected gestational age. Other outcomes reported in journal charts during infant period (before 24 months of corrected gestational age) or/and at long term follow-up.

26 Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Titles and abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two other review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer. One author will abstract data and an additional author will provide over reading with discrepancies resolved through discussion (with a third author, if needed). To obtain relevant, unreported data from studies we will contact the authors of the article. Extracted information will include: first author, year of publication, study setting; study population and participant demographics and baseline characteristics (gestational age, birthweight, surgical age, surgical weight); details of the intervention (type of surgery) and control conditions (type of management); study methodology; recruitment and study completion rates; prevalence of primary and secondary outcomes, times of measurement; type of diagnostic method (laryngoscopic or clinical diagnosis); time of follow-up.

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two review authors will independently assess the risk of bias in included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies reporting Prevalence Data. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

We plan to statistically pool results when >=2 studies are present for the same outcome. A pooled prevalence proportion and 95% CI will be used for primary outcomes. To analyze dichotomous consequences we will use odds ratio's and 95% CI as the measure of association. DerSimonian and Laird random effect models with inverse variance weighting will be used for all analyses. A Freeman-Tukey Double Arcsine Transformation will be used to stabilize the variances prior to pooling for prevalence estimates. Heterogeneity will be assessed with Cochrane's Q and I-squared with high heterogeneity indicated by a Q p-value 50%. All analyses will be conducted using Stata 14 (College Station, TX).

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

If significant heterogeneity is present, several subgroups will be explored to explain heterogeneity. Potential modifiers of prevalence include time of birth (extremely premature versus premature), birthweight, age at surgery, weight at surgery, type of surgery, diagnostic method (clinical diagnosis versus laryngoscopic examination). Potential modifiers of consequences include reason for surgery (a large PDA, failed pharmacological treatment, contraindicated pharmacological treatment), comorbidities, time of examination, time of follow-up, outcome measures reported in included studies. To analyze potential prevalence modification by subgroups we will use stratified estimates with significance tests of homogeneity of proportions (i.e., $p<0.05$).

Review general information

30 Type and method of review

Select the type of review and the review method from the drop down list.

Epidemiologic, Systematic review

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Norway

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
A paper will be submitted to a leading journal in this field.
Do you intend to publish the review on completion?
Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)
Systematic review
meta-analysis
extremely premature
premature
patent ductus arteriosus
persistent ductus arteriosus
surgical ligation
left recurrent laryngeal nerve
incidence
follow-up
vocal cord paresis

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.
Completed but not published

39 Any additional information

Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

Supplemental File 2. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Supplemental File 2. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplemental File 3. Study eligibility and exclusion criteria

Inclusion criteria	
Design	We will include prospective and retrospective observational studies.
Setting	Neonatal intensive care unit
Participants	Extremely premature children (≤ 28 weeks/≤ 1000g) with a clinically significant patent ductus arteriosus.
Intervention	Isolated surgical ligation of a patent ductus arteriosus.
Comparison	Extremely premature infants with patent ductus arteriosus, who received pharmacotherapy (non-steroidal anti-inflammatory drugs like ibuprofen, indomethacin or acetaminophen) and/or conservative management (diuretics, fluid restriction, digoxin, mechanical ventilation) instead of surgery.
Outcomes	Primary: Incidence of left vocal cord paralysis Secondary: Any reported outcome following left vocal cord paralysis.
Exclusion criteria	Exclusion of case-series and case-report studies, editorials, reviews, summaries and comments. Studies where less than 80% of the cohort are extremely premature or no subpopulation of EP infants were described.

Supplemental File 4. Search Strategy

Database: Cochrane Library
Hits: 77
Date Run: 20/12/16 10:53:11.306
Limitations: None

ID	Search Hits
#1	MeSH descriptor: [Ductus Arteriosus, Patent] explode all trees 240
#2	(patent ductus arteriosus or persistent ductus arteriosus) .ti,ab,kw 6
#3	#1 or #2 246
#4	MeSH descriptor: [Infant, Extremely Low Birth Weight] explode all trees 99
#5	MeSH descriptor: [Infant, Premature] explode all trees 3216
#6	(preterm infant* or premature infant* or low birth weight infant* or preterm neonate* or premature neonate* or low birth weight neonate* or extremely premature infant*) .ti,ab,kw 93
#7	#4 or #5 or #6 3360
#8	MeSH descriptor: [Ligation] explode all trees 642
#9	(ligation or ligature or surgical clip or clipping or closure or surgery or surgical or suture) 169342
#10	#8 or #9 169342
#11	#3 and #7 and #10 77

Database: MEDLINE(R) <1946 to Present> Ovid Technologies, Inc. Email Service
Hits: 1211
Date run: 20/12/16
Limitations: None
Search Strategy:

1 ductus Arteriosus, patent.mp. or Ductus Arteriosus, Patent/ (8624)
2 (persistent ductus arteriosus or patent ductus arteriosus).mp. (7952)
3 1 or 2 (11611)
4 infant, low birth weight/ or infant, very low birth weight/ or infant extremely low birth weight/ or infant,premature/ or infant, extremely premature/ (68874)
5 (preterm infant* or premature infant* or low birth weight infant*).mp. (43905)
6 (preterm neonate* or premature neonate* or low birth weight neonate*).mp. (6790)
7 4 or 5 or 6 (85646)
8 ligation/ (22455)
9 (ligation or ligature or surgical clip or clipping or closure or surgery or surgical or suture).mp. (1985810)
10 8 or 9 (1985810)
11 3 and 7 and 10 (1211)

Database: Embase <1974 to 2016 December 19>
Hits: 1573
Date Run: 20/12/16
Limitations: None
Search Strategy:
1 exp patent ductus arteriosus/ (14625)
2 (persistent ductus arteriosus or patent ductus arteriosus).mp. (15869)
3 1 or 2 (16218)
4 low birth weight/ or extremely low birth weight/ or very low birth weight/ (43514)
5 Prematurity/ or premature/ (95708)
6 (preterm infant* or premature infant* or low birth weight infant* or extremely premature infant*).mp. (49588)
7 (preterm neonate* or premature neonate* or low birth weight neonate*).mp. (8532)
8 4 or 5 or 6 or 7 (130545)
9 ligation/ (42905)
10 (ligation or ligature or surgical clip or clipping or surgery or surgical or suture).mp. [mp=title, abstract,
heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] (3461101)
11 9 or 10 (3461101)
12 3 and 8 and 11 (1573)

Database: PsycINFO <1806 to December Week 2 2016>
Hits: 18
Date run: 20/12/16
Limitations: None
Search Strategy:
1 Ductus arteriosus, patent/ (0)
2 (persistent ductus arteriosus or patent ductus arteriosus).mp. (59)
3 1 or 2 (59)
4 infant, low birth weight/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant,
premature/ or infant, extremely premature/ (0)
5 (preterm neonate* or premature neonate* or low birth weight neonate*).mp. (343)
6 (preterm infant* or premature infant* or low birth weight infant*).mp. (4056)
7 4 or 5 or 6 (4234)
8 ligation/ (0)
9 (ligation or ligature or surgical clip or clipping or closure or surgery or surgical or suture).mp. [mp=title,
abstract, heading word, table of contents, key concepts, original title, tests & measures] (45761)
10 8 or 9 (45761)
11 3 and 7 and 10 (18)

#	Query	Results
S11	S3 AND S7 AND S10	226
S10	S8 OR S9	214 544
S9	(ligation* or ligature* or surgical clip* or clipping* or closure* or surgery* or suture*)	214 544
S8	MH "ligation"	570
S7	S4 OR S5 OR S6	19 573
S6	(preterm infant* or premature infant* or preterm neonate* or premature neonate* or low birth weight infant*)	19 573
S5	(MH "Infant, Premature")	12 066
S4	(MH "Infant, Low Birth Weight") OR "infant, low birth weight" OR (MH "Infant, Very Low Birth Weight")	6,128
S3	S1 OR S2	946
S2	("persistent ductus arteriosus" or "patent ductus arteriosus")	675
S1	MH "Ductus arteriosus, patent"	683

Supplemental File 5. Newcastle - Ottawa Quality Assessment Scale for cohort studies.

Note: A study can be awarded a maximum of 1 star (⁕) for each numbered item within the Selection and Outcome categories. A maximum of 2 stars (**) can be given for Comparability.

Category	Description	Comments
Selection		
1.Representativeness of the exposed cohort	a) Truly representative of the average **extremely premature infant undergoing surgical ligation of patent ductus arteriosus** in the community* b) Somewhat representative of the average **extremely premature infant undergoing surgical ligation of patent ductus arteriosus** in the community *	EP = Extremely premature; born ≤ 28 weeks gestational age (GA) and/ or ≤ 1000g birthweight (BW). Inclusion criteria: 1) Description of more than 80% extremely premature infants infants in the cohort. 2) Description of total number of EP infants in the cohort and number of EP infants who had left vocal cord paresis after surgical ligation of patent ductus arteriosus, allowing a sub-analysis for extremely premature infants.
2. Selection of the non-exposed cohort	a) Drawn from the same community as the exposed cohort*	Non exposed cohort: Extremely premature infants with patent ductus arteriosus, not undergoing surgical ligation.
3. Ascertainment of exposure	a) Secure record (e.g., surgical records)*	Medical records documents exposure to surgical ligation of patent ductus arteriosus.
4. Demonstration that outcome of interest was not present at start of study	Yes*	Preoperative laryngoscopy examination of the vocal cords.
Comparability		
1.Comparability of cohorts on the basis of the design or analysis	a) Study controls for ….(select the most important factor) * b) Study controls for any additional factor*	a) Gestational age b) Birth weight, surgical weight
Outcome		
1) Assessment of outcome	a) Independent blind assessment*	Postoperative laryngoscopy examination of all infants in cohort (not only symptomatic infants).
2) Was follow-up long enough for outcomes to occur	a) Yes (select an adequate follow up period for outcome of interest) *	Laryngoscopy post PDA surgery
3) Adequacy of follow up of cohorts	a) Complete follow up - all subjects accounted for* b) Subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost) *	b) Assuming that it is not completely random which children who gets lost to follow-up, we set the limit on 20% loss to follow-up.

Supplemental File 6. Articles excluded from full-text screen, with reasons.

Not described LVCP in results (84)

Study	Year of publication
Avsar[1]	2016
Blesa Sanchez[2]	2010
Brooks[3]	2005
Canarelli[4]	1993
Cassady[5]	1989
Cho[6]	2010
Chock[7]	2014
Chorne [8]	2007
Clyman[9]	2009
Cooke[10]	1978
Coran[11]	1975
Coster[12]	1989
Cotton[13]	1978
Dasmahapatra[14]	1986
Dodge-Khatami[15]	2009
Dzukou[16]	2011
Fonseca[17]	2014
Gomez[18]	1980
Herrin[19]	1977
Hsiao[20]	2009
Hsu[21]	2012
Hwang[22]	2005
Isayama[23]	2015
Iwase[24]	2003
Janz-Robinson[25]	2015
Jhaveri[26]	2010
Kaempf[27]	2012
Kewitz[28]	1991
Kilman[29]	1974
Ko[30]	2009
Ko[31]	2013
Korbmacher[32]	2004
Kwinta[33]	2009
Lee[34]	2006
Lee[35]	2014
Lemon[36]	1986
Lewis[37]	1974
Limpert[38]	2003
Little[39]	2003
Locali[40]	2008
Lokku[41]	2016
Madan[42]	2009
Margaryan[43]	2009

Markush[44]	2014
Matuszczak-Wleklak[45]	2003
Mazzera [46]	2002
Merritt[47]	1978
Merritt[48]	1982
Metin [49]	2012
Mikhail[50]	1972
Mirea[51]	2012
Monteiro[52]	2007
Moore[53]	2012
Mortier[54]	1996
Murphy[55]	1974
Nelson[56]	1976
Nghiem[57]	1980
Niitu[58]	1984
Noori[59]	2009
Oc[60]	2012
Ochoa[61]	1981
Ochoa-Ramirez[62]	1983
Pace Napoleone[63]	2006
Piaszczynski [64]	2000
Rivera Sepulveda[65]	2013
Sasidharan[66]	1991
Sathanandam[67]	2016
Satur[68]	1991
Seghaye[69]	1997
Segura- Roldan[70]	1982
Sivakumar [71]	2007
Smith[72]	1981
Storch[73]	1986
Sung[74]	2014
Szymankiewicz[75]	2004
Tauzin[76]	2012
Ting [77]	2016
Tsang[78]	2005
Tscheliessnigg[79]	1981
Vida [80]	2009
Wilkerson[81]	1985
Youn[82]	2014
Zahn[83]	2015
Zahn[84]	2016

Not described a population of > 80% extremely premature or not described subpopulation of extremely premature (22)

Study	Year of publication
Benjacholmas[85]	2009
Carpes[86]	2011
Clarke[87]	1976
Fan[88]	1989
Davis[89]	1988
Demirturk[90]	2011
Eggert[91]	1982
Ekici[92]	2006
Koehne[93]	2001
Kozlov[94]	2014
Laborde[95]	1997
Mandhan[96]	2006
Naik-Mathuria[97]	2008
Niinikoski[98]	2000
Raval[99]	2007
Russel[100]	1998
Stankowski[101]	2016
Tantraworasin[102]	2012
Tashiro[103]	2014
Villa [104]	2004
Villa [105]	2006
Youn[106]	2013

No PDA surgery (2)

Study	Year of publication
Laughon[107]	2007
Truong[108]	2007

Not appropriate study design (2)

Study	Year of publication
Lopez Sousa[109]	2014
Malcolm[110]	2008

Dublicate (1)

Study	Year of publication
Ghosh[111]	1986

Other (1)

Author	Year of publication
Ziemer (chapter in book)[112]	1990

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Supplemental File 7. Quality assessment, Newcastle-Ottawa Scale for cohort studies

	Selection				**Comparability**	**Outcome**			**Overall**
First author, year	Representativeness of exposed cohort	Selection of non exposed cohort	Ascertainment of Exposure	Demonstration that outcome of interest not present at start	Comparability of cohorts on basis of design/ analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Alexander, 2009	*	*	*	-	* *	-	*	*	7/9
Benjamin, 2010	*	-	*	-	N/A	-	*	*	4/9
Clement, 2008	*	-	*	-	N/A	-	*	*	4/9
Ghosh, 1985	*	-	*	-	N/A	-	*	*	4/9
Heuchan, 2012	*	-	*	-	N/A	-	*	*	4/9
Hines, 2003	*	-	*	-	N/A	-	*	*	4/9
Hutchings, 2013	*	-	*	-	N/A	-	*	*	4/9
Ibrahim, 2015	*	-	*	-	N/A	-	*	*	4/9
Kang, 2013	*	-	*	-	N/A	-	*	*	4/9
Lee, 2008	*	-	*	-	N/A	-	*	*	4/9
Mandhan, 2009	*	-	*	-	N/A	-	*	*	4/9
Natarajan, 2010	*	-	*	-	N/A	-	*	*	4/9
Nichols, 2014	*	-	*	-	N/A	-	*	*	4/9
Pereira, 2006	*	-	*	-	N/A	-	*	*	4/9
Robie, 1996	*	-	*	-	N/A	-	*	*	4/9
Rukholm, 2012	*	-	*	-	N/A	-	*	*	4/9
Røksund, 2010	*	*	*	-	**	-	*	*	7/9
Smith, 2009	*	-	*	-	N/A	*	*	*	5/9
Spanos, 2009	*	-	*	-	N/A	-	*	-	3/9
Sørensen, 2010	*	-	*	-	N/A	-	*	*	4/9
Zbar, 1996	*	-	*	-	N/A	-	*	*	4/9

II

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ORIGINAL RESEARCH
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Voice and Exercise Related Respiratory Symptoms in Extremely Preterm Born Children After Neonatal Patent Ductus Arteriosus

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Objective: To investigate voice characteristics and exercise related respiratory symptoms in extremely preterm born 11-year-old children, focusing particularly on associations with management of a patent ductus arteriosus (PDA).

Study design: Prospective follow-up of all children born in Norway during 1999–2000 at gestational age <28 weeks or with birthweight <1,000 g. Neonatal data were obtained prospectively on custom-made registration forms completed by neonatologists. Voice characteristics and exercise related respiratory symptoms were obtained at 11 years by parental questionnaires.

Result: Questionnaires were returned for 228/372 (61%) eligible children, of whom 137 had no history of PDA. PDA had been noted in 91 participants, of whom 36 had been treated conservatively, 21 with indomethacin, and 34 with surgery. Compared to the children treated with indomethacin or conservatively, the odds ratio (95% confidence interval) for the surgically treated children were 3.4 (1.3; 9.2) for having breathing problems during exercise, 16.9 (2.0; 143.0) for having a hoarse voice, 4.7 (1.3; 16.7) for a voice that breaks when shouting, 4.6 (1.1; 19.1) for a voice that disturbs singing, and 3.7 (1.1; 12.3) for problems shouting or speaking loudly. The significance of surgery *per se* was uncertain since the duration of mechanical ventilation was associated with the same outcomes.

Conclusion: Extremely preterm born children with a neonatal history of PDA surgery had more problems with voice and breathing during exercise in mid-childhood than those whose PDA had been handled otherwise. The study underlines the causal heterogeneity of exercise related respiratory symptoms in preterm born children.

Keywords: patent ductus arteriosus, extremely premature infant, extremely low birth weight infant, voice quality, respiratory symptoms, cohort study

INTRODUCTION

Extremely preterm (EP) birth may lead to long-term complications, including respiratory problems of various etiologies (1). Survival at this early stage requires respiratory interventions, such as oxygen treatment and positive pressure ventilation, often with endotracheal intubation and mechanical ventilation (2, 3). Most of these lifesaving measures also cause various types of airway injuries with long-term consequences, challenging the diagnostic skills of health care providers (4–6).

Asthma, by far the most prevalent airway disorder, tends to be a first diagnostic option in young people with airway symptoms, often solely based on parental reports (7, 8). This practice inevitably leads to diagnostic errors, and is particularly unfortunate in EP-born individuals, given their wide causal repertoire (9–11). For example, bronchial obstruction and hyperresponsiveness are well described features after EP-birth as well as in asthma (12–16). Although linked to different immunological profiles (14, 16–19), large proportions of EP-born children are exposed to asthma medication (20). Recent literature has highlighted that also upper airway pathology creates respiratory symptoms that are misunderstood as asthma in EP-born children (21–23). We should keep in mind that the larynx is the narrowest part of the airway tree, representing a large proportion of total airway resistance (24). Thus, even minor injuries might hamper airflow when ventilatory requirements are high, such as during exercise. The larynx might be traumatized from repeated intubations or from prolonged use of mechanical ventilation (21, 25, 26). Moreover, surgical treatment of a patent ductus arteriosus (PDA) has been linked to left vocal cord paralysis (LVCP) in several studies, explained by the close proximity between the PDA and the left recurrent laryngeal nerve (11, 27, 28). Few studies have investigated symptoms of upper airway abnormalities in EP-born children (21, 26). We need more knowledge on these issues in order to develop evidence based guidelines for work-up of respiratory complaints in this group. Previous studies have suggested a role for laryngoscopy (11, 29–31); however, this notion needs support from more studies.

In this study, we used parental reports of voice abnormalities and exercise related respiratory symptoms to explore potential presence of upper airway pathology in a nationwide cohort of 11-year-old children born extremely preterm. Further, we investigated associations between these symptoms and neonatal PDA and its management.

MATERIALS AND METHODS

Study Population

This investigation was part of a Norwegian nationwide prospective cohort study of all children born with gestational age (GA) 23^0–27^6 weeks or birth weight (BW) below 1,000 g born during 1999–2000 (2). Of 638 children, 174 were stillborn or died in the delivery room, 86 died in the neonatal intensive care unit (NICU), and two declined participation (2). Three children died after discharge from NICU and one died later during the follow-up period, leaving 372 children eligible for inclusion. A "clinically significant PDA" had been diagnosed in 143 survivors, of whom 47 had undergone PDA surgery (**Figure 1**).

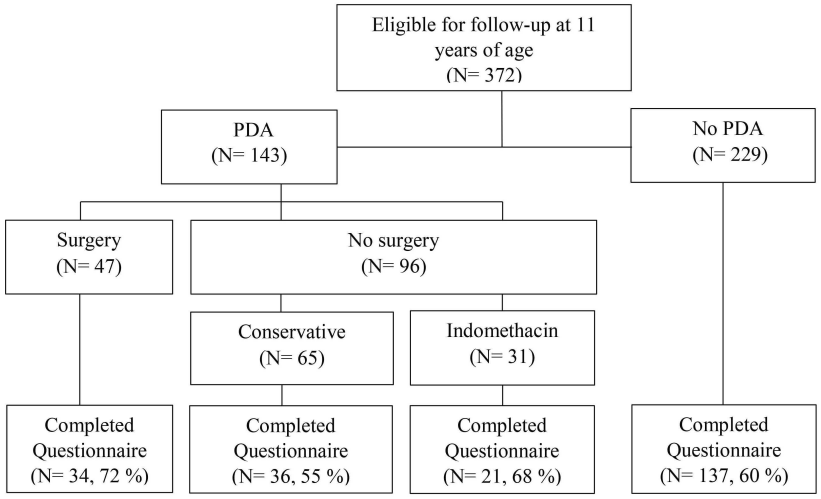
Sources and Collection of Data

Information on the neonatal characteristic and clinical course in the NICU was obtained from compulsory notifications to the Medical Birth Registry of Norway and custom-made study registration forms (2). GA was based on ultrasound at 17–18 weeks of gestation. Small for gestational age (SGA) was defined as a BW less than the 5th· percentile for GA and gender according to Norwegian growth curves (32). Bronchopulmonary dysplasia (BPD) was defined as still dependency on oxygen supplementation at 36 weeks' GA. The respiratory medical history of this cohort has been published (20, 33). PDA was diagnosed at the discretion of the participating NICUs, with algorithms based on echocardiographic assessment of the left atrium to the aortic root ratio (above 1.3–1.5 depending on clinical situation) and clinical signs as listed by Evans in 1993 (bounding hyper dynamic pulses and signs of cardiac or respiratory insufficiency) (34). Infants with a diagnosed PDA were treated either conservatively with fluid retention, diuretics, or unspecified symptomatic support, or the PDA was actively treated with either indomethacin or surgical closure performed by suture or clip.

At 11 years of age, data on previous and current symptoms were obtained from parental questionnaires. The questions: "*Does the child have breathing problems beyond what is normal during physical exertion?*" and "*Does the child make 'scraping sounds' or other abnormal sounds from the throat during physical exertion?*" were custom made for the project. The questions regarding exercise related wheeze, asthma (ever) and use of asthma medications were obtained from the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) (35). Current asthma was defined as [1] a physician's diagnosis of asthma combined with either respiratory symptoms or use of asthma medication in the previous 12 months, *or* [2] asthma medication and symptoms in the past 12 months even if no recall of prior physician's diagnosis. Asthma medication included inhaled corticosteroids, short or long acting β2-agonists and oral leukotriene modifiers. The six questions about voice characteristics were based on the Voice Handicap Index version 5 questionnaire (36). All questions were translated to Norwegian language, and the questions analyzed in this study are described in **Supplementary Table I**.

Statistical Methods

Outcome variables were voice characteristics and exercise related respiratory symptoms obtained from questionnaires at age 11 years. We investigated these binary outcomes in relation to a neonatal history of PDA vs. no PDA, and in relation to the mode of treatment in the children with a neonatal history of PDA. Those who underwent surgical closure (labeled "surgery") were compared with those who did not undergo surgery ("no-surgery"). The "no-surgery" group included children who had been treated conservatively or with indomethacin, as initial analyses comparing the conservative and the indomethacin group showed that they did not differ in terms of neonatal



Abbreviations: Conservative: children who had PDA and was treated conservatively with fluid retention, diuretics or unspecified symptomatic support, Indomethacin: children who had PDA and received indomethacin treatment, N: number of subjects, No surgery: children who had PDA and was treated conservatively or treated with indomethacin, PDA: patent ductus arteriosus; Surgery: children receiving surgical PDA treatment.

FIGURE 1 | Follow-up of a national cohort of all 372 children born extremely preterm in Norway during 1999 and 2000 at a gestational age <28 weeks and/or with a birth weight <1,000 g, according to management of patent ductus arteriosus in the neonatal period.

variables and outcomes. Questions with graded response alternatives were transposed to dichotomous variables (no/yes) (**Supplementary Table I**).

Group differences were tested using independent samples *t*-test and chi-square test or Fischer's exact test, as appropriate. We further investigated associations by odds ratios (OR) with 95% confidence intervals (CI) using binary logistic regression. The ORs were estimated with crude and adjusted models, adjusted for days on mechanical ventilation and GA. We did not present analyses with adjustment for postnatal steroids because there is no causal link between use of postnatal steroids and PDA surgery. Potential confounders were adjusted for one by one in order to avoid that the total number of variables entered into the final regression equations exceeded 1/10 of the number of events. All analyses were performed using IBM SPSS statistics version 24 for Windows.

Ethics

The regional ethical committee of Western Norway approved the study (REC number 2009/2271). Informed written consents were obtained from the participant's parents.

RESULTS

Subjects

Questionnaires were returned for 228 of the 372 (61%) eligible children; including 91 of 143 children with a neonatal history of PDA and 137 of 228 children without PDA. Among the 91 children with PDA, 34 (37%) were treated with surgery, 36 (40%) received conservative treatment, and 21 (23%) received indomethacin (**Figure 1**). Six children in the surgery group had received indomethacin. Among the surgically treated children, those lost to follow-up had lower GA and BW, and spent more days on invasive mechanical ventilation. Further details on neonatal characteristics of children who were assessed and lost to follow-up at 11 years of age are presented in **Supplementary Table II**.

Perinatal Characteristics

The children with a neonatal history of a PDA had lower GA, were more often intubated at birth, received more postnatal steroids and surfactant, had spent more days on continuous positive airway pressure (CPAP) and had more often developed BPD compared to children without PDA (**Table 1**). Those with PDA who were treated with surgical closure were born at lower GA, had spent more days on mechanical ventilation, and more often received postnatal steroids compared to the children with PDA who were not treated with surgery.

Questionnaire Based Data of Respiratory and Voice Related Symptoms at 11 Years of Age

Our data showed that exercise related respiratory symptoms or voice problems were more common in children with- than

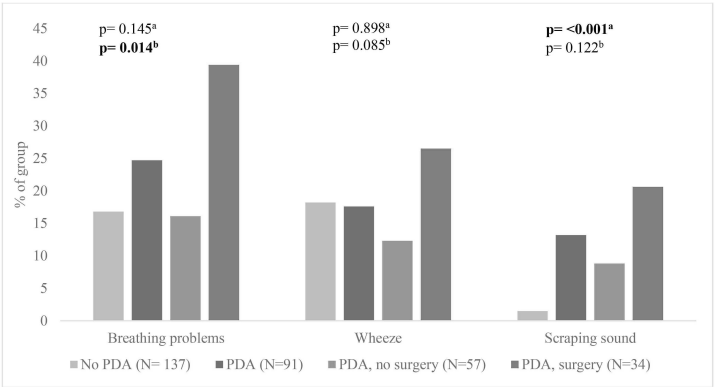
TABLE 1 | Neonatal characteristics of 228 extremely premature born children (<28 weeks GA/ <1,000 g BW) participating at the follow-up at 11 years of age.

	No PDA (*N* = 137)	PDA (*N* = 91)	PDA, no surgery (*N* = 57)	PDA, surgery (*N* = 34)	Mean difference (95% CI) No PDA vs. PDA	*p*	Mean difference (95% CI) no surgery vs. surgery	*p*
Characteristics, mean (SD)								
GA (weeks)	27.07 (1.7)	26.07 (1.4)	26.32 (1.3)	25.6 (1.4)	1.03 (0.6–1.4)	**<0.01**	0.73 (0.15–1.31)	**0.01**
Birth weight (gram)	865 (166.1)	866 (162.8)	886 (154.5)	832 (172.9)	−0.95 (-44.6–43.0)	0.97	53.5 (-16.1–123.0)	0.13
Start of PDA treatment, days after birth §								
Indomethacin			10.7 (7.4)	9.5 (5.2)				
PDA Surgery				13.4 (9.6)				
Days on invasive mechanical ventilation								
Mean (SD)	7.1 (15.7)	11.1 (14.0)	8.1 (9.3)	16.2 (18.6)	−3.96 (−7.8–0.04)	0.05	8.1 (1.2–15.0)	**0.02**
Median (range)	2 (0–113)	6 (0–83)	5 (0–44)	10.0 (0–83)				
Days on CPAP	22.8 (18.8)	28.4 (19.4)	29.7 (19.7)	26.1 (18.8)	−5.5 (−10.5; −0.6)	**0.03**	3.69 (−4.7–12.0)	0.38
Characteristics N (%)								
SGA	36 (26)	8 (9)	7 (12)	1 (3)		**0.001**		0.25
Sex (female)	63 (46)	41 (45)	28 (49)	13 (38)		0.185		0.31
BPD (O_2-suppl. at 36 weeks GA)	49 (36)	62 (68)	35 (61)	27 (79)		**<0.001**		0.08
Tracheal intubation at birth*	83 (64)	75 (82)	45 (79)	30 (88)		**0.001**		0.42
Surfactant	103 (75)	85 (93)	54 (95)	31 (91)		**<0.001**		0.67
Prenatal steroids	103 (75)	57 (63)	36 (63)	21 (62)		**0.04**		0.89
Postnatal steroids	37 (27)	45 (50)	23 (40)	22 (65)		**0.001**		**0.03**
Cerebral Palsy at 5 years of age	6 (4)	6 (7)	4 (7)	2 (6)		0.55		0.99

Independent t-test, chi-square test or Fischer's exact test was used as appropriate.

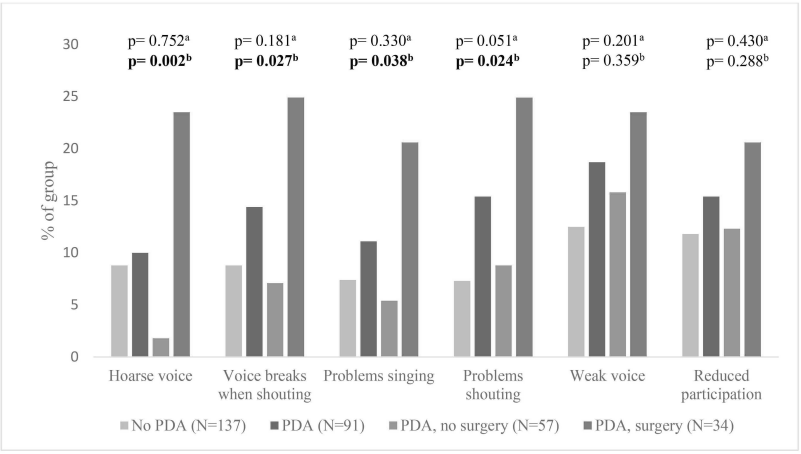
BPD, bronchopulmonary dysplasia; CI, confidence interval; CPAP, continuous positive airway pressure. GA, gestational age; IMV, invasive mechanical ventilation; PDA, patent ductus arteriosus; SD, standard deviation; SGA, small for gestational age.

**Missing data: Tracheal intubation at birth: Eight cases missing from the "no PDA" group and two cases missing from the "PDA"/"PDA, no surgery" groups. §Start of PDA treatment: Data are missing for nine children regarding age at day of PDA surgery. 21 children in the "PDA, no surgery" group received indomethacin treatment and six children in the "PDA, surgery" group received indomethacin treatment before surgery. Values in bold indicates a p-value of less than 0.05.*



P-values for group differences between PDA vs. no PDA[a] and surgery vs. no surgery[b]. Breathing problems: proportion who answered "a little more than normal" or "a lot more than normal" to question 1: "Does the child have breathing problems beyond what is normal during physical exertion? Wheeze: Proportion who answered "yes" to question 2: "During the last 12 months, has the child had heavy breathing or wheezing from the chest during or after physical exercise or play?" Scraping sound: proportion who answered "a little" or "a lot" to question 3: "Does the child make «scraping sounds» or other abnormal sounds from the throat during physical exertion?" Abbreviations: PDA: patent ductus arteriosus.

FIGURE 2 | Reported respiratory symptoms during or after physical activity among a national cohort of extremely preterm born children at 11 years of age according to diagnosis and treatment of patent ductus arteriosus in the neonatal period.



P-values for group differences between no PDA vs. PDA[a] and no surgery vs. surgery[b]. The bar graphs represents the proportion who answered affirmative ("A little", "Moderately", "A lot more" or "Extremely") to the following questions: Hoarse voice: "Is the child`s voice more hoarse compared to other children at the same age?", Voice cracks when shouting: "Does the voice «crack» when the child shouts?", Problems singing: "Does the voice influence the child`s participation in singing?", Problems shouting: " Does the child have problems with shouting or talking with a loud voice?", Weak voice: "Is the child`s voice so weak or unclear that it limits the possibility of being heard in a noisy environment?", Reduced participation: "Is the child`s voice influencing participation in school or regular social activities?" Abbreviations: PDA: patent ductus arteriosus.

FIGURE 3 | Reported voice characteristics among a national cohort of extremely preterm born children at the age of 11 years according to diagnosis and management of patent ductus arteriosus in the neonatal period.

without a neonatal history of PDA. However, differences were only statistically significant for scraping sound during physical exertion (**Figures 2**, **3**). There were no important differences in reports of asthma or use of asthma medications (**Figure 4**).

In children who had a neonatal history of PDA, surgical closure was associated with more frequent reports of breathing problems during physical exertion (**Figure 2**) and voice related symptoms (**Figure 3**) compared to the no-surgery group. There were no differences between the surgery group and the no-surgery group regarding current asthma, current use of asthma medication or ever having had asthma, but a higher proportion of the surgery group had previously received asthma medication compared to the no-surgery group (**Figure 4**). In total, one or more symptoms related to respiration during exertion or voice were reported for 20 (61%) of the participants in the surgery group and 17 (31%) in the no-surgery group ($p = 0.006$).

Logistic Regression Analyses

Exercise Related Respiratory Symptoms

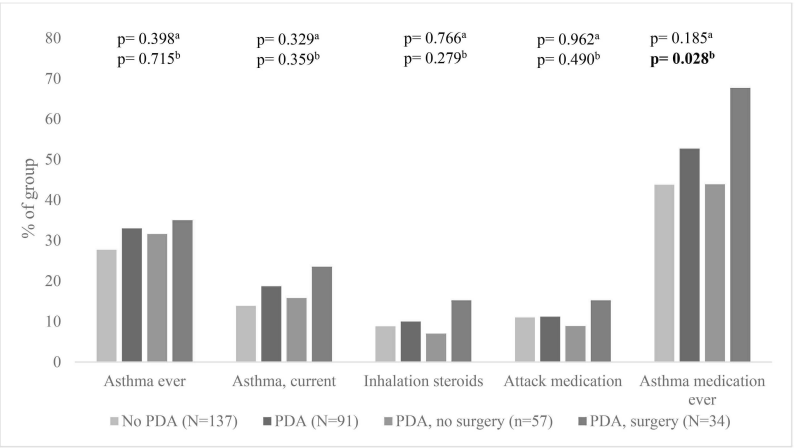
The odds ratio (OR) for having scraping sounds during physical exertion was increased among children with a PDA diagnosis (OR: 10.25; 95% CI: 2.24–47.0; $p = 0.03$) compared to the group without PDA, but not for other symptoms (not shown in tables). Among children with PDA, the crude odds of having breathing problems during physical exertion were higher in the surgery group relative to the no-surgery group (**Table 2**). After adjustment for number of days on mechanical ventilation, the OR of having breathing problems during physical exertion was still increased, but confidence intervals were wide. Adjusting for GA did not have impact on the OR.

Voice Characteristics

The OR for having symptoms related to voice was not increased among children with a PDA diagnosis, compared to the group without PDA. Among children with PDA, the crude odds of having a hoarse voice, a voice that breaks when shouting, a voice that affects participation in singing or a voice that leads to problems talking loudly/shout, were higher in the surgery group compared to the no-surgery group (**Table 3**). Adjusted for number of days on mechanical ventilation, the ORs were no longer increased for any of the voice characteristics. Adjusted for GA, the ORs were still increased for having a hoarse voice or a voice that cracks when shouting.

DISCUSSION

We found that voice and exercise related respiratory symptoms were more common in 11-year-old children born extremely preterm with a neonatal history of PDA surgery, compared to children whose PDA had been managed otherwise. However, the significance of surgery *per se* remains uncertain since adjusting



P-values for group differences between no PDA vs. PDA[a] and no surgery vs. surgery [b]. Asthma ever: parent reporting that the child has had asthma. Asthma, current: a doctor's diagnosis of asthma combined with either respiratory symptoms or use of asthma medication in the previous 12 months, or asthma medication and symptoms in the past 12 months even if no recall of prior doctor's diagnosis. Inhalation steroids: current use of inhaled corticosteroids. Attack medication: current use of short- or long acting β2-agonists. Asthma medication ever: use of inhaled corticosteroids, short or long acting β2-agonists and oral leukotriene modifiers after discharge from neonatal intensive care unit, but not current use. Abbreviations: PDA: patent ductus arteriosus.

FIGURE 4 | Reports of asthma and use of asthma medications among a national cohort of extremely preterm born children at 11 years of age according to diagnosis and treatment of patent ductus arteriosus in the neonatal period.

TABLE 2 | The odds ratio of having respiratory symptoms during or after physical activity at 11 years of age in a national cohort of extremely preterm born children according to treatment for patent ductus arteriosus (no surgery vs. surgery) in the neonatal period.

	PDA treatment	*N* (%)	Crude OR (95% CI)	*p*	aOR1 (95% CI)	*p*	aOR2 (95% CI)	*p*
Breathing problems	No surgery	9/56 (16)	3.4 (1.3–9.2)	**0.02**	2.6 (0.9–7.4)	0.08	3.2 (1.1–9.0)	**0.03**
	Surgery	13/33 (39)						
Wheeze	No surgery	7/57 (12)	2.6 (0.9–7.7)	0.09	2.5 (0.8–7.9)	0.11	2.8 (0.9–8.8)	0.08
	Surgery	9/34 (27)						
Scraping sound	No surgery	5/57 (9)	2.7 (0.8–9.3)	0.12	1.8 (0.5–6.8)	0.41	2.4 (0.7–8.7)	0.17
	Surgery	7/34 (21)						

Breathing problems: proportion who answered "a little more than normal" or "a lot more than normal" to question 1: "Does the child have breathing problems beyond what is normal during physical exertion?" Wheeze: Proportion who answered "yes" to question 2: "During the last 12 months, has the child had heavy breathing or wheezing from the chest during or after physical exercise or play?" Scraping sound: proportion who answered "a little" or "a lot" to question 3: "Does the child make ≪scraping sounds≫ or other abnormal sounds from the throat during physical exertion?" aOR1, adjusted for total number of days on invasive mechanical ventilation. aOR2, adjusted for gestational age; CI, confidence interval; OR, odds ratio; PDA, patent ductus arteriosus. Values in bold indicates a p-value of less than 0.05.

for days of mechanical ventilation significantly weakened the associations.

Previous studies have described that EP-born children with left vocal fold paralysis (LVCP) following PDA surgery had prolonged dependency of mechanical ventilation compared to surgically treated children without LVCP (11, 28, 37, 38). Unfortunately, the respective duration of mechanical ventilation before vs. after surgery could not be estimated in our study. Thus, prolonged mechanical ventilation in the surgery group could be *caused* by a possible LVCP or other complications following surgery (39). However, it could also reflect *confounding by indication*; i.e., those treated surgically were also those with the most severe disease, therefore spending most days ventilated (40). Both mechanisms might have been operative, but we do not have data to disentangle this scenario. Days on mechanical ventilation was associated with symptoms in all subgroups, also in those with no history of PDA, although at a lower odds ratio. The observed association (co-linearity) between days on mechanical ventilation and surgical PDA treatment complicates interpretations of the regression models. We therefore report both adjusted and unadjusted data in **Tables 2**, **3**. However, taken together the data indicate that neonatal PDA surgery leads to more voice and

TABLE 3 | The odds ratio of having voice symptoms at 11 years of age in a national cohort of extremely preterm born children according to treatment (no surgery vs. surgery) for patent ductus arteriosus in the neonatal period.

	PDA treatment	*N* (%)	Crude OR (95% CI)	*p*	aOR1 (95% CI)	*p*	aOR2 (95% CI)	*p*
Hoarse voice	No surgery	1/56 (2)	16.9 (2.0–143)	**0.009**	9.6 (1.0–93.8)	0.05	14.1 (1.6–122)	**0.02**
	Surgery	8/34 (24)						
Voice cracks when the child shouts	No surgery	4/56 (7)	4.7 (1.3–16.7)	**0.017**	3.2 (1.2–20.7)	0.10	3.9 (1.1–14.4)	**0.04**
	Surgery	9/34 (27)						
Voice influences participation in singing	No surgery	3/56 (5)	4.6 (1.1–19.1)	**0.04**	2.8 (0.6–13.1)	0.19	3.7 (0.9–16.2)	0.08
	Surgery	7/34 (21)						
Problems shouting or talking loudly	No surgery	5/57 (9)	3.7 (1.1–12.3)	**0.03**	2.6 (0.7–9.3)	0.14	3.2 (0.9–10.9)	0.07
	Surgery	9/34 (27)						
Weak or unclear voice	No surgery	9/57 (16)	1.6 (0.6–4.8)	0.36	1.0 (0.3–3.4)	0.96	1.5 (0.5–4.6)	0.46
	Surgery	8/34 (24)						
Voice influences participation in school or social activities	No surgery	7/57 (12)	1.9 (0.6–5.8)	0.29	1.3 (0.4–4.4)	0.73	1.8 (0.5–5.8)	0.35
	Surgery	7/34 (21)						

N (%) represents proportion who answered affirmative ("A little," "Moderately," "A lot more" or "Extremely") to the following questions: Hoarse voice: "Is the child's voice more hoarse compared to other children at the same age? Voice cracks when the child shouts: Does the voice ≪crack≫ when the child shouts?," Voice influences participation in singing: "Does the voice influence the child's participation in singing?," Problems shouting or talking loudly: "Does the child have problems with shouting or talking with a loud voice?," Weak or unclear voice: "Is the child's voice so weak or unclear that it limits the possibility of being heard in a noisy environment?," Voice influences participation in school or social activities: "Is the child's voice influencing participation in school or regular social activities?." aOR1, adjusted for total number of days on invasive mechanical ventilation; aOR2, adjusted for gestational age; CI, confidence interval; OR, odds ratio; PDA, patent ductus arteriosus. Values in bold indicates a p-value of less than 0.05.

exercise related respiratory symptoms in mid-childhood, possibly influenced also by prolonged mechanical ventilation.

Management of PDA in EP-born neonates is debated. Options include a conservative approach, pharmacologic intervention, or surgical ligation, the latter usually used as a last resort (41, 42). Knowledge on long-term outcomes must count in these discussions. There are few studies reporting on voice characteristics and exercise related respiratory symptoms in children and adults exposed to neonatal PDA surgery (30). Although LVCP is a well-described complication, an unknown fraction may pass unnoticed or are misinterpreted during the neonatal period as symptoms may be vague, transient and uncharacteristic (27, 29, 37, 38, 43). Importantly, we know that pediatric LVCP does not usually recover (11, 44–46). Therefore, symptoms may continue to be overlooked or erroneously related to other disorders or even to malingering, later in life. We do not have research based data to substantiate this notion. However, early life events are rarely considered by respiratory specialists (5), and LVCP is probably not on top of the physicians' list when trying to interpret airway symptoms. In a regional study of 11 EP born adults who had undergone PDA surgery in the 1980s, seven had LVCP of whom six reported trouble with their voice. None of them were comfortable with singing or speaking loudly, and all disclosed prolonged inspirium, wheeze or stridor when tested on a treadmill (11). Importantly, three of them had a long history of "difficult-to-treat asthma," but they could substantially reduce medication after receiving the LVCP diagnosis. In our study, we found no association between PDA surgery and current asthma medication; however, a higher proportion of the surgically treated children had used asthma medication. Thus, breathing problems could initially have been perceived as asthma, and medication subsequently stopped due to lack of effect.

In the present study, we also identified children with respiratory and voice related symptoms among children with no history of PDA, or who had not undergone PDA surgery, implying that these symptoms are of multi-factorial origin. Prolonged mechanical ventilation is associated with subglottic stenosis and injury to the vocal cords (47), which may lead to stridor and affect voice (48). Walz et al. (25) found that prolonged intubation (more than 4 weeks) was associated with long-term reduced voice quality. In univariate analysis, both the presence of a PDA and surgical closure of a PDA were associated with lower score on voice related quality of life. In multivariate analysis, PDA did not contribute to the model, but PDA surgery was not included. French et al. (26) reported that 58% of school aged children born before 25 weeks' gestation had moderate to severe hoarseness, and that the number of intubations (more than five) was associated with voice disorders. The authors suggested that the voice abnormalities could be related to laryngeal injury from endotracheal intubation. As only three of the 67 tested children had undergone PDA surgery, they argued that surgery could not have contributed to the voice problems in their cohort (26). Simpson et al. (21) found that 25/35 very preterm born children presented with dysphonia at 11 years of age, and increased dysphonia severity was predicted by lower GA, increased number of intubations and days of mechanical ventilation. Only three subjects had undergone PDA surgery, but they represented 3/14 subjects with moderate to severe dysphonia. Presence of dysphonia was associated with reports of previous wheeze, asthma diagnosis and former use of asthma medications. However, there was no difference in lung function between groups with- or without dysphonia, and the authors suggested upper airway pathology and dysfunctional breathing contributing to increased reports of respiratory symptoms (21).

The major limitations of this study were the relatively small sample size and the fact that we relied on parental observation of respiratory and voice related symptoms. We know from asthma research that there are differences between parents' and children's perceptions (49). However, in this age group parental information is usually what we have to go by in clinical work. As in all follow-up studies, attrition influences interpretation; in our case underlined by differences between responders and non-responders listed in the appendix. Importantly, laryngoscopies had not been performed, precluding knowledge as to whether LVCP, or other laryngeal abnormalities contributed to the increased odds of respiratory and voice related symptoms in the PDA surgery group. Inability to ascertain why infants exposed to PDA surgery needed more days on mechanical ventilation challenged attempts to interpret the role of this variable in the regression models and thus in the causal chain leading to symptoms.

CONCLUSION

Extremely preterm born school-children who had undergone neonatal PDA surgery had more voice and exercise related respiratory symptoms than children exposed to other modes of PDA treatment. Although these symptoms are likely to have a compound etiology, when present in children exposed to neonatal PDA surgery, they must prompt a search for upper airway abnormalities, and not lead to empirical prescription of asthma medication. We must not forget early life events when dealing with respiratory symptoms.

DATA AVAILABILITY STATEMENT

Data from the study are available upon request. There are legal restrictions on sharing these data publicly due to the data containing sensitive and identifiable information. The data set contains information like birthweight, gestational age, birth data and gender - information that may be used to directly identify individuals as Norway is a small country and as extremely preterm birth applies to relatively few individuals in each hospital each year. In the informed consents signed by the guardians of the participants of this study, and granted by the regional committee for medical ethics in Helse Vest, guardians were not asked about data sharing.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Regional Commitee for Medical and Health Research Ethics west (REC number 2009/2271). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR'S NOTE

Preliminary data from this study was presented as an abstract at The European Respiratory Congress in 2018, where copyright is retained by the author or employer [as part of the conditions of the author(s)'s employment].

AUTHOR CONTRIBUTIONS

TH, TM, OR, MV, and HC designed the data collection instruments, collected the data, contributed to interpretation of the data, and reviewed and revised the manuscript for important intellectual content. ME contributed to the analyses and interpretation of the data, and reviewed and revised the manuscript for important intellectual content. RN contributed to the statistical analyses and interpretation of the data, and reviewed and revised the manuscript for important intellectual content. MSE carried out the statistical analyses and the interpretation of the data, drafted the article, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00150/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Table I Questions about respiration during or after physical activity and voice symptoms.

Respiration during/after physical activity		Answers	No surgery (N=57)	Surgery (N=34)	Missing N (%)
1.	Does the child have breathing problems beyond what is normal during physical exertion?	[0]No	47	20	54 (37.8)
		[1]A little more than normal	9	13	
		[1]A lot more than normal			
2.	During the last 12 months, has the child had heavy breathing or wheezing from the chest during or after physical exercise or play?	[0]No	50	25	52 (36.4)
		[1]Yes	7	9	
3.	Does the child make «grinding sounds» or other abnormal sounds from the throat during physical exertion?	[0]No	52	27	52 (36.4)
		[1]A little	5	6	
		[1]A lot	0	1	
Voice					
4.	Is the child`s voice more hoarse compared to other children at the same age?	[0]Not at all	55	26	53 (37.1)
		[1]A little	0	6	
		[1]Moderately	1	0	
		[1]A lot more	0	2	
		[1]Extremely	0	0	
5.	Does the voice «break» when the child shouts?	[0]Not at all	52	25	53 (37.1)
		[1]A little	3	8	
		[1]Moderately	1	0	
		[1]A lot more	0	1	
		[1]Extremely	0	0	
6.	Does the voice influence the child`s participation in singing?	[0]Not at all	53	27	53 (37.1)
		[1]A little	2	4	
		[1]Moderately	1	3	
		[1]A lot more	0	0	
		[1]Extremely	0	0	
7.	Does the child have problems with shouting or talking with a loud voice?	[0]Not at all	52	25	52 (36.4)
		[1]A little	4	5	
		[1]Moderately	1	2	
		[1]A lot more	0	2	
		[1]Extremely	0	0	
8.	Is the child`s voice so weak or unclear that it limits the ability of being heard in a noisy environment?	[0]Not at all	48	26	52 (36.4)
		[1]A little	7	5	
		[1]Moderately	1	0	
		[1]A lot more	1	3	
		[1]Extremely	0	0	
9.	Is the child`s voice influencing participation in school or regular social activities?	[0]Not at all	50	27	52 (36.4)
		[1]A little	6	4	
		[1]Moderately	0	1	
		[1]A lot more	1	1	
		[1]Extremely	0	1	

Abbreviations: Missing: Representing how many of the 143 eligible children with PDA who did not respond to the question, 0: Coded as “No” or absence of characteristic in statistical analysis, 1: Coded as “Yes” (all degrees of yes) or presence of characteristic in statistical analysis. The questions were handed out in Norwegian language in this study, but they were translated back to English for the readers of this publication.

Supplementary Table II Neonatal characteristics of the 372 extremely premature born children (<28 weeks GA/<1000g BW) participating in the study or lost to follow-up at 11 years of age.

	No PDA (N=229)				PDA (N=143)				PDA, no surgery (N=96)				PDA surgery (N=47)			
	Participated at 11 years (N=137)	Lost to follow-up (N=92)	MD (95%CI)	p	Participated at 11 years (N=91)	Lost to follow-up (N=52)	MD (95%CI)	p	Participated at 11 years (N=57)	Lost to follow-up (N=39)	MD (95%CI)	p	Participated at 11 years (N=34)	Lost to follow-up (N=13)	MD (95%CI)	p
Characteristics, mean (SD)																
GA (weeks)	27.1 (1.7)	26.6 (1.8)	0.4 (-0.0 - 0.9)	0.06	26.0 (1.4)	25.7 (1.3)	0.33 (-0.14 - 0.80)	0.17	26.3 (1.3)	26.1 (1.2)	0.21 (-0.32 - 0.74)	0.43	25.6 (1.35)	24.5 (1.05)	1.1 (0.2 - 1.9)	**0.02**
BW (gram)	865 (166)	857 (179)	8 (-38 - 53)	0.72	866 (163)	834 (184)	32 (-27 - 90)	0.29	886 (155)	888 (170)	-2 (-69 - 64)	0.95	832 (173)	673 (124)	159 (53 - 265)	**0.004**
Days on IMV	7.1 (15.7)	7.3 (16.0)	0.2 (-4.4 - 4.0)	0.94	11.1 (14.0)	14.5 (19.8)	-3.37 (-8.99 - 2.24)	0.24	8.1 (9.3)	7.7 (10.6)	0.38 (-3.67 - 4.4)	0.85	16.2 (18.6)	34.8 (26.9)	18.7 (4.8 - 32.5)	**0.01**
Days on CPAP	22.8 (18.2)	24.2 (19.6)	1.4 (-6.3 - 3.6)	0.60	28.4 (19.4)	26.4 (18.4)	1.92 (-4.62 - 8.46)	0.56	29.7 (19.7)	22.7 (15.0)	7.02 (-0.02 - 14.06)	0.05	26.1 (18.8)	37.6 (23.6)	11.6 (-24.8 - 1.7)	0.09
Characteristics, N (%)																
SGA	36 (26)	20 (22)		0.43	8 (9)	5 (10)		0.99	7 (12)	3 (8)		0.74	1(3)	2 (15)		0.18
Sex (female)	74 (54)	37 (40)		**0.04**	41 (45)	20 (39)		0.44	28 (49)	16 (41)		0.43	13 (38)	4 (31)		0.74
BPD	49 (36)	33 (36)		0.99	62 (68)	21 (40)		**0.001**	35 (61)	9 (23)		**<0.001**	27 (79)	12 (92)		0.41
Tracheal intubation (birth)*	83 (64)	45 (52)		0.06	75 (84)	44 (86)		0.75	45 (82)	31 (82)		0.98	30 (88)	13 (100)		0.56
Surfactant	103 (75)	60 (65)		0.10	85 (93)	48 (92)		0.99	54 (95)	35 (90)		0.44	31 (91)	13 (100)		0.55
Prenatal steroids	103 (75)	63 (69)		0.27	57 (63)	34 (65)		0.74	36 (63)	23 (59)		0.68	21 (62)	11 (85)		0.18
Postnatal steroids	37 (27)	23 (25)		0.74	45 (50)	24 (46)		0.70	23 (40)	12 (31)		0.34	22 (65)	12 (92)		0.08
Cerebral Palsy	6 (4)	9 (10)		0.11	6 (7)	8 (15)		0.09	4 (7)	4 (10)		0.71	2 (6)	4 (31)		**0.04**
GMFCS level 1	4	3			0	2			0	0			0	0		
2	0	1			2	2			2	2			0	2		
3	2	1			1	1			0	1			1	0		
4	0	1			2	1			2	0			0	2		
5	0	3			1	2			0	1			1	0		

Independent t-test, chi-square test or Fischer`s exact test was used as appropriate. Abbreviations: BPD: bronchopulmonary dysplasia (i.e. oxygen supplement at gestational age 36 weeks), BW: birth weight, CI: confidence interval, CPAP: continuous positive airway pressure. GA: gestational age, GMFCS: Gross Motor Function Classification System (1-5), IMV: invasive mechanical ventilation, MD: mean difference, PDA: patent ductus arteriosus, SD: standard deviation, SGA: small for gestational age, *Missing data: Tracheal intubation at birth: Eight cases from “no PDA, participated”, five cases from “no PDA, lost to follow-up”, two cases from “no surgery, participated”, and one case from “no surgery, lost to follow-up”.

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Left Vocal Cord Paralysis, Lung Function and Exercise Capacity in Young Adults Born Extremely Preterm With a History of Neonatal Patent Ductus Arteriosus Surgery—A National Cohort Study

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Background: Left vocal cord paralysis (LVCP) is a known complication of patent ductus arteriosus (PDA) surgery in extremely preterm (EP) born neonates; however, consequences of LVCP beyond the first year of life are insufficiently described. Both voice problems and breathing difficulties during physical activity could be expected with an impaired laryngeal inlet. More knowledge may improve the follow-up of EP-born subjects who underwent PDA surgery and prevent confusion between LVCP and other diagnoses.

Objectives: Examine the prevalence of LVCP in a nationwide cohort of adults born EP with a history of PDA surgery, and compare symptoms, lung function, and exercise capacity between groups with and without LVCP, and vs. controls born EP and at term.

Methods: Adults born EP (<28 weeks' gestation or birth weight <1,000 g) in Norway during 1999–2000 who underwent neonatal PDA surgery and controls born EP and at term were invited to complete questionnaires mapping voice-and respiratory symptoms, and to perform spirometry and maximal treadmill exercise testing. In the PDA-surgery group, exercise tests were performed with a laryngoscope positioned to evaluate laryngeal function.

Results: Thirty out of 48 (63%) eligible PDA-surgery subjects were examined at mean (standard deviation) age 19.4 (0.8) years, sixteen (53%) had LVCP. LVCP was associated with self-reported voice symptoms and laryngeal obstruction during exercise, not with lung function or peak oxygen consumption (VO_2peak). In the PDA-surgery group, forced expiratory volume in 1 second z-score (z-FEV_1) was reduced compared to EP-born controls ($n = 30$) and term-born controls ($n = 36$); mean (95% confidence interval) z-FEV_1 was −1.8 (−2.3, −1.2), −0.7 (−1.1, −0.3) and −0.3 (−0.5, −0.0), respectively.

For VO_2peak, corresponding figures were 37.5 (34.9, 40.2), 38.1 (35.1, 41.1), and 43.6 (41.0, 46.5) ml/kg/min, respectively.

Conclusions: LVCP was common in EP-born young adults who had undergone neonatal PDA surgery. Within the PDA-surgery group, LVCP was associated with self-reported voice symptoms and laryngeal obstruction during exercise, however we did not find an association with lung function or exercise capacity. Overall, the PDA-surgery group had reduced lung function compared to EP-born and term-born controls, whereas exercise capacity was similarly reduced for both the PDA-surgery and EP-born control groups when compared to term-born controls.

Keywords: infant: extremely premature, infant: extremely low birth weight, vocal cord paralysis, cohort studies, patent ductus arteriosus, ligation, bronchopulmonary dysplasia, exercise test

INTRODUCTION

Extreme preterm (EP) birth is associated with a number of perinatal complications causing short- and long-term morbidity (1, 2). A patent ductus arteriosus (PDA) is diagnosed in ∼40% of very low birth weight (<1,500 g) neonates and in 66% of EP-born neonates (3, 4). This shunt may give rise to cardiovascular dysfunction with pulmonary overcirculation and systemic hypoperfusion associated with worsening of lung disease, prolonged mechanical ventilation, increased risk of pulmonary hemorrhage, necrotizing enterocolitis, and intraventricular hemorrhage (5). Treatment options for PDA include a conservative symptomatic approach, pharmacological intervention, or surgical closure, the latter option usually representing a last resort (3, 6).

The left recurrent laryngeal nerve loops around the aorta in close proximity to the ductus arteriosus and left-sided vocal cord paralysis (LVCP) caused by iatrogenic nerve injury is a recognized complication of PDA surgery (7). Affected neonates may present with a weak cry, stridor, hoarseness, aspiration, and feeding problems (8, 9). Symptoms may be vague, and the condition can therefore pass unrecognized unless particularly examined for (10). Studies on EP-born neonates that report routine post-operative laryngoscopy have found incidences of LVCP ranging from 11 to 67% (7, 11).

Long-term consequences of LVCP in EP-born subjects beyond the first year of life are insufficiently described. A previous small study on EP-born adults who underwent neonatal PDA surgery discussed the possibility that LVCP occurring in the neonatal period may contribute to the long-term development of airway obstruction in this population (12), however, further research is needed on this topic. Moreover, both voice problems and breathing difficulties during physical activity could be expected with an impaired laryngeal inlet (13). More knowledge on long-term consequences of LVCP in the preterm population may prevent confusion between LVCP and other diagnoses with similar symptoms such as asthma or exercise-induced laryngeal obstruction (EILO).

As a group, premature infants who undergo PDA surgery may be particularly vulnerable to long-term health problems. PDA surgery has been associated with both bronchopulmonary dysplasia (BPD) and poor neurological outcomes (5, 8). Furthermore, several studies have found EP-born subjects to have reduced exercise capacity compared to term-born peers (14). We hypothesized that EP-born adults with a neonatal history of PDA surgery are at increased risk of impaired pulmonary and cardiorespiratory function, and that LVCP is associated with poorer outcomes.

We aimed to investigate the prevalence of LVCP in young adults born EP who underwent open PDA surgery in Norway during 1999–2000. Secondly, we aimed to compare self-reported voice and breathing symptoms, lung function, exercise capacity, and laryngeal obstruction during exercise between subjects with and without LVCP. Finally, we aimed to compare the lung function and exercise capacity in those who underwent PDA surgery with those of comparable EP-born controls and term-born controls.

METHODS

Subjects and Study Design

This was a nationwide observational follow-up study of all individuals born in Norway at gestational age (GA) <28 weeks or birth weight (BW) <1,000 gram during 1999–2000 (15). The inclusion process, data collection, and outcome at discharge from the neonatal intensive care unit (NICU) have been described in previous reports (16). PDA surgery was performed at four different hospitals. The indication for surgery was determined at the discretion of the neonatologists responsible for neonatal care and was based on clinical signs and echocardiographic evaluation.

The present study was conducted during 2018–2020, enrolling three groups (**Figure 1**):

(1) PDA-surgery: All individuals who had undergone neonatal PDA surgery and were enrolled in the nationwide cohort described above. This PDA-surgery group has two subgroups: those with and those without LVCP.
(2) EP-born controls: A regional sub-sample (Western Norway) of the same nationwide cohort from which the PDA-surgery group was recruited; however, with no history of neonatal PDA surgery.

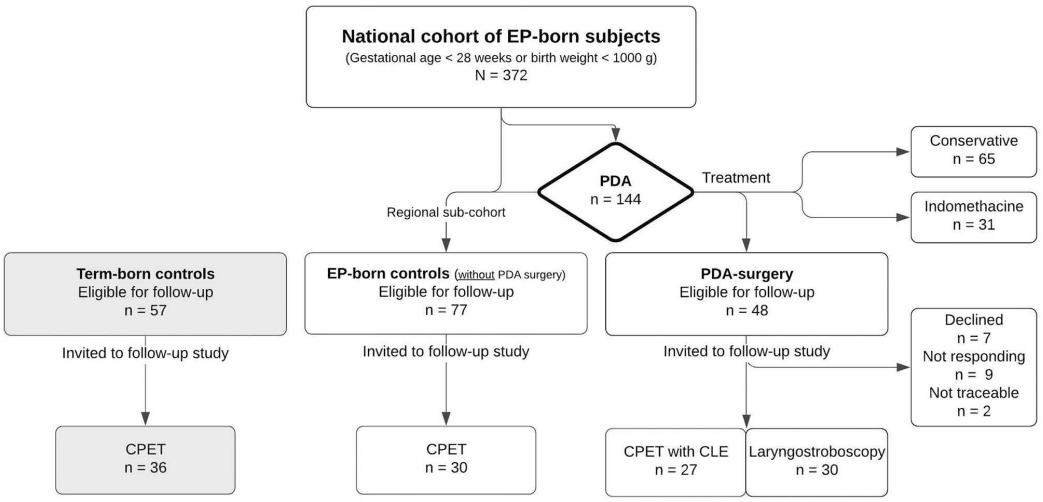

FIGURE 1 | Flow chart of the follow-up study of adults born extremely preterm with a neonatal history of patent ductus arteriosus surgery. CLE, continuous laryngoscopy exercise; CPET, cardiopulmonary exercise test; EP, extremely preterm (gestational age <28 weeks or birth weight <1,000 g); PDA: patent ductus arteriosus.

TABLE 1 | Early characteristics of the extremely preterm born adults enrolled in the national follow-up study on long-term consequences of neonatal patent ductus arteriosus surgery.

	PDA-surgery assessed		PDA-surgery not assessed			EP-born controls		
Characteristics	***n* = 30**		***n* = 18**		p^a	***n* = 30**		p^b
Female gender, *n* (%)	14	(47)	4	(22)	0.13	17	(57)	0.61
Birthweight, grams, mean (SD)[1]	792	(178)	781	(169)	0.83	845	(165)	0.24
Age of gestation, weeks, median (range)[2]	26	(23–29)	25	(23–27)	0.94	27	(24–31)	<0.001
Small for gestational age, *n* (%)	4	(13)	3	(17)	1.00	13	(43)	0.02
Prenatal steroids, *n* (%)	20	(67)	13	(72)	0.76	27	(90)	0.06
Surfactant, *n* (%)	27	(90)	18	(100)	0.28	24	(80)	0.47
Postnatal steroids, *n* (%)	20	(67)	14	(78)	0.52	8	(27)	0.004
Invasive ventilation, *n* (%)	29	(97)	17	(94)	1.00	25	(83)	0.20
Invasive ventilation, days, median (range)[2]	13	(1–87)	24	(1–52)	0.65	4	(1–21)	0.003
CPAP treatment, days, median (range)[2]	28.5	(0–92)	18	(4–58)	0.33	26	(0–72)	0.53
Patent ductus arteriosus, *n* (%)	30	(100)	18	(100)	1.00	11	(37)	<0.001
Age patent ductus arteriosus surgery, median (range)[2]	11	(4–34)	10	(2–36)	0.61	–	–	–
Bronchopulmonary dysplasia, *n* (%)	24	(80)	15	(83)	1.00	11	(37)	0.001
Normal neonatal cerebral ultrasound, *n* (%)	18	(60)	5	(28)	0.04	24	(80)	0.16

CPAP, continuous positive airway pressure; EP, Extremely preterm (gestational age <28 weeks or birthweight <1,000 g); PDA: patent ductus arteriosus. Bronchopulmonary dysplasia defined by oxygen supply and/or ventilatory support at gestational age 36 weeks. Prenatal steroids were recorded if given at least 24 h before delivery. Small for gestational age was defined as under the 10th percentile for gestational age (26). p) Fisher's exact test were used unless [1]independent t-test (equal variance not assumed) or [2]Mann-Whitney U-test is specified. [a]Differences between the group of subjects assessed and not assessed among those who had undergone PDA surgery; [b]Differences between the assessed PDA-surgery group and EP-born controls.

(3) Term-born controls: At 11 years of age, term born children were recruited as controls for the regional subsample of the EP-born children. The term born children were identified from birth protocols at the maternity ward and were invited as the next-born child of the same gender as the EP born child, with GA >37 weeks and BW >3,000 grams, corresponding to the Norwegian 10th-centile for BW.

TABLE 2 | Comparison of demographic and anthropometric variables between the groups of extremely preterm born subjects with- or without LVCP, EP-born controls and term-born controls.

			PDA-surgery					EP-born controls			Term-born controls			
	Total $n = 27$ (12 females)		LVCP $n = 14$ (5 females)		No LVCP $n = 13$ (7 females)			$n = 30$ (17 females)			$n = 36$ (13 females)			
Variables	Mean	SD	Mean	SD	Mean	SD	p^a	Mean	SD	p^b	Mean	SD	p^c	p^d
Age, years	19.4	0.7	19.3	0.7	19.5	0.8	0.40	20.4	1.0	<0.001	20.2	1.0	0.001	0.38
Height, *cm*	169.4	9.1	171.1	10.1	167.5	7.9	0.31	167.2	8.9	0.37	177.5	9.7	0.001	<0.001
Females	163.4	6.1	164.0	5.3	163.1	7.0	0.80	162.1	5.7	0.55	168.1	8.9	0.14	0.05
Males	174.1	8.4	175.1	10.1	172.8	5.6	0.58	173.9	7.9	0.95	182.8	5.0	<0.001	0.002
Weight, *kg*	63.8	12.7	65.5	12.4	61.9	13.2	0.47	65.4	16.5	0.68	73.7	14.7	0.006	0.04
Females	61.3	11.6	62.1	15.2	60.7	9.6	0.85	58.2	12.9	0.52	66.2	16.1	0.39	0.16
Males	65.8	13.5	67.4	11.0	63.4	17.4	0.63	74.8	16.3	0.13	77.9	12.3	0.009	0.55
BMI, kg/m^2	22.1	3.5	22.3	3.5	21.9	3.7	0.80	23.3	5.3	0.33	23.3	3.6	0.22	0.97
Females	22.8	3.4	22.9	4.7	22.7	2.5	0.92	22.2	5.4	0.75	23.2	4.0	0.78	0.58
Males	21.6	3.7	22.0	2.9	21.0	4.8	0.69	24.7	4.9	0.08	23.3	3.4	0.17	0.38

BMI, body mass index; EP, Extremely preterm (gestational age <28 weeks or birthweight <1,000 g); LVCP, left vocal cord paralysis; PDA, patent ductus arteriosus. p) Independent sample t-test (equal variance not assumed); [a]LVCP vs. no LVCP; [b]PDA-surgery group vs. EP-born controls; [c]PDA-surgery group vs. term-born controls; [d]EP-born controls vs. term-born controls.

Pulmonary Function

Vyntus® PNEUMO spirometer (Vyaire Medical GmbH, Leibnizstrasse, Hoechberg, Germany) was used to perform spirometry according to guidelines (17). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and FEV_1/FVC were recorded. Raw data were transformed to z-scores using the reference equations of the Global Lung Function Initiative (18).

Cardiopulmonary Exercise Test

Peak exercise capacity was determined using a computerized incremental treadmill (Woodway PPS 55 Med, Weil am Rhein, Germany) exercise test according to a modified Bruce protocol (19) using a Vyntus CPX unit powered by SentrySuite software (Vyaire Medical GmbH, Hoechberg, Germany). Speed and elevation were increased every 90 s from an initial slow-walking phase. The test was stopped when the subject indicated severe exhaustion, preferably supported by a respiratory exchange ratio (RER) exceeding 1.05 or heart rate exceeding 95% of predicted maximal heart rate (20).

Variables of gas exchange and airflow were measured breath by breath and averaged over 10 s. The highest values for oxygen uptake determined during the last 60 s were recorded as peak values (VO_2peak). VO_2peak was reported as ml/kg/min and as the percentage of predicted using reference equations from a large sample of Norwegian subjects of relevant age (21). Exercise performance was described by the completed distance (meters) on the treadmill. The percentage inspiratory time to total time in a respiratory cycle (T_i/T_{tot}%) was used to describe the breathing pattern. Breathing reserve was the difference between maximal voluntary ventilation (FEV_1 x 35) and peak minute ventilation reported as the percentage of maximal voluntary ventilation.

Continuous Laryngoscopy Exercise (CLE) Test

CPET in the PDA-surgery group was performed with concomitant continuous transnasal flexible video-laryngoscopy (ENF TYPE V2, video processor CV-170, OLYMPUS, Tokyo, Japan) as described previously (22). LVCP was identified and later verified by laryngeal stroboscopy. The video recordings of the laryngeal inlet during treadmill running were assessed and rated for laryngeal obstruction according to a modified version of the classification described by Maat et al. (23). Because of laryngeal asymmetry in subjects with LVCP, a modified CLE-score (0–24 points) was developed, assessing the right and left glottic and supraglottic areas separately. The visually assessed medial rotation of the aryepiglottic folds and medialization of the vocal folds were scored ranging from normal (0 points) to maximal (3 points) at moderate (fast walking) and at maximal effort. The left and right sides were scored separately. The total modified CLE-score was the sum of the sub-scores at moderate and maximal exercise.

Questionnaires

All participants were asked to complete an online questionnaire mapping several health issues. The PDA-surgery group filled in

TABLE 3 | Self-reported respiratory- and voice symptoms between groups of adults born EP with- or without LVCP and EP-born controls.

	PDA-surgery				EP-born controls	
Symptoms	**LVCP** ***N*** **= 14**	**No LVCP** ***N*** **= 13**	**OP** ***N*** **= 3**	***p*** [a]	***N*** **= 23**	***p*** [b]
Hoarse voice, *n* (%)	8 (57)	1 (8)	3 (100)	0.01	3 (13)	0.09
Voice affects participation in singing, *n* (%)	8 (57)	1 (8)	3 (100)	0.01	–	
Voice that cracks when shouting, *n* (%)	7 (50)	2 (15)	3 (100)	0.10	–	
Weak or unclear voice which limits the possibility for being heard in a noisy environment, *n* (%)	8 (57)	4 (31)	3 (100)	0.25	–	
Voice affects participation in school-work or social activities, *n* (%)	4 (29)	3 (23)	3 (100)	1.00	–	
None of the symptoms above, *n* (%)	2 (14)	9 (69)	0 (0)	0.006	–	
Asthma medications last 12 months, *n* (%)	3 (21)	1 (8)	1 (33)	0.60	4 (17)	1.00
Breathing problems beyond normal during normal physical exertion, *n* (%)	9 (64)	6 (46)	3 (100)	0.45	7 (30)	0.09
"Scraping" sound or abnormal sounds during physical exertion, *n* (%)	6 (42)	2 (15)	2 (67)	0.21	2 (9)	0.09

EP, extremely preterm (gestational age <28 weeks and/or birthweight <1,000 g); LVCP, left vocal cord paralysis; OP, other pathology; PDA, patent ductus arteriosus. p) Fisher's exact test [a]LVCP vs. no LVCP; [b]PDA-surgery group (LVCP + no LVCP) vs. EP-born controls.

an additional paper-based questionnaire adapted from the Voice Handicap Index with questions regarding voice symptoms (24). The question on physical activity was adapted from the European Community Respiratory Health Survey II questionnaire (25). The questions "*Do you have breathing problems beyond normal during physical exertion*?" *Do you make scraping sounds or other abnormal sounds from the throat during physical exertion? Is your voice hoarser than in others of the same age?* and *"Does your voice affect participation in singing?"* were custom-made for the project.

Statistical Methods

Data were analyzed using the statistical software SPSS version 26 (IBM SPPS Statistics, NY, USA) and MedCalc version 19.5.3 (MedCalc Software Ltd, Osted, Belgium). Group comparisons were performed using the independent samples *t*-tests (equal variance not assumed) with 95% confidence intervals (95% CI), Mann-Whitney *U*-tests, or Fisher's exact tests, as appropriate. Analysis of covariance was used when the outcome for completed distance and VO_2peak was adjusted for gender and self-reported physical activity (hours of exercise per week) and to adjust for bronchopulmonary dysplasia (BPD) when comparing lung function variables between the PDA-surgery group and the EP-born control group. To examine whether the difference in VO_2peak between all EP-born and term-born controls differed by gender, an interaction term for gender and group affiliation was included. Linear regression with the modified CLE-score and gender as predictors was used to investigate whether VO_2peak was associated with the CLE-score after adjusting for gender. *P*-values ≤ 0.05 was characterized as statistically significant.

Ethics

The Regional Committee for Medical and Health Research Ethics in Western Norway approved the study. Informed written consents were obtained from all participants, or their parents if subjects were not competent to give consent.

RESULTS

Thirty of 48 (63%) eligible subjects in the nationwide PDA-surgery cohort consented to participate (**Figure 1**). One participant was unable to perform spirometry, and two were unable to run on the treadmill because of neurodevelopmental disability. Neonatal and demographic characteristics are given in **Tables 1**, **2**.

Left Vocal Cord Paralysis

In the PDA-surgery group, sixteen (53%) subjects were diagnosed with LVCP. Two subjects (7%) had laryngeal stenosis in addition to LVCP, and one subject (3%) presented right-sided arytenoid prolapse with overlying left-sided arytenoid fold making vocal cord assessment during phonation difficult, and LVCP could therefore not be determined (these three subjects are referred to as *other pathology* and they were excluded from further analysis). Thirteen subjects (43%) had a normal laryngeal exam (no LVCP or major anatomic pathology). One subject with LVCP and all three subjects with *other pathology* were aware of their laryngeal pathology before entering this study, the remaining 12 were not. Within the PDA-surgery group, those with LVCP had more often received postnatal steroids compared to those with a normal larynx, whereas other neonatal characteristics were similar (**Supplementary File**).

Only 14% of those with LVCP compared to 69% of those without LVCP reported no voice-related symptoms ($p = 0.006$) (**Table 3**). Around 50% reported abnormal sounds from the throat and breathing problems during physical exertion, with no differences between the groups with and without LVCP. All three subjects with *other pathology* reported voice symptoms and breathing problems during physical exertion.

TABLE 4 | Comparison of spirometry results between groups of adults born EP with- or without LVCP, EP-born controls and term-born controls.

	PDA-surgery							EP-born controls			Term-born controls			
	Total $N = 26$ (12 females)		LVCP $n = 13$ (5 females)		No LVCP $n = 13$ (7 females)			$n = 30$ (17 females)			$n = 36$ (13 females)			
Variables	**Mean**	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**	p^a	**Mean**	**95%CI**	p^b	**Mean**	**95%CI**	p^c	p^d
FVC, *L*	4.11	3.68, 4.55	4.32	3.67, 4.97	3.90	3.26, 4.55	0.34	4.32	3.95, 4.68	0.46	5.17	4.80, 5.53	<0.001	0.001
FVC, *z-score*	−0.92	−1.44 to −0.40	−0.80	−1.35 to −0.25	−1.05	−2.02, 0.07	0.64	−0.16	−0.49 to 0.18	0.02	−0.10	−0.32 to 0.12	0.005	0.77
FEV_1, *L*	3.10	2.76, 3.44	3.25	2.69, 3.80	2.96	2.49, 3.42	0.39	3.49	3.21, 3.76	0.08	4.31	4.03, 4.59	<0.001	<0.001
FEV_1, *z-score*	−1.76	−2.31 to −1.21	−1.79	−2.52 to −1.06	−1.73	−2.68 to −0.79	0.92	−0.68	−1.07 to 0.29	0.002	−0.28	−0.51 to −0.04	<0.001	0.08
FEV_1/FVC ratio	0.76	0.72, 0.80	0.75	0.69, 0.82	0.77	0.71, 0.83	0.74	0.81	0.79, 0.84	0.03	0.84	0.82, 0.86	<0.001	0.17
FEV_1/FVC, *z-score*	−1.50	−2.01 to −0.98	−1.52	−2.36 to −0.68	−1.47	−2.19 to −0.74	0.92	−0.81	−1.20 to −0.42	0.03	−0.36	−0.61 to −0.11	<0.001	0.06

EP, Extremely preterm (gestational age <28 weeks or birthweight <1,000 g); FEV_1: forced expiratory in 1 s; FVC, forced vital capacity; LVCP: left vocal cord paralysis; PDA: patent ductus arteriosus; 95%CI: 95% confidence interval. p) Independent sample t-test (equal variance not assumed); [a]LVCP vs. no LVCP; [b]PDA-surgery group vs. EP-born controls; [c]PDA-surgery group vs. term-born controls; [d]EP-born controls vs. term-born controls.

Lung Function

The three participants with *other pathology* were excluded from the analyses of lung function and exercise capacity. Within the PDA-surgery group, we did not find statistically significant differences in spirometry values between subjects with or without LVCP. However, clinically relevant differences could not be excluded given the wide the confidence intervals (**Table 4**).

The PDA surgery group had reduced z-FVC, z-FEV_1, and z-FEV_1/FVC, compared to the EP-born controls and the term-born controls (**Table 4**; **Figure 2**; **Supplementary File**). Neonatal BPD was present in 80% of the PDA-surgery group and in 37% of the EP-born controls, and BPD was associated with reduced z-FVC and z-FEV_1. Adjusting for BPD, z-FEV_1 was still significantly lower in the PDA-surgery group compared to the EP-born group with a mean (95%CI) difference of 0.89 (1.17, 1.61), $p = 0.02$.

Exercise Capacity

All participants ran to perceived maximal exhaustion and all achieved RER above 1.05 or heart rate above 95% predicted. Within the PDA-surgery group, we did not find statistically significant differences in completed distance, VO_2peak (ml/kg/min as well as the percentage of predicted), or self-reported physical activity for subjects with and without LVCP (**Table 5**; **Supplementary File**). However, clinically relevant differences could not be excluded given the wide confidence intervals. T_i/T_{tot}% was higher in the participants with LVCP compared to those without LVCP, and also higher than in the EP-born controls and the term-born controls. Mean (95% CI) difference between those with LVCP vs. all the other groups combined was 2.8% (1.6, 4.1) $p < 0.001$.

The PDA-surgery group had similar exercise capacity and self-reported physical activity as the EP-born control group. All EP-born participants combined (PDA-surgery and EP-born controls), ran a shorter distance, had lower VO_2peak (ml/kg/min), and reported less physical activity compared to term-born controls (**Table 5**; **Figures 2**, **3**; **Supplementary File**). Adjusted for gender, mean (95% CI) difference in completed distance and VO_2peak between all the EP-born participants combined vs. the term-born controls was 218 (114, 322) meters, $p < 0.001$, and 4.9 (1.8, 8.0) ml/kg/min, $p = 0.002$, respectively. There was no significant interaction effect between gender and group affiliation (all EP-born and term-born) on VO_2peak ($p = 0.16$). After additional controlling for physical activity, the completed distance on the treadmill was still shorter for EP-born participants compared to the term-born control group [mean (95% CI) difference 150 (39, 260) meters, $p = 0.009$]. Moreover, VO_2peak difference was slightly reduced [3.2 (−0.2, 6.7) ml/kg/min] and no longer statistically significant ($p = 0.07$).

Continuous Laryngoscopy Exercise Findings (PDA-Surgery Participants Only)

In the PDA-surgery group, 27/30 participants performed a CLE test. Among these, the modified CLE-score at moderate and maximal effort could not be determined in three subjects, and the

TABLE 5 | Comparison of cardiopulmonary exercise measures in the group of adults born EP with- or without LVCP, EP-born controls and term-born controls.

	PDA-surgery							EP-born controls			Term-born controls			
	Total *N* = 25 (12 females)		LVCP *n* = 13 (5 females)		No LVCP *n* = 12 (7 females)			*n* = 30 (17 females)			*n* = 36 (13 females)			
CPET variables	**Mean**	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**	p^a	**Mean**	**95%CI**	p^b	**Mean**	**95%CI**	p^c	p^d
Peak heart rate, *beat/min*	191	185, 197	191	181, 201	191	183, 199	0.98	193	190, 196	0.54	195	191, 198	0.27	0.43
RER at peak exercise, units	1.24	1.21, 1.28	1.22	1.16, 1.27	1.27	1.22, 1.31	0.16	1.27	1.23, 1.30	0.24	1.26	1.24, 1.28	0.36	0.65
Ti/Ttot, %	51.0	49.9, 52.1	52.4	51.2, 53.6	49.4	47.8, 51.0	0.004	49.7	48.7, 50.7	0.09	49.5	48.6, 50.3	0.03	0.75
Breathing reserve, %	17	11, 23	20	13, 28	13	3, 23	0.19	16	11, 22	0.93	11	6, 16	0.12	0.11
Peak respiratory rate, *breaths/min*	46	42, 50	43	38, 48	49	42, 55	0.13	48	44, 51	0.47	54	50, 58	0.003	0.01
Females	47	41, 53	44	35, 53	50	40, 60	0.27	46	42, 51	0.76	51	45, 57	0.36	0.19
Males	44	39, 50	43	35, 50	47	34, 61	0.42	49	44, 54	0.18	56	50, 61	0.004	0.06
Peak minute ventilation, *L/min*	89	74, 99	90	74, 105	89	75, 103	0.94	101	92, 110	0.07	134	123, 144	<0.001	<0.001
Females	77	67, 86	72	51, 93	80	66, 94	0.43	90	80, 99	0.07	102	93, 110	<0.001	0.03
Males	101	86, 115	101	80, 121	101	68, 135	0.95	118	106, 129	0.06	152	141, 162	<0.001	<0.001
Distance, *meter*	892	805, 978	935	783, 1,086	835	779, 890	0.19	858	763, 953	0.59	1,117	1,017, 1,216	0.001	<0.001
Females	856	627, 1,084	932	305, 1,558	780	682, 878	0.50	777	667, 887	0.49	917	810, 1,024	0.59	0.06
Males	914	840, 988	936	809, 1,063	879	820, 937	0.35	964	801, 1,127	0.55	1,230	1,104, 1,355	<0.001	0.01
Peak VO_2, *ml/kg/min*	37.5	34.9, 40.2	38.5	33.6, 43.4	36.5	33.9, 39.0	0.43	38.1	35.1, 41.1	0.76	43.6	41.0, 46.5	0.002	0.007
Females	35.8	31.0, 40.5	38.1	23.9, 52.3	34.1	31.8, 36.4	0.48	36.4	32.6, 40.2	0.82	38.5	35.0, 42.0	0.32	0.40
Males	39.2	36.1, 42.3	38.8	33.7, 43.9	39.8	35.6, 44.0	0.70	40.4	35.2, 45.5	0.67	46.6	43.3, 49.9	0.001	0.04
Peak VO_2, *% of predicted*	79.6	73.5, 85.8	80.3	68.1, 92.4	79.0	74.9, 79.3	0.83	83.1	76.5, 89.6	0.44	90.2	85.5, 94.9	0.007	0.08
Females	85.0	73.6, 96.4	90.6	56.3, 124.9	81.0	75.5, 86.6	0.49	87.4	78.1, 96.6	0.73	92.2	83.9, 100.4	0.28	0.41
Males	74.7	68.8, 80.5	73.8	64.1, 83.5	76.1	68.3, 83.9	0.65	77.4	67.8, 87.1	0.60	89.1	82.9, 95.3	0.001	0.04

CPET, cardiopulmonary exercise test; EP, Extremely preterm (gestational age <28 weeks and/or birthweight <1,000 g); LVCP, left vocal cord paralysis; PDA, patent ductus arteriosus; RER, respiratory exchange ratio; Ti/Ttot, Inspiratory time/Total inspiratory and expiratory time ratio; VO_2, oxygen consumption; 95% CI, 95% confidence interval. Breathing reserve is the difference between maximal voluntary ventilation (FEV_1 x 35) and peak minute ventilation reported as the percentage of maximal voluntary ventilation. (p) Independent sample t-test (equal variance not assumed); [a]LVCP vs. no LVCP; [b]PDA-surgery group vs. EP-born controls; [c]PDA-surgery group vs. term-born controls; [d]EP-born controls vs. term-born controls.

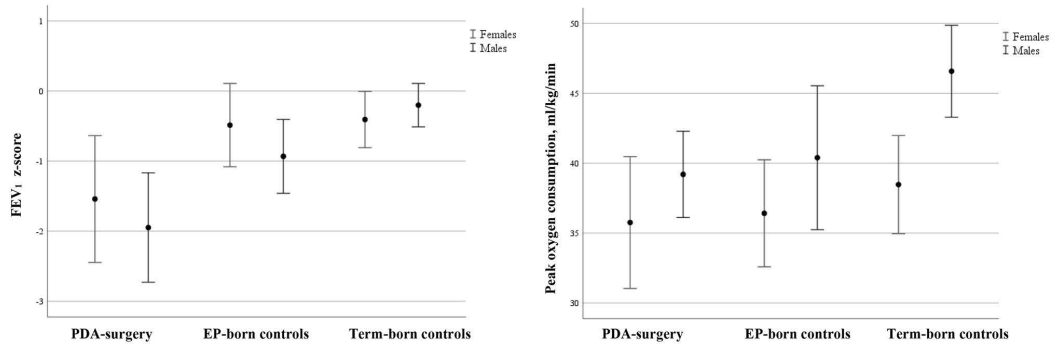

FIGURE 2 | Comparison of lung function and oxygen consumption between EP adults who underwent neonatal patent ductus arteriosus surgery, EP-born controls, and term-born controls. Error bars of mean with 95% CI for FEV_1 z-score and peak oxygen consumption (ml/kg/min) for the PDA-surgery group, EP-born controls, and term-born controls stratified by gender. *Abbreviations*: EP: extremely preterm (gestational age <28 weeks and/or birth weight <1,000 g); PDA: patent ductus arteriousus.

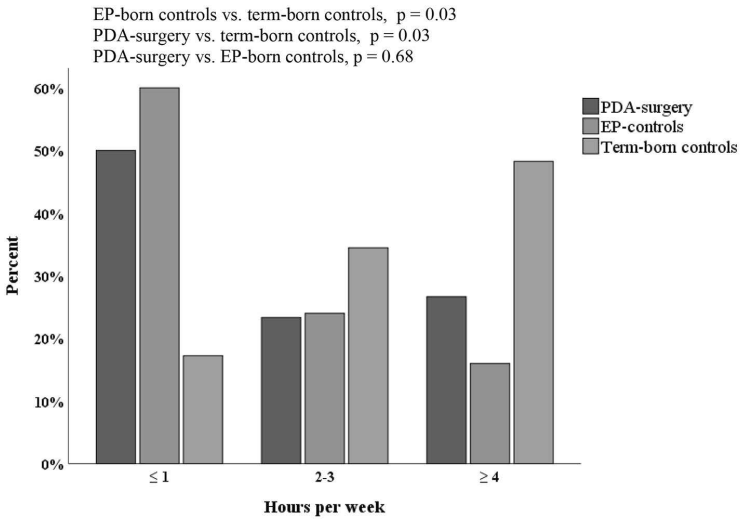

FIGURE 3 | Self-reported physical activity among the EP-born participants who underwent neonatal PDA surgery, EP-born controls and term-born controls. Answer to the self-reported question *"How many hours per week do you attend sports, exercise, or exert yourself so much that you get out of breath and/or sweat?"* Response rate: PDA-surgery: $n = 30/30$, EP-born controls: $n = 25/30$, Term-born controls: $n = 29/36$ p) Chi-square test. EP, extremely preterm (gestational age <28 weeks and/or birth weight <1,000 g); PDA, patent ductus arteriousus.

total score was derived from the sub-scores at rest and maximal effort, or at rest and moderate effort.

In the group with LVCP, all but one had a modified CLE-score >4, indicating laryngeal obstruction during exercise. In those with no LVCP, only three subjects had a modified CLE-score >4 (**Figure 4**), which suggests they had the specific diagnosis of EILO as all had normal larynx at rest (27). **Figure 5** demonstrates the laryngeal inlet in three participants, one with a normal larynx and two with LVCP.

The group of subjects reporting breathing difficulties during exercise and those reporting abnormal sounds from the throat during exercise did not have a higher modified CLE-score than those without these symptoms (**Supplementary File**). Furthermore, the modified CLE-score was not associated with VO_2peak after adjusting for gender ($p = 0.40$).

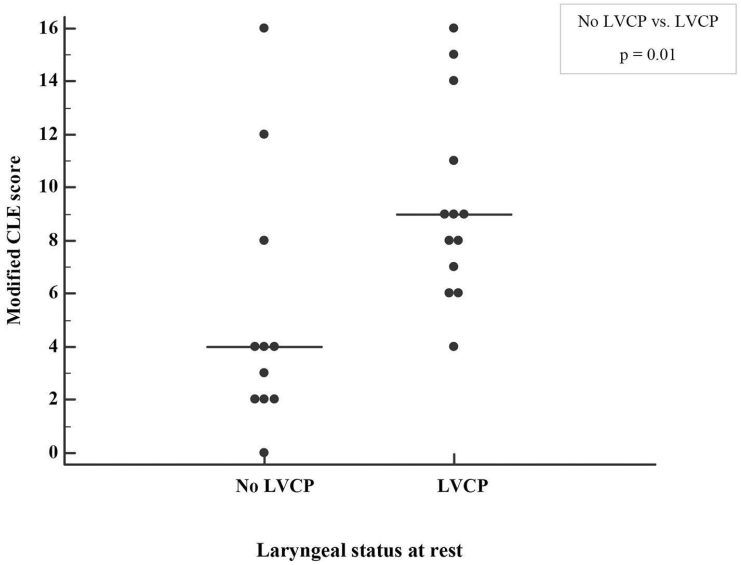

FIGURE 4 | Laryngeal obstruction during exercise graded by a modified continuous laryngoscopy exercise (CLE) score in the adults born EP with or without left vocal cord paralysis (LVCP). The median CLE-scores are indicated by horizontal lines. p) Mann-Whitney *U*-test.

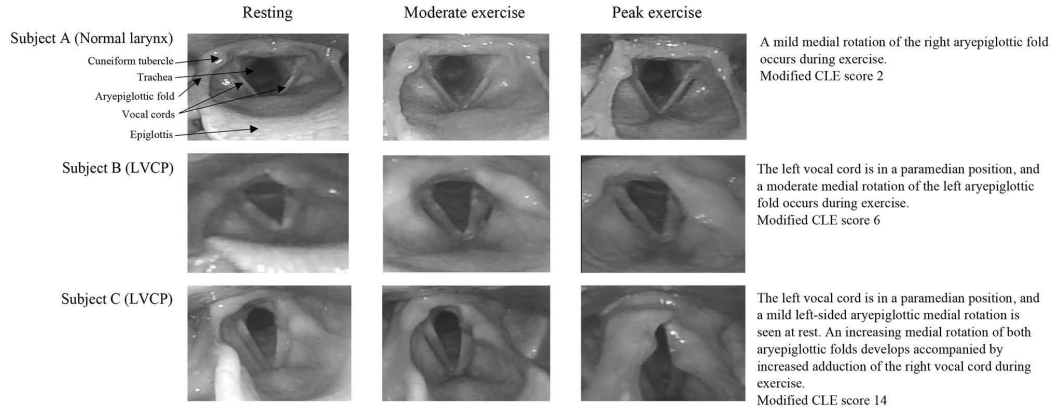

FIGURE 5 | Images of the larynx during exercise in EP-born individuals who had undergone neonatal PDA surgery.

DISCUSSION

This is the first study to report the prevalence of LVCP in a national cohort of young adults with a history of EP birth and surgical closure of PDA during their neonatal period. Within the PDA-surgery group, more than half of the participating subjects were diagnosed with LVCP, which was associated with characteristic voice symptoms, prolonged inspiratory to total respiratory time, and laryngeal obstruction during exercise. We did not find an association between LVCP and lung function or exercise capacity, however, the power to detect such associations was low due to the limited sample size. Overall, the PDA-surgery group had impaired lung function compared to EP-born as well as term-born controls, whereas exercise capacity was similarly reduced for both PDA-surgery and EP-born controls compared to term-born controls.

Studies examining LVCP after PDA surgery in EP-born neonates have mainly been performed in the immediate postoperative period or during infancy (28). Our group has previously identified LVCP in 7 of 11 EP-born adults

participating in a small local cohort study (12). In this national study, the prevalence of LVCP was 53%, compared to the 32% reported in a meta-analysis of studies examining all infants after PDA surgery (28). Performing laryngeal examinations on neonates is challenging, and pathology may be overlooked (29). This may explain the high prevalence of LVCP in studies assessing adults who are easier to examine. We do not have complete information on whether clips or ligature were used for PDA closure; hence, we could not assess a possible influence from the mode of surgery.

Dysphonia is a known long-term complication of preterm birth and is associated with extreme prematurity, emergency intubations, and multiple intubations, as well as PDA surgery (13, 30, 31). Unilateral vocal cord paralysis is associated with social and physical limitations and reduced health-related quality of life (32). There were more reports of voice symptoms in the subjects with LVCP; however, about one-third of subjects without LVCP also reported voice symptoms. Several of the subjects with LVCP in our study reported that their voice affected their participation in singing, social activities, and schoolwork. Surgical treatment and voice therapy may improve voice quality, and we encourage that a laryngeal examination is performed after neonatal PDA surgery (33).

Local traumas related to intubation and prolonged time on invasive mechanical ventilation are known risk factors for laryngeal injury (34). We found that 3/30 (10%) of the participants who underwent laryngoscopy had major laryngeal pathology other than LVCP. All three reported voice symptoms and breathing problems during exercise and all were aware of their malfunctioning larynx prior to study enrollment, contrasting the participants with LVCP, where only one had been aware of their pathology in advance. This certainly underlines the importance of suspecting laryngeal pathology in EP-born individuals with voice or respiratory complaints and to include an upper airway assessment to achieve a comprehensive understanding of their symptoms.

BPD and PDA

In the PDA-surgery group in this present study, more had BPD and the lung function was poorer in adulthood, compared to the EP-born control group. There is convincing evidence that preterm-born survivors with or without BPD have an increased risk for poor adult lung function (35). The association between PDA surgery and BPD has been reported earlier (8, 36), and may be explained by more severe neonatal respiratory illness, as PDA surgery tends to be performed as "rescue therapy" in infants with already advanced lung disease and/or failed pharmacological treatment of PDA (5, 37). However, population-based observational studies have suggested that early surgical ligation is an independent risk factor for BPD (38, 39). A re-examination of the only randomized controlled trial investigating the effects of prophylactic PDA ligation vs. delayed ligation revealed a significant increase in BPD incidence in those who were ligated prophylactically (40). Animal studies support a link between PDA ligation and the development of chronic lung disease by increased expression of genes involved in pulmonary inflammation and decreased alveolar fluid clearance (41). However, these issues are incompletely understood.

Exercise Capacity, Physical Activity, and Laryngeal Obstruction During Exercise

In individuals with LVCP, the para-median position of a paralyzed left vocal cord would be expected to interfere with the normal exercise-induced dilation of the glottis, and thus potentially compromise airflow capacity and exercise capacity. We found that subjects with LVCP had prolonged inspiration and a tendency for a lower peak respiratory rate at peak exercise. By laryngoscopy, we observed severe laryngeal obstruction during exercise in several individuals affected with LVCP (**Figure 5**). However, LVCP and the modified CLE-score were not associated with VO_2peak. This finding is in line with our previous study, where no association between VO_2peak and LVCP was found in EP-born adults (12). The results from these two studies suggest that it is possible to obtain average exercise capacity despite a relatively severe laryngeal obstruction.

A number of long-term sequelae of EP birth may affect subsequent exercise capacity, such as cardiopulmonary and neuromuscular impairment, reduced skeletal muscle mass, and behavioral issues such as less participation in physical activity (2). A review of 22 studies on exercise capacity concluded that children and adults born preterm have 13% lower VO_2peak (ml/min/kg) than term-born, in line with the ∼11% (-4.9 ml/kg/min) lower VO_2peak observed for all our EP-born participants combined (14). Similar to previous reports, we found that a lower amount of physical activity may be an explanatory factor for the relatively modest deficit in VO_2peak (42). It is still not determined if an increased level of physical activity will lead to improved exercise capacity in EP-born adults. Morales Mestre et al. conducted a randomized intervention study on EP-born children diagnosed with BPD and found that a structured exercise program improved exercise capacity (43). We encourage more research to be invested in this area to expand the knowledge on participation in physical activity and trainability in the EP-born population.

Strengths and Limitations

The strengths of this study were a population-based design with several centers responsible for the PDA surgery, and a high rate of participation. It was a limitation that only the PDA-surgery group was examined with laryngoscopy. Undiscovered LVCP or other laryngeal pathology might have been present in the EP-born control group, due to e.g., pressure from a large PDA or a large pulmonary trunk (44). Furthermore, laryngoscopy was not performed in the neonatal period and preoperative pathology or spontaneous postoperative improvement of LVCP could not be assessed. Cardiopulmonary exercise data for the PDA-surgery group were obtained from CLE-tests, which we have shown can be used interchangeably with data obtained from a regular CPET (22). Information on physical activity was self-reported and not determined by a more objective method like accelerometry or diary. Furthermore, the question on physical activity did not include aspects of mode and intensity, factors that may have affected the correlation between VO_2peak and physical activity.

The number of eligible subjects was determined by the number of EP-born infants who underwent PDA surgery in Norway during 1999–2000. The sample size was relatively small with large variation within the groups, resulting in a reduced

power to detect differences in the subgroup analyses. About one-third of the eligible EP-born adults who had undergone PDA surgery were lost to follow-up (**Figure 1**). Recruiting young adults with a busy schedule is challenging and individuals with voice or breathing symptoms might have been more motivated to participate than individuals without such symptoms. The estimated prevalence of LVCP in this cohort lies within the range of 16/48 (33%) to 34/48 (71%) if no one or all non-participating subjects were diagnosed with LVCP. Furthermore, the study protocol requested treadmill running which might have motivated those able to and familiar with running to participate. More subjects in the participating group had a normal neonatal cerebral ultrasound compared to the non-participating group, implying a selection of subjects with less neurological sequela (**Table 1**).

Management of PDA in EP-born individuals is still under debate (45). Reports suggesting associations with negative post-operative outcomes have contributed to a decline in the rate of PDA surgery in the last decade (46). However, selection by indication represents a challenge and may not have been fully accounted for when reporting on outcomes (5, 47). Choice of surgical procedure may also affect outcomes. Surgical ligation has been associated with higher rates of LVCP than surgical clipping (48). Unfortunately, we did not have complete information on surgical methods in our data set. New catheter-based procedures add options for PDA closure also for infants <1,000 g (49). Irrespective of future guidelines for PDA management, a population of EP-born subjects with a history of neonatal PDA surgery already exists. Therefore, clinicians caring for EP-born children and adults should be aware of symptoms and long-term outcomes associated with PDA-surgery and LVCP to ensure proper follow-up.

CONCLUSIONS

In this nationwide study, LVCP was present in 53% of EP-born young adults who had undergone neonatal PDA surgery. Within the PDA-surgery group, LVCP was associated with self-reported voice symptoms and laryngeal obstruction during exercise. We did not find an association between LVCP and lung function and exercise capacity, however; the power to detect such associations was low. Overall, the PDA-surgery group had impaired lung function compared to EP-born and term-born controls, whereas exercise capacity was similarly reduced for both PDA-surgery and EP-born controls compared to term-born controls.

Clinicians caring for EP-born children and adults should be aware of possible laryngeal sequelae after PDA surgery. Furthermore, EP-born subjects with a history of PDA surgery represent a population that needs follow-up to monitor lung function. Despite a high-risk start to life, EP-born individuals who underwent PDA surgery seem to achieve an exercise capacity only modestly decreased compared to term born individuals.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because in accordance with the approvals granted for this study by the Regional Committee on Medical Research Ethics and the Norwegian Data Inspectorate, the data files are stored securely and in accordance with the Norwegian Law of Privacy Protection. The data file cannot be made publicly available as this might compromise the respondents' privacy. Some of the participating centers are small and the number of extremely preterm births is limited with a risk of identifying anonymous participants. A subset of the data file with anonymized data can be made available to interested researchers upon reasonable request, providing Norwegian privacy legislation and GDPR are respected, and that permission is granted from The Norwegian Data Inspectorate and the data protection officer at Haukeland University Hospital. Requests to access the datasets should be directed to Maria Vollsæter, maria.vollseter@helse-bergen.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committees for Medical and Health Research Ethics West, The University of Bergen, 5021 Bergen, Norway. Informed written consents were obtained from all participants, or their parents if subjects were not competent to give consent.

AUTHOR CONTRIBUTIONS

ME and MSE have coordinated and collected data, organized data, carried out the analyses, drafted the initial manuscript, and revised the manuscript. MV has designed the data collection instruments, collected and organized data, and has reviewed and revised the manuscript. LS, OG, and IE have collected and organized data and critically reviewed the manuscript for important intellectual content. KH has given advice on the analysis of data, participated in the interpretation of the data, and critically reviewed the manuscript for important intellectual content. KØ, OR, and TH have provided funding, designed the data collection instruments, coordinated and supervised data collection, and have critically reviewed the manuscript for important intellectual content. HC has conceptualized and designed the study, designed the data collection instruments, drafted the initial manuscript, and has critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.780045/full#supplementary-material

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Supplementary Material

Supplementary table 1 Neonatal characteristics of the enrolled extremely preterm born adults who had undergone patent ductus arteriosus surgery

Characteristics	**PDA-surgery**						
	LVCP n = 14		No LVCP n = 13		Other pathology n = 3		*p*
Female gender, *n (%)*	5	(36)	7	(54)	2	(67)	0.45
Birthweight, *grams, mean (SD)* [1)]	767	(174)	820	(197)	786	(144)	0.47
Age of gestation, *weeks, median (range)*[2)]	25	(23-27)	26	(23-29)	25	(24-26)	0.32
Small for gestational age, *n (%)*	2	(14)	2	(8)	0	(0)	1.00
Prenatal steroids, *n (%)*	9	(64)	9	(69)	2	(67)	1.00
Surfactant, *n (%)*	13	(93)	12	(92)	2	(67)	1.00
Postnatal steroids, *n (%)*	12	(86)	5	(38)	3	(100)	0.02
Invasive ventilation, *n (%)*	14	(100)	12	(92)	3	(100)	0.48
Invasive ventilation, days, *median (range)* [2)]	15	(1-85)	10	(2-87)	17	(15-83)	0.30
CPAP treatment, days, *median (range)* [2)]	32.5	(0-92)	27	(2-58)	31	(23-50)	0.58
Age PDA surgery, *median (range)* [2)]	7.5	(4-31)	11	(4-35)	23	(11-27)	0.31
Bronchopulmonary dysplasia, *n (%)*	12	(86)	10	(77)	2	(67)	0.65
Normal cerebral ultrasound, *n (%)*	7	(50)	9	(69)	2	(67)	0.44

Abbreviations: CPAP: continuous positive airway pressure; EP: extremely preterm (gestational age < 28 weeks or birthweight < 1000 g); LVCP: left vocal cord paralysis; OP: other pathology; PDA: patent ductus arteriosus.

Bronchopulmonary dysplasia defined by oxygen supply and/or ventilatory support at gestational age 36 weeks. Small for gestational age was defined as under the 10th percentile for gestational age. Prenatal steroids were recorded if given at least 24 hours before delivery.

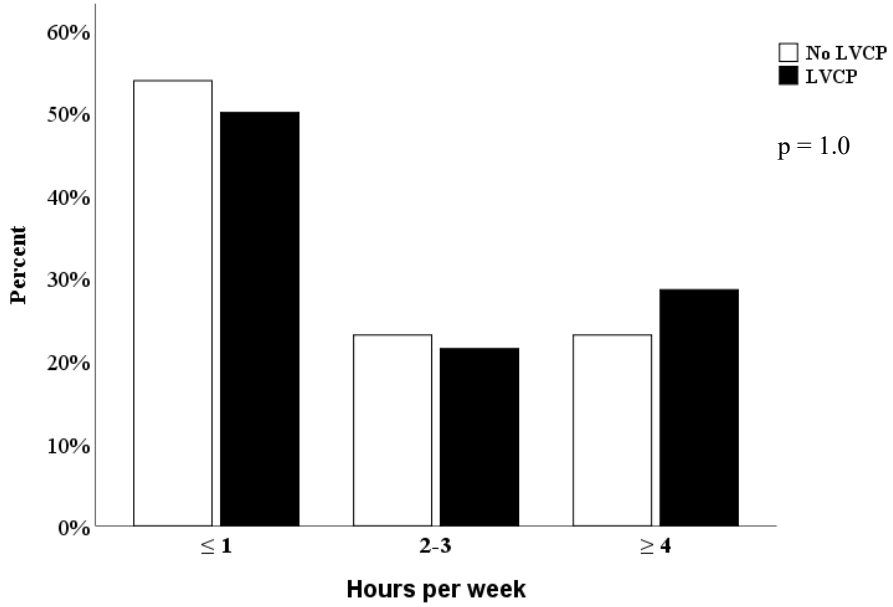
p) Fisher's exact test were used unless 1) independent t-test (equal variance not assumed) or 2) Mann-Whitney U test is specified.

Supplementary table 2 Differences in lung function and cardiopulmonary exercise measures between the group of young adults born EP with- or without LVCP, EP-born controls and term-born control

	Within PDA-surgery group: LVCP vs. no LVCP			**PDA-surgery group vs. EP-born controls**			**PDA-surgery group vs. term-born controls**			**EP-born controls vs. term-born controls**		
Spirometry variables	Mean diff	95%CI	p	Mean diff	95%CI	p	Mean diff	95%CI	p	Mean diff	95%CI	p
FVC, *z-score*	0.24	-0.83, 1.32	0.64	-0.77	-1.37, -0.16	0.02	-0.83	-1.39, -0.27	0.005	-0.06	-0.45, 0.34	0.77
FEV_1, z-score	-0.06	-1.19, 1.08	0.92	-1.08	-1.75, -0.42	0.002	-1.48	-2.08, -0.89	<0.001	-0.40	-0.85, 0.05	0.08
FEV_1/FVC, z-score	-0.05	-1.10, 1.00	0.92	-0.69	-1.32, -0.05	0.03	-1.14	-1.70, -0.57	<0.001	-0.45	-0.91, 0.01	0.06
CPET variables												
Peak heart rate, *beat/min*	0.2	-12.3, 12.6	0.98	-2.0	-8.8, 4.7	0.54	-3.9	-10.8, 3.1	0.27	-1.8	-6.3, 2.7	0.43
RER at peak exercise, units	-0.05	-0.12, 0.02	0.16	-0.03	-0.08, 0.02	0.24	-0.02	-0.06, 0.02	0.36	0.01	-0.03, 0.05	0.65
Ti/Ttot, %	3.0	1.1, 4.9	0.004	1.3	-0.2, 2.7	0.09	1.5	0.1, 2.8	0.03	0.2	-1.1, 1.5	0.75
Breathing reserve, *%*	7.5	-4.1, 19.2	0.19	0.3	-7.2, 7.9	0.93	5.8	-1.5, 13.1	0.12	5.5	-1.3, 12.2	0.11
Peak minute ventilation, *L/min*	0.7	-19.2, 20.6	0.94	-11.9	-24.7, 0.9	0.07	-44.4	-58.4, -30.5	<0.001	-32.5	-45.9, -19.2	<0.001
Females	-7.9	-29.3, 13.6	0.43	-11.9	-25.0, 1.1	0.07	-24.9	-36.7, -13.1	<0.001	-12.9	-24.6, -1.3	0.03
Males	-0.9	-34.8, 33.0	0.95	-16.7	-34.3, 0.9	0.06	-51.0	-67.7, -34.2	<0.001	-34.3	-48.4, -20.2	<0.001
Distance, *meter*	100	-57, 257	0.19	34	-91, 159	0.59	-225	-354, -96	0.001	-258	-393, -124	<0.001
Females	152	-466, 769	0.50	78	162, 319	0.49	-61	-301, 178	0.59	-140	-286, 7	0.06
Males	57	-73, 188	0.35	-50	-224, 124	0.55	-316	-457, -174	<0.001	-266	-463, -68	0.01
Peak VO_2, *ml/kg/min*	2.0	-3.3, 7.3	0.43	-0.6	-4.5, 3.3	0.76	-6.1	-9.8, -2.4	0.002	-5.5	-9.5, -1.6	0.007
Females	4.0	-10.1, 18.1	0.48	-0.7	-6.4, 5.1	0.82	-2.7	-8.3, 2.9	0.32	-2.1	-7.0, 2.9	0.40
Males	-1.0	-6.9, 4.8	0.70	-1.2	-6.9, 4.6	0.67	-7.4	-11.7, -3.1	0.001	-6.2	-12.1, -0.3	0.04
Peak VO_2, *% of predicted*	1.3	-11.3, 13,8	0.83	-3.4	-12.2, 5.3	0.44	-10.6	-18.2, -3.0	0.007	-7.2	-15.1, 0.8	0.08
Females	9.5	-24.5, 43.6	0.49	-2.4	-16.3, 11.6	0.73	-7.1	-20.5, 6.2	0.28	-4.8	-16.6, 7.0	0.41
Males	-2.3	-13.3, 8.7	0.65	-2.7	-13.5, 8.1	0.60	-14.4	-22.6, -6.3	0.001	-11.7	-22.7, -0.63	0.04

Abbreviations: Diff: difference; RER: respiratory exchange ratio; Ti/Ttot: Inspiratory time/Total inspiratory and expiratory time ratio; VO_2: oxygen consumption.
Breathing reserve is the difference between maximal voluntary ventilation (FEV_1 x 35) and peak minute ventilation as percentage of maximal voluntary ventilation;
95%CI: 95% confidence interval.
p) Independent sample t-test (equal variance not assumed).
Number of subjects: LVCP: n = 13 (5 females), No LVCP: n=12 (7 females), PDA-surgery: n=25 (12 females), EP-born controls: n=30 (17 females), term-born controls: n=36 (13 females). Mean difference = the first mentioned group minus the last-mentioned group.

Supplementary figure 1 Self-reported physical activity among the EP-born participants who underwent neonatal PDA surgery with and without left vocal cord paralysis (LVCP)

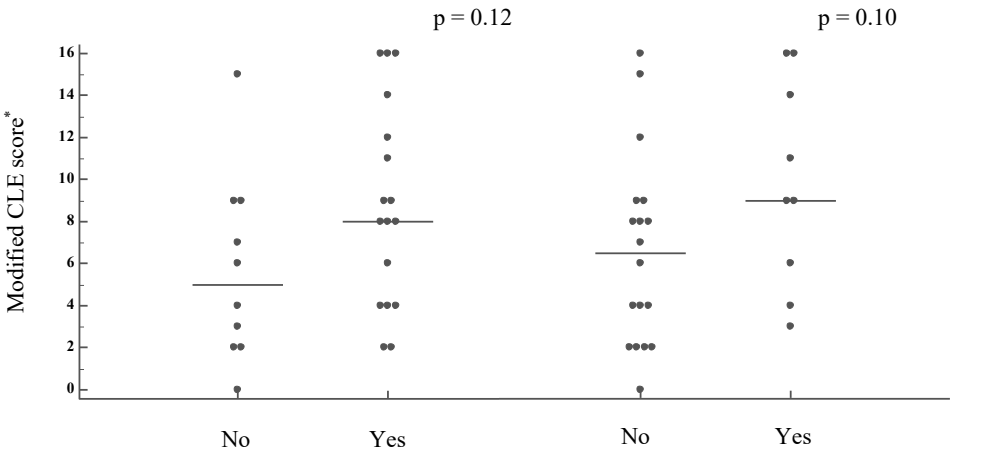


Answer to the self-reported question *"How many hours per week do you attend sports, exercise, or exert yourself so much that you get out of breath and/or sweat?"*

Response rate: No LVCP: n = 13/13, LVCP: n = 14/14,

p) Fisher's exact test

Supplementary figure 2 Comparison of visually assessed laryngeal obstruction during exercise (modified CLE score) according to self-reported breathing symptoms in extremely preterm born adults that underwent neonatal patent ductus arteriosus surgery



*) Higher modified CLE score indicate more laryngeal obstruction

Median values are indicated by vertical lines

p) Mann-Whitney U test

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