Respiratory distress syndrome in moderately late and late preterm infants and selected long-term neurodevelopmental outcomes

PhD Dissertation

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Acknowledgements

This PhD dissertation is based on four studies carried out at the Department of Clinical Epidemiology (KEA) and Department of Pediatrics at Aarhus University Hospital. These four studies are just the final chapter of my 10-year affiliation with the Department. Through my time as a research year student, a PhD student, and several other positions at KEA, I have seen the department grow, and I feel a close bond with it. Thus, I find it hard to believe that this is the end of my KEA era.

I would like to thank Henrik Toft Sørensen, who made this PhD possible. Thank you for believing in me – not only through my PhD but through my entire time in your department. I feel lucky and am deeply grateful that you gave me this opportunity. You showed me the world of clinical epidemiology and taught me to do clinical research. Your enthusiasm and encouragement have kept me motivated throughout my time here at KEA.

I warmly thank John Rosendahl Østergaard for sharing your extensive clinical knowledge and research expertise and for your time and supportive concerns along the way. It has helped me to look at my project with a new perspective—for the better. I would also like to thank Lars Pedersen for your statistical support and for your help providing all of my data.

A special thanks to Morten Olsen: for excellent mentorship, for a persistent effort to answer my many questions, for giving me constructive feedback, and for always leaving a door open. I could not have done this without your help and guidance.

Through the years, I have worked with a lot of great colleagues here at the Department of Clinical Epidemiology, and to all of you: thank you all for your patience and for creating a friendly atmosphere and an inspiring environment to work in. A warm thanks goes to Dr. Nicolas Madsen for welcoming me to the Cincinnati Children's Hospital Medical Center, and to his wife and children for inviting me to their home. I felt like a part of your family despite my short stay in Cincinnati—thank you.

This work was made possible through financial support from the Clinical Epidemiological Research Foundation ('Klinisk Epidemiologisk Forskningsfond'), Denmark, and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

Finally, a deep and sincere thanks goes to my wonderful family, Micklas, Alberte, Mattis, and Morten. Thank you for your patience and support and for believing in me.

Sandra Kruchov Thygesen, March 2016

Dissertation papers

Paper I

Thygesen SK, Olsen M, Christiansen CF. Positive predictive value of the infant respiratory distress syndrome diagnosis in the Danish National Patient Registry. **Clinical Epidemiology**. 2013;5:295-298.

Paper II

Respiratory Distress Syndrome in Preterm Infants and Risk of Epilepsy in a Danish Cohort

Sandra Kruchov Thygesen, Morten Olsen, Lars Pedersen, Victor W. Henderson, John R. Østergaard, Henrik Toft Sørensen

Submitted

Paper III

Respiratory distress syndrome in moderately late and late preterm Infants and risk of cerebral palsy

Sandra Kruchov Thygesen, Morten Olsen, John R. Østergaard, Henrik Toft Sørensen

Submitted

Paper IV

Risk of attention deficit–hyperactivity disorder in children with and without a history of infant respiratory distress syndrome

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In draft

Abbreviations

ADHD	Attention deficit–hyperactivity disorder
CI	Confidence interval
CP	Cerebral palsy
CPAP	Continuous positive airway pressure
CPR	Central Person Registry
DCRS	Danish Civil Registration System
DMBR	Danish Medical Birth Registry
DNCPR	Danish National Cerebral Palsy Registry
DNPR	Danish National Patient Registry
DPCRR	Danish Psychiatric Central Research Registry
DQ	Developmental quotient
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
GMFCS	Gross Motor Function Classification System
HR	Hazard ratio
ICD-8	International Classification of Diseases, 8th revision
ICD-10	International Classification of Diseases, 10th revision
ICH	Intracranial hemorrhage
IRDS	Infant respiratory distress syndrome
IVH	Intraventricular hemorrhage
MeSH	Medical Subject Heading
NICU	Neonatal intensive care unit
OR	Odds ratio
PVL	Periventricular leukomalacia
PPV	Positive predictive value

Table of contents

1. Introduction

Infant respiratory distress syndrome (IRDS) is the leading respiratory disorder among preterm infants (birth <37 gestational weeks). The disorder is caused by immaturity of the lungs, and if left untreated, severe IRDS can lead to death.[1] However, over the last three to four decades, pre- and perinatal treatment has improved, leading to increased survival both of children born preterm and of preterm children with IRDS.[2,3] Although an increase in extremely preterm (birth <28 weeks of gestation) and very preterm infants (birth 28–31 weeks of gestation) has kept the overall prevalence of IRDS unchanged (0.3%),[4] moderately late and late preterm infants (defined as birth at 32–36 weeks)[5-10] represent more than 80% of all preterm infants born before 37 weeks of gestation.[11,12] Thus, the majority of infants with IRDS are still moderately late and late preterm infants.

Although studies on the prognosis of IRDS have reported an increased risk of morbidity, such as intracranial hemorrhage/intraventricular hemorrhage (ICH/IVH) (10.5%),[13] several important issues have yet to be well examined in the literature. The prognosis of IRDS has mostly been investigated in extremely preterm or very preterm infants.[14-17] Furthermore, short-term morbidities, occurring within the first month of birth, have been the main focus of research. Other than ICH/IVH, short-term morbidities include complications like bronchopulmonary dysplasia, patent ductus arteriosus, and necrotizing enterocolitis.[5,18-23]

Morbidities like ICH/IVH increase the risk of selected long-term neurodevelopmental impairments,[24] such as epilepsy and cerebral palsy (CP). Although attention deficit–hyperactivity disorder (ADHD) can be categorized as a neurodevelopmental disorder, the underlying mechanism may be different than for epilepsy and CP. It is possible that for this outcome, hypoxia may be the mediating factor influencing the risk of ADHD diagnosis.[25] Thus, the purpose of this dissertation was to examine the long-term prognosis for important neurodevelopmental outcomes in moderately late and late preterm children diagnosed with IRDS within hours of birth. Accuracy of data on IRDS in the Danish National Patient Registry (DNPR) is a prerequisite for these examinations.

The dissertation is based on four studies that are included as appendices. In the text, each appendix is referred to by its Roman numeral (I–IV). Study I is a validation study examining the positive predictive value (PPV) of IRDS in the DNPR based on the International Classification of Diseases, 8th revision (ICD-8) and 10th revision (ICD-10). Studies II–IV investigated three important neurodevelopmental outcomes: epilepsy (study II), CP (study III), and ADHD (study IV).

To properly frame these studies, an introduction to the history of IRDS as well as the current knowledge about IRDS, including definition, treatment, prevalence, and prognosis, will be presented. Information on the definitions and diagnostic characteristics of neurodevelopmental impairments, including epilepsy, CP, and ADHD, will be reviewed, followed by an overview of the existing literature

on the validity of IRDS as well as a review of the existing literature within the scope of this dissertation's objectives. The subsequent chapters include a summary of the methods used in studies I, II, III, and IV and the main results, followed by a discussion, which includes the conclusions, methodological considerations, and discussion of the results in relation to the existing literature. The thesis continues with perspectives of our findings and a summary in English and Danish followed by the references and appendices, and concluding with the four studies themselves.

2. Background

2.1. History of infant respiratory distress syndrome

Hyaline membrane disease, today known as IRDS, was first described in 1903 by Hochheim through observation of two newborns who died from respiratory failure. At the time, it was widely accepted that mortality arose as a result of aspirated amniotic fluid.[26] In 1929, Neergaard reported the decreased surface tension between the air and the lungs to be fundamental to the stabilization of the alveoli.[27] However, not until 1947 was this observation further investigated by Gruenwald,[28] who suggested an association between the surface tension in the alveoli and the collapsed lungs, based on the discovery of surface-active substances in the lungs.[28]

During the same period, two independent researchers who were investigating chemical warfare agents were evaluating how nerve gases affect the lungs. In 1955, Pattle discovered that a biologically produced molecule covered the surface of the alveoli to reduce surface tension.[29] In 1957, John Clements was the first to measure the surface tension and later defined the active substance that covered the alveoli as surfactant.[30] These findings caught the attention of Marie Ellen Avery, a pediatrician, and in 1959, she and her colleague, Dr. Jeremiah Mead, reported that death from IRDS was caused by an insufficient quantity of surfactant on the surface of the alveoli.[31] She further reported that the lack of surfactant was related to immaturity and low birth weight.[31] However, because no treatment existed at this time, almost all infants with IRDS died within hours of birth.[32,33]

Then, on August 7, 1963, the son of the late President John F. Kennedy was born during gestational week 34 after an emergency caesarean section.[34] He was diagnosed with IRDS and died only 2 days after birth. This event had a huge impact on the subsequent research on surfactant through an increase in National Institutes of Health funding within the area of neonatal research. The focused awareness and attention on neonatal disorders led to increased funding and stimulated the search for a cure. Soon after, the first studies were published on synthetic surfactant.[35,36] However, it would not be for another 20 years, in 1980, that the first study on humans/infants would be conducted by Fujiwara et al., who reported improved oxygenation after treatment with synthetic surfactant.[37]

2.2. Pathophysiology and clinical characteristics

Infant respiratory distress syndrome occurs within hours of birth.[38] Lack of surfactant leads to collapsed alveoli, which results in impaired gas exchange in the lungs. This impairment induces a state of hypercapnia because of poorly ventilated alveoli, among other factors, which then leads to hypoxia, and acidosis.[38,39] The clinical appearance of children with IRDS is tachypnea (defined by a respiratory rate of more than 60 breaths per minute), nasal flaring, and/or chest retractions, which is seen as a visible sinking of the chest while inhaling.[40,41] A grunting sound may also be audible, caused by a forced expiration

against a closed glottis. Sometimes cyanosis can be observed, a bluish color of the skin that is caused by a low concentration of oxygen in the body.[18,42,43]

2.3. **Treatment**

Only 2 years after the death of President Kennedy's son, in 1965, the first neonatal intensive care unit (NICU) was established at Yale Hospital in New Haven, Connecticut, USA, and, in 1975, the subspecialty of neonatology was introduced.[44] Dunn et al. was the first to report a reduced IRDS-specific mortality rate by treatment of continuous positive airway pressure (CPAP).[45] Continuous positive airway pressure stabilizes the lungs by reducing the atelectasis of the alveoli. Further improvement of the IRDS-specific survival was reported soon after, when adult ventilator models, positive end-expiratory pressure, were adapted for preterm infants as the first ventilators designed for children.[46]

In 1972, Liggins et al. reported a decreased prevalence of IRDS and lower mortality of children born to mothers who had been randomized to use of antenatal steroids compared with the placebo group in a clinical trial that was conducted to prevent preterm delivery in pregnant women.[47] This finding was later confirmed by several other studies.[2,48] Despite these results, antenatal corticosteroid treatment was not recommended by the National Institutes of Health until 1994.[49] These recommendations arose as a result of findings showing that prophylactic therapy with antenatal corticosteroid induced maturation of the fetus's organs, including the lungs.[33] A review from 2006 by Roberts et al. cited an overall reduction in neonatal death (relative risk 0.69; 95% confidence interval [CI] 0.58 to 0.81) with antenatal corticosteroid treatment.[2]

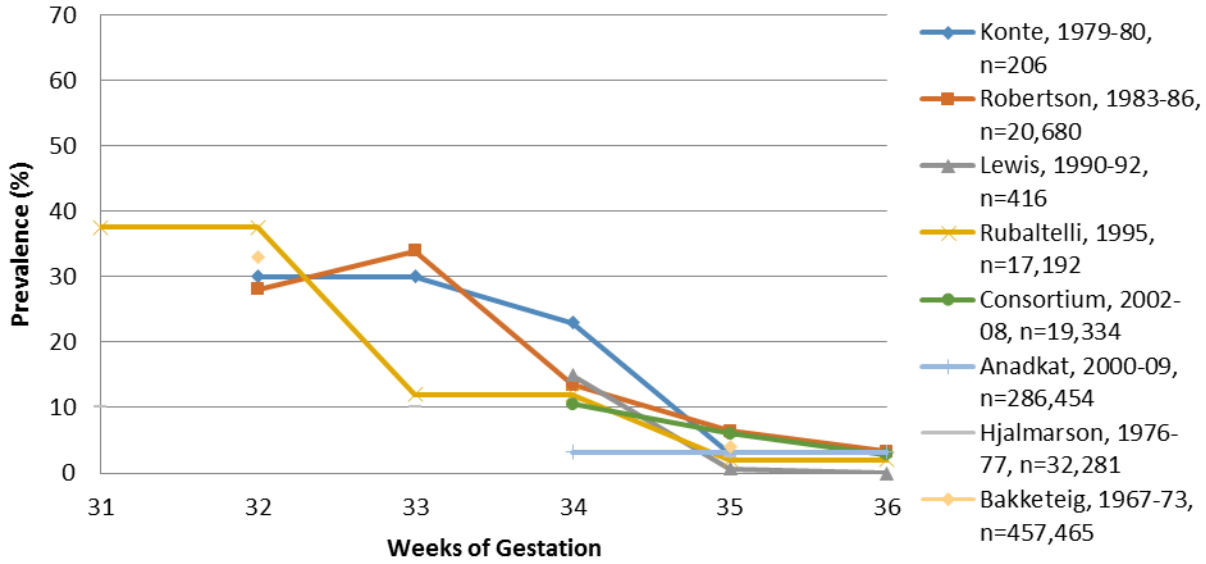
After the first study reported improved outcomes for children with IRDS after treatment with synthetic surfactant,[37] many other studies followed.[50,51] Since then, the research on surfactant has improved our knowledge and led to new diagnostic, prognostic, and therapeutic tools to better understand the causes and treatments of IRDS.[52] Various types of synthetic surfactant have been developed, and survival has improved dramatically; some report a 28% decline in IRDS-specific mortality.[3,33,53,54]

2.4. Prevalence

Given that IRDS occurs within hours of birth and no time at risk thus can be assessed, the correct measure for the occurrence of this disease is prevalence, an estimate that identifies the number of diseased individuals at a specific point. Nevertheless, estimates of IRDS are regularly reported as incidences.[6,8,55] Overall, the prevalence of IRDS is approximately 0.3% of live-born children in Denmark,[4] varying with gestational age (Figure 1). Surfactant is detectable in the lungs from week 24, although it does not reach functional maturity until week 34.[1,39] Thus, IRDS is seen only in children born preterm. Many improvements in preventive care, such as use of prenatal corticosteroid, have worked to decrease the

prevalence of IRDS; however, recent biological innovations, such as in vitro fertilization, have led to an increasing number of multiple births, resulting in more frequent preterm births.[56] Thus, while the overall prevalence of IRDS has not changed, the prevalence within each gestational week has decreased over time.[6,8,9,57,58]

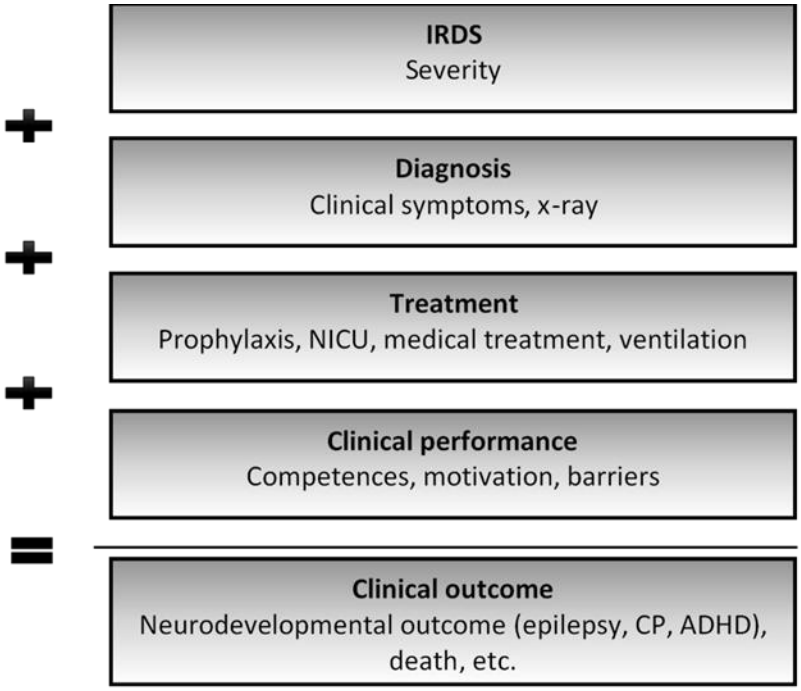
Figure 1. Prevalence of IRDS over calendar time in infants born between gestational ages 32 and 36 full weeks.



2.5. Prognosis

Various factors can affect IRDS prognosis, such as the severity of the disorder itself, availability and use of diagnostic tests, treatment, and clinical performance (Figure 2).[59] Studies that seek to determine the outcome for this patient population are important because they can help us to understand the course of specific diseases such as IRDS and the impact they have on neurodevelopmental outcomes. Outcome studies have the potential to help the clinicians change the prognosis of the disease by knowing where to initiate or improve treatment practices to decrease severity of sequelae and to prevent death.[60]

Figure 2. Determinants of the outcome of IRDS.[59]



The most frequent outcomes reported in children with IRDS are short-term complications occurring within days or weeks, such as ICH/IVH, necrotizing enterocolitis, patent ductus arteriosus, bronchopulmonary dysplasia, and death.[5,18-23] In the 1970s, doubts were raised regarding neurological outcomes of premature children with IRDS after mechanical ventilation was introduced.[61] Since then, several treatment methods of IRDS have been tested.[41] Treatment with synthetic surfactant has been reported to reduce the overall IRDS-specific mortality from 50% to about 5%[3] whereas another study reported a decreased mortality in mechanically ventilated children from 80% to 25%.[62] However, Lee et al.[53] argued that the reduction in mortality arose as a result of overall improvement in all initiatives taken since the focus on preterm infants became a high priority, rather than because of a specific treatment.

Generally, a high awareness and improvement in treatment strategies of IRDS have improved overall morbidity and mortality.[63,64] However, some therapies, such as prenatal and early childhood use of corticosteroids,[65,66] increase the risk of neurodevelopmental impairments whereas other therapies, like inhaled nitric oxide, have been variably reported to have a protective effect[67] or no effect[68] on neurodevelopmental outcomes.

We chose to look at moderately late and late preterm infants for several reasons. First, there were adequate proportions of infants with IRDS and infants with no IRDS to enable comparison. Second, compared to moderately late and late preterm infants, infants born at an earlier gestational age have different baseline characteristics and comorbidities and thus a very high baseline risk of the outcomes under study in this thesis.[69,70] This high baseline risk may decrease the relative impact of IRDS and

conceal a true association. Third, about 80% of preterm infants are born between 32 and 36 weeks of gestation, when IRDS still has a prevalence up to 20–30%. Therefore, the cohort of interest included solely those at 32–36 weeks of gestational age to more concretely determine the impact of this disease on our outcomes of interest.

2.6. Using medical databases and registries in IRDS research

In Denmark, the National Health Service provides free, tax-supported health care to all Danish citizens, which guarantees equal access to both primary and secondary health care facilities.[71] Since April 1968, the Danish Civil Registration System (DCRS) has electronically captured all records of date of birth, emigration, and death for all Danish citizens via a uniquely assigned Civil Personal Registration (CPR) number, which is given at birth or upon immigration.[72] Linkage of all public Danish registries, such as the Danish Medical Birth Registry (DMBR) and the Danish National Patient Register (DNPR),[73,74] is achieved through use of the CPR number. With daily updates in DCRS, there is virtually no loss to follow-up.[72] Based on this setup, there are great opportunities to do long-term follow-up studies on children diagnosed with IRDS.

Different types of data sources are used in the four studies of IRDS. Administrative databases used to study the prognosis of IRDS included data linked from the DCRS, DMBR, and DNPR, among others. These databases are secondary data sources with information collected/established for other than research purposes. The information within the databases is prospectively collected and continuously updated, providing a great advantage for research given the potential for very large sample sizes with almost no loss to follow-up or bias owing to non-response.

The limitations of secondary data are related to the fact that the choice of variables and the methods of data collection are not under the control of the researcher.[75] Thus, use of secondary data sources potentially implies that less detailed data are available on, for example, potential confounders or severity of disease. Furthermore, a prerequisite for carrying out epidemiological studies is valid data. Therefore, it is crucial to verify the validity of the relevant data on diagnoses, etc., before conducting the studies.

2.7. Neurodevelopmental impairment

The term ‘developmental brain dysfunction’ describes an abnormal brain function that constitutes a group of neurodevelopmental and neuropsychiatric disorders and comprises a portion of several clinical diagnoses.[76] Neurodevelopmental disorders emerge during childhood, often before school age.[77] However, neurological status may change over time; thus, a normal neurodevelopmental assessment in early age does not exclude the possibility of a suspect or abnormal assessment later in life.[78,79] The brain

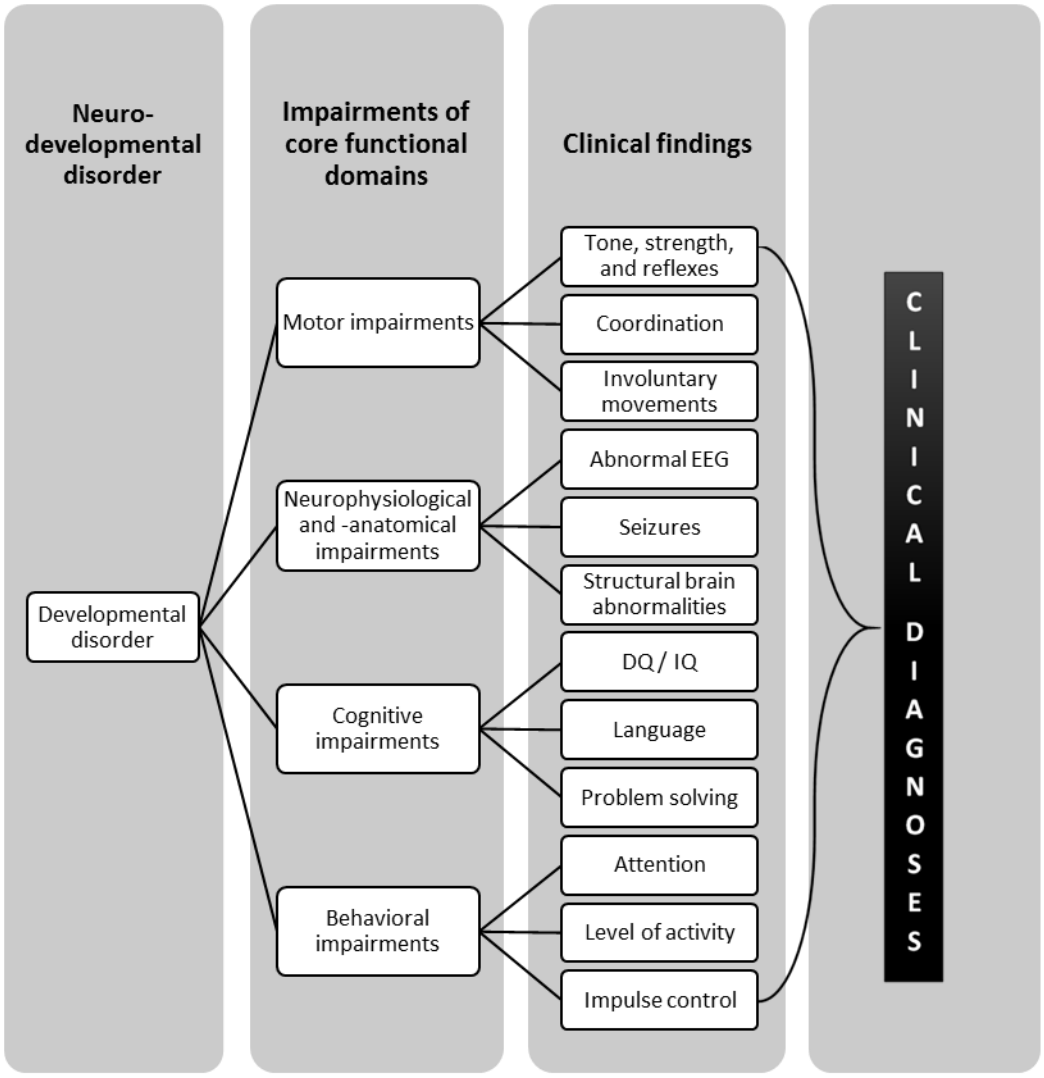
dysfunction leads to impairments in the core functional domains of behavior, cognition, communication, and motor functioning, which results in delays in reaching developmental milestones.[80] Depending on the severity of the brain dysfunction and the involvement of the different domains of impairments, a diagnosis of a specific neurodevelopmental disorder may be given (Figure 3).[76] Within the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), the category of neurodevelopmental disorders covers a wide range of specific learning, motor, and intellectual developmental disorders, as well as ADHD, autism spectrum disorders, and neuropsychiatric disorders, such as bipolar disorders and schizophrenia.[77] Outside the DSM-5, neurodevelopmental disorders such as epilepsy and CP are described.[77] The various neurodevelopmental disorders are based on the specific pattern of symptoms and syndromes, which often overlap, leading to co-occurring conditions, e.g., epilepsy and CP.[81-87]

We chose three neurodevelopmental disorders that were all based on different population-based registries in Denmark. Epilepsy is a well-defined diagnosis, recorded in the DNPR based on the ICD-8 and ICD-10 diagnosis codes (Paper II, Appendix A); the disorder has been validated in the DNPR with a high PPV (75%–81%).[88,89] Cerebral palsy is also a well-defined diagnosis. The disorder is captured in the DCPR based on the ICD-10 diagnosis code (Paper III, Appendix A) and has been reported with a high completeness of 85% when comparing to the DNPR.[90] Epilepsy and CP both present with clinical findings that are reliable for diagnostics, and based on the severity of the condition, all children diagnosed with epilepsy and/or CP are followed with frequent visits to the specialist/physician.

Attention deficit–hyperactivity disorder is also a commonly diagnosed neurodevelopmental disorder among adolescents. In contrast to epilepsy and CP, ADHD is based solely on a clinical assessment of behavioral features. Of note, ADHD also may co-occur with CP.[77,87]

Other neurodevelopmental disorders could potentially be examined using the Danish population-based registries, such as autism spectrum disorders or schizophrenia. In addition, performance measures like audiovisual, psychosocial, and fine and gross motor tests/scores are a possible outcome,[40,91] or cognitive function measured by, e.g., intelligence quotient could be investigated.[92]

Figure 3. Neurodevelopmental disorders – overview of areas of impairment and clinical findings.[76]



2.8. Common risk factors for neurodevelopmental disorders

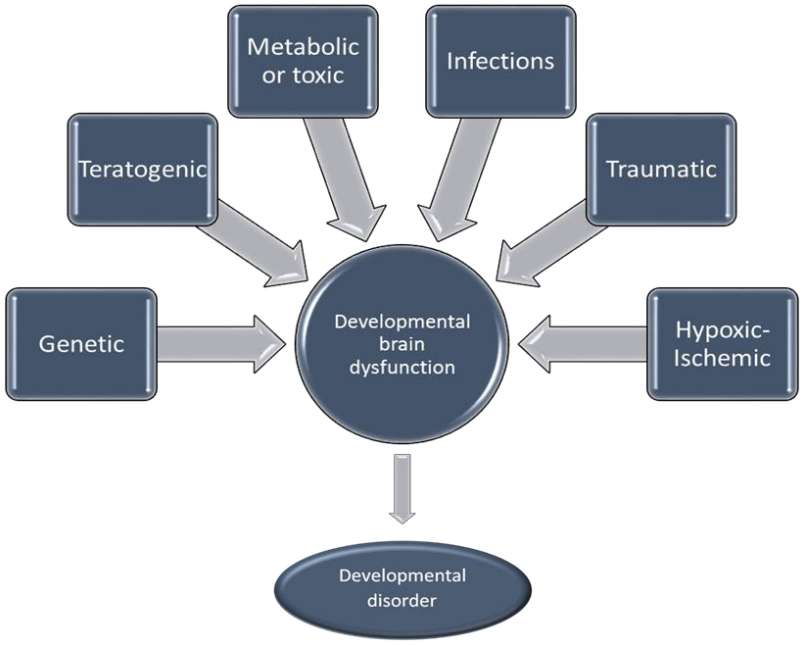
Multiple factors have consistently been associated with increased risk for neurodevelopment disorders. Environmental and genetic factors are linked with several neurodevelopmental disorders, but they cannot explain the entire effect.[93]

The heterogeneity of this umbrella of neurodevelopment disorders thus makes it difficult to define the actual risk factors. Several risk factors that affect the developing brain have been suggested (Figure 4). Teratogenic factors, like maternal smoking and alcohol intake,[94,95] as well as metabolic and toxic influences, such as maternal dysfunction of the endocrine system or exposure to toxic agents (e.g., lead solvents) have been reported to adversely affect the vulnerable developing fetal brain,[96,97] resulting in disturbances in core functional domains. Other types of insults, such as ICH/IVH and periventricular

leukomalacia (PVL), are major risk factors[98] and may arise as a result of various causes, such as infection,[99] trauma,[100] or hypoxic-ischemic events, like IRDS.[79,89,101-104]

The timing of pre-, peri-, and neonatal events and their relationship to the pathogenesis of neurodevelopmental disorders is complex and incompletely understood. A prenatal event is not likely to be the sole cause of the neurodevelopmental impairment(s) because it may represent only one factor in a sequence and/or it may be only one of the multiple interacting factors. Thus, investigating how combinations or sequences of events (and their timing) might affect the risk of a neurodevelopmental disorder is important.[76,80,105]

Figure 4. Risk factors for neurodevelopmental disorders.



2.9. Epilepsy

Epilepsy is one of the most common serious neurologic disorders. Epilepsy accounts for about 0.5% of the global disease burden,[106-108] and about 40% of incident cases of epilepsy occur in children under the age of 15 years.[109]

Epilepsy is characterized by recurrent unprovoked seizures. Overall, they are classified as generalized (involving both hemispheres of the brain) or partial (involving only a localized focus in the brain), although the list of subtypes includes many different subtypes and syndromes that vary with age of onset.[109]

Previous studies have suggested that several risk factors, like preterm birth, inadequate perinatal care, and low Apgar score, are associated with a higher risk of epilepsy.[89,110-115] However, the multifactorial etiology of this disorder is not well understood, although triggers include insults to the central nervous system. These triggers include ICH/IVH and hypoxic-ischemic damage.[98,109]

2.10. Cerebral palsy

Cerebral palsy is a well-recognized neurodevelopmental disorder and the most common cause of physical disability in early childhood.[116] The disorder affects about two per 1000 live-born children. It is characterized by spasticity, movement disorders, muscle weakness, and posture. Often the disorder is accompanied by other neurodevelopmental impairments, such as specific cognitive deficits, behavioral problems, disturbances of sensation, and/or seizure disorders.[117] Cerebral palsy varies in severity and anatomical location of disability, depending on the location and extent of brain damage, and though it is chronic in nature, it is changeable over time. Despite the severity of the disorder, children with CP most often live to adulthood. Generally, they need a high amount of specialist services, both medically and educationally, which places a large burden on the health care system and society.

Because there is no cure for CP, it is of utmost importance to find effective strategies for primary prevention. As a prerequisite, the etiology of CP needs further investigation. The causation is heterogeneous and poorly understood, though predisposing ante-, peri-, and postnatal factors have been found to alter the developing brain, which may lead to CP.[118] Among others, these factors include preterm birth, hypoxic insults, ICH/IVH, and PVL.[83,119-122]

2.11. Attention deficit–hyperactivity disorder

Attention deficit–hyperactivity disorder is among the most common psychiatric morbidities in children. Depending on the diagnostic conventions and assessment method, the overall prevalence has been estimated at about 4–10%, worldwide.[123,124] The condition is clinically characterized by symptoms of impulsivity, hyperactivity, and/or inattention. The disorder may be combined with other neurodevelopmental impairments, such as specific developmental disorders of learning, language, and motor development, autism spectrum disorder, and CP.[125] Furthermore, an individual may be genetically predisposed to ADHD. For about half of affected children, the disorder may persist into adulthood.[126,127] Several other factors have been suggested to contribute to the development of ADHD, including pre- and perinatal factors.[102,127] Previous studies have suggested that ischemic-hypoxic conditions, including IRDS, increase the risk of ADHD.[102,128]

2.12. Literature review

We conducted a literature review to determine if other studies had investigated the prognosis of IRDS with regard to neurodevelopmental disorders, including epilepsy, CP, and ADHD. We found no studies of this type and thus decided to conduct three population-based prognosis studies (studies II–IV). Because valid data on IRDS were essential for conducting these studies, we started by performing a systematic literature search to find if previous studies had reported on the validity of IRDS in the DNPR. However, we found no such study; thus, we decided to conduct our own validation study. We searched in various databases, including Bibliotek.dk, SveMed+, PubMed, Embase, Cochrane Library, CINAHL, PsycINFO, Scopus, and Web of Science. Searches were restricted to 'English, Danish, Norwegian, Swedish language literature'. By using major Medical Subject Headings (MeSH), we searched the databases. If the search revealed only a few hits, we used non-major MeSH topics or free text term.

From the papers listed in the search results, relevant titles and abstracts were reviewed and singled out based on the PICO criteria (population, exposure, comparison, and outcome).[129,130] We went through the reference lists of the chosen articles or related articles for other relevant publications. We searched for publications by key authors and additional literature in books and on official health authorities' webpages.

Table 1. Summary of existing literature in the field of each study

Study I: Positive predictive value of IRDS in the DNPR			
Author, year	Design, setting, period, data sources	Population, exposure, controls, outcome	Results, limitations
No studies were found			

Study II: Respiratory distress syndrome in preterm infants and risk of epilepsy			
Author, year	Design, setting, period, data sources	Population, exposure, controls, outcome	Results, limitations
Whitehead *et al.*[131] - Pediatrics - 2005	- Cohort study - Canada - 1986–2000 - NSAPD, CEDaR, EEG records	- Residents of mainland Nova Scotia - Pre-, peri-, and neonatal factors/events - Epilepsy	IRDS was associated with epilepsy. Mild IRDS: 2.0 (95% CI: 1.1–3.7), univariate analysis Severe IRDS: 4.5 (95% CI: 3.0–6.7), univariate analysis In the multivariate analysis, included associated covariates or intermediate factors, which may thus be the reason for no association

Study III: Respiratory distress syndrome in preterm infants and risk of CP			
Author, year	Design, setting, period, data sources	Population, exposure, controls, outcome	Results, limitations
Stelmach *et al.* [132] - J Child Neurol. - 2005	- Case-control study - Estonia (one county) - 2000 - chart review	- Surviving infants without congenital malformations (one county, source) - Ante- and perinatal factors - CP (n=158) - Matched controls (n=268)	IRDS was associated with CP; OR 18.0 (95% CI: 7.16–45.1) Univariate analysis with no adjustment for potential confounders, imprecise estimates because of small sample size
Dite *et al*.[133] - Aust NZ J Obstet Gynaecol. - 1998	- Case-control study - Australia - 1983–1990 - VCPR, VPDCU	- Surviving infants without congenital malformations (on region, source) - Maternal, ante-, and perinatal factors - CP (moderate to severe) (n=204) - Matched controls (n=816)	IRDS was associated with CP; OR 9.4 (95% CI: 1.8–48) Univariate analysis with no adjustment for potential confounders, imprecise estimates
Blair *et al.* [122] - Paediatr Perinat Epidemiol. - 1993	- Case-control study - Australia - 1975–1980 - WACPR, WAMNBD, medical record review	- Surviving infants (source) - Ante- and perinatal factors - CP (n=183) - Matched controls (n=549)	IRDS was associated with CP; OR 2.3 (95% CI: 1.27–4.30) Univariate analysis with no adjustment for potential confounders, imprecise estimates

Hirvonen *et al.* [134] - Pediatrics - 2014	- Cohort study - Finland - 1991–2008 - MBR, Cause-of-Death Register, Register of Congenital Malformation, HDR, Reimbursement register of the Social Insurance Institution	- All infants without more than one major congenital malformation (source=1,018,302) - MP and LP infants (n=46,731) - CP (n=2,242)	IRDS as a risk factor for CP: GA [32–33] WOG: OR 1.05 (0.66–1.66) GA [34–36] WOG: OR 0.34 (0.17–0.68) Logistic regression analysis, using multivariate entry models, including multiple intermediate covariates in the model simultaneously
Dale *et al.* [135] - Dev Med Child Neurol. - 1980	- Case-control study - Australia - 1966–1975 - Medical record review, referral agencies	- Children born at one hospital (source) - Spastic CP (n=208) - Controls (n=207)	IRDS and CP were significantly associated. 1966–70: 31% in cases vs. 4.3% in controls 1971–75: 44% in cases vs. 6.6% in controls Single-center study
Drougia *et al.* [136] - Early Hum Dev. - 2007	- Case-control study - Greece - 1989–2003 - Medical record review	- At one NICU - CP (n=78) - Matched controls (n=556)	IRDS was associated with CP. 1989–1996: OR 1.8 (95% CI: 0.9–3.7), univariate analysis 1997–2003: OR 4.6 (95% CI: 1.1–21), univariate analysis In the multivariate analysis, included associated covariates or intermediate factors, which thus may be the reason for no association Single-center study
Takahashi *et al.* [137] - Early Hum Dev. - 2005	- Case-control study - Japan - 1990–1998 - Medical record review	- Infants in 22-33 WOG at one NICU - Ante- and postnatal events - CP (n=50) - Matched controls (n=150)	IRDS was associated with CP Univariate analysis with OR 5.1 (95% CI: 2.1–12.1) Multivariate analysis adj. for postnatal factors, OR 2.8 (95% CI: 0.6–13.4) Imprecise estimates, including associated covariates or intermediate factors in the multivariate model Single center study
McGrath *et al.* [79] - Pediatrics - 2005	- Cohort study - Canada - 1980–1982 - NSAPD, CEDaR, EEG records	- Cohort study, - Neonatal morbidities, including IRDS - Neurologic outcomes, including CP	Neonatal morbidities were associated with selected neurologic outcomes – including CP SPT (including IRDS)

Study IV: Respiratory distress syndrome in preterm infants and risk of ADHD			
Author, year	Design, setting, period, data sources	Population, exposure, controls, outcome	Results, limitations
Getahun *et al.*[102] - Pediatrics - 2012	- Case-control study - California - 1995–2010 - KPSC	- Singletons born to KPSC at GA=28–42 WOG, no ASD, at least 5 years of age - ADHD and ≥2 prescriptions for ADHD-specific medication (n=13,613) - Matched controls (n=68,065)	IRDS was associated with ADHD. GA [28–33] WOG: aOR 1.4 (95% CI: 1.0–2.0) GA [34–36] WOG: aOR 1.4 (95% CI: 1.1–2.0) IRDS was not the only exposure of interest.

Abbreviations: aOR=adjusted odds ratio; ASD=autism spectrum disorder; GA=gestational age; HDR=Hospital Discharge Register; IRDS=infant respiratory distress syndrome; KPSC=Kaiser Permanente Southern California; LP=late preterm (34–36 weeks of gestation); MBR=Medical Birth Registry; MP=moderately preterm (32–34 weeks of gestation); MSEL=Mullen Scales of Early Learning; NICU=neonatal intensive care unit; OR=odds ratio; PPHN=persistent pulmonary hypertension; VCPR=Victorian Cerebral Palsy Registry; VPDCU=Victorian Perinatal Data Collection Unit; WACPR=Western Australia Cerebral Palsy Register; WAMNB=Western Australian Midwives' Notification of Births data; WOG=weeks of gestation.

Medline search query: relevant papers out of total number of Medline hits+other relevant papers=total number of relevant publications:
Study I: "positive predictive value" [free text term] AND "respiratory distress" [free text term]: 0/128+0=0 in total
Study II: "(((“Respiratory Distress Syndrome, Newborn” [Mesh]) OR (“Hyaline Membrane Disease” [Mesh])) AND (“Epilepsy” [Mesh])) OR (("Epilepsy"[Majr]) AND ("Risk"[Majr])): 0/169+1=1 in total
Study III: (((“Respiratory Distress Syndrome, Newborn” [Mesh]) OR (“Hyaline Membrane Disease” [Mesh])) AND (“Cerebral Palsy” [Mesh])) OR (("Cerebral Palsy"[Majr]) AND ("Risk"[Majr])): 3/56+5=8 in total
Study IV: "(((“Respiratory Distress Syndrome, Newborn” [Mesh]) OR (“Hyaline Membrane Disease” [Mesh])) AND (“Attention Deficit Disorder with Hyperactivity” [Mesh])) OR (("Attention Deficit Disorder with Hyperactivity "[Majr]) AND ("Risk"[Majr])): 0/21+1=1 in total

2.12.1. Positive predictive value of IRDS

For estimates in a given study to be valid, it is necessary to base the analysis on valid data. As such, for all studies included in this dissertation, understanding the accuracy of an IRDS diagnosis in regard to the existence of the condition itself is mandatory. We found no studies that validated the IRDS diagnosis, even when extending the literature search to include respiratory distress. Therefore, a study of this type preceded studies that sought to determine the prognosis of IRDS.

2.12.2. Infant respiratory distress syndrome and epilepsy

To our knowledge, only a single study has included epilepsy as an outcome for the prognosis of IRDS. A Canadian cohort study conducted by Whitehead[131] in 2006 examined neonatal and pregnancy-related predictors of epilepsy during childhood. Although the association between IRDS and epilepsy was not their main outcome, this study found a relative risk of epilepsy in children with mild IRDS of 2.0 (95% CI: 1.1–3.7) and in children with severe IRDS of 4.5 (95% CI: 3.0–6.7), compared to children without IRDS. The estimates emerged through univariate analysis and did not account for several potential confounding factors, such as gestational age. Furthermore, they did not look specifically at IRDS as such, but had a wide range of pre-, peri, and neonatal predictors. Because this study did not report findings of multivariate analysis in which IRDS would have been included as an exposure of interest, the impact of IRDS on epilepsy, accounting for confounding and effect modification, is unknown.

2.12.3. Infant respiratory distress syndrome and CP

Few known studies exist on the long-term prognosis of CP following IRDS. Six case-control studies have reported a potential association between IRDS and CP.[132,133,135-138] Their estimates ranged from an odds ratio (OR) of 1.8 (95% CI: 0.9–3.7) to an OR of 18.0 (95% CI: 7.16–45.1); the estimates, however, were based on univariate analyses with no adjustment for potential confounding factors. Only in one of the studies (Takahashi et al.[137]) did the association persist in significance to be included in the multivariate model [OR 2.8 (95% CI: 0.6–13.4)]. However, as a result of the study design, the studies were limited by small sample sizes or did not include absolute risk estimates. In addition, they included several pre-, peri-, and neonatal factors; thus, analysis did not focus on IRDS as a specific exposure of interest, per se.

Hirvonen et al.[134] conducted a Finnish cohort study (n=1,018,302) in children born between 1991 and 2008. They found no association between IRDS and CP in children born at 32–33 weeks of gestation [OR 1.05 (95% CI: 0.66–1.66)]; however, in children born at 34–36 weeks of gestation, they found a protective effect of IRDS and CP [OR 0.34 (95% CI: 0.17–0.68)]. The study did not report the selected potential confounders that were used in the adjusted multivariate model. Furthermore, they included

multiple pre-, peri-, and neonatal factors; thus, the analysis did not focus on IRDS as a specific exposure of interest, as such.

In 2000, McGrath et al.[79] conducted a follow-up study (n=188) of infants in the United States and found an increased risk of adverse neurodevelopmental outcomes, such as IRDS, among preterm infants. The exposed infants were identified from the NICU and classified into four subgroups by increase in the severity of a composite of multiple neonatal diseases. The neurological status were assessed at hospital discharge, at 18 months, 30 months, and at 4 and 8 years of age. Neurological status involved three levels of the disorders and impairments based on their degree of severity, including seizures, CP, and ADHD. However, this study was a single-center study of only severe cases of IRDS admitted to the NICU. Moreover, IRDS was not the focal exposure.

2.12.4. Infant respiratory distress syndrome and ADHD

Ischemic-hypoxic conditions, caused by acute or chronic perinatal events, have been reported to have adverse effects on the developing brain.[25,102,139] In a case-control study on children born at a gestational age of 28–42 weeks, Getahun et al.[102] reported an increased risk of ADHD in children who experience ischemic-hypoxic conditions, such as birth asphyxia, preeclampsia, and IRDS (n=308,634). In the adjusted analysis, these authors found an OR for ADHD of 1.4 (95% CI: 1.0–2.0) for children with IRDS born between 28 and 33 weeks of gestation, and a similar OR of 1.4 (95% CI: 1.1–2.0) for children with IRDS who were born between 34 and 36 weeks of gestation. However, as a result of the study design, the study did not include absolute risk estimates

3. Aims and hypotheses

Study I aimed to estimate the PPV of newborn children diagnosed with IRDS at birth in the DNPR, based on the ICD-8 and ICD-10.

Study II aimed to examine the association between epilepsy and moderately late and late preterm children born 1979–2009 and diagnosed with IRDS. We hypothesized that children with IRDS would have a higher risk of epilepsy compared to children without IRDS.

Study III aimed to examine the association between CP and moderately late and late preterm children born 1997–2007 and diagnosed with IRDS. We hypothesized that children with IRDS would have a higher risk of CP compared to children without IRDS.

Study IV aimed to examine the association between ADHD and moderately late and late preterm children born 1990–2009 and diagnosed with IRDS. We hypothesized that children with IRDS would have a higher risk of ADHD compared to children without IRDS.

4. Materials and methods

Material and methods of the four studies are summarized in Table 2 and further described in detail below.

4.1. Setting

All four studies were based on national data in Denmark. The Danish National Health System provides free, tax-supported health care for all Danish residents. This support includes equal and unrestricted access to treatment in both primary and all secondary health care units.[140] A unique central personal registration number (the CPR number) is assigned by the DCRS to all Danish citizens upon birth or immigration; this number holds information about date of birth and gender and allows for individual linkage among all Danish databases.[72]

4.2. Data sources

4.2.1. The Danish Medical Birth Registry (Studies II, III, and IV)

The database holds information on all births in Denmark since 1973.[73,74] Each record includes data on pre- and perinatal characteristics of the child, such as vital status at birth, gestational age, multiplicity, and 5-minute Apgar score. The DMBR further includes data on the mothers, including age at delivery and self-reported smoking status (since 1991).

4.2.2. The Danish Civil Registration System (DCRS) (Studies I, II, III, and IV)

The DCRS is a central administrative registry that contains data beginning from April 1968. In addition to date of birth, this registry further holds information on vital status, including date of death or date of emigration. The DCRS is electronically updated daily and ensures virtually complete follow-up.[72]

4.2.3. The Danish National Patient Registry (DNPR) (Studies I, II, III, and IV)

Since 1977, the DNPR has collected data on all diagnoses and procedures for patients discharged from all Danish non-psychiatric hospitals based on ICD-8 until 1993 and ICD-10 from 1994. Beginning in 1995, all outpatient and emergency room visits have been included.[141,142] Reporting to the DNPR is mandatory. Each contact, including both in- and outpatient visits, is recorded with one primary discharge diagnosis code representing the main reason for the contact and one or more optional secondary diagnosis codes that refer to additional conditions that affect the course of the admission. The discharge diagnoses are assigned by the discharging physician. To ensure data validity, multiple validation studies on a variety of diagnoses have previously been conducted on the data in the DNPR and in general have yielded high PPVs.[143,144]

4.2.4. The Danish National Cerebral Palsy Registry (DNCPR) (Study III)

The DNCPR became a nationwide registry in 1997 and includes information on children diagnosed with CP, listing subtype and severity. It is estimated that the registry captures more than 85% of children with CP.[90] Additional information includes data on, e.g., developmental quotient (DQ) and motor deficits, as measured by the Gross Motor Function Classification System (GMFCS). Children are included if they have CP with pre- or perinatal origin, defined by occurrence within 28 days of birth. Moreover, they need to fulfill the diagnostic criteria for CP, including deficiencies determined via magnetic resonance imaging (MRI) or computed tomographic (CT) scan. Based on a review of the clinical findings documented in the medical record, children with a CP diagnosis have all been validated by an external child neurologist at the age of 4–5 years.

4.2.5. The Danish Psychiatric Central Research Registry (DPCRR) (Study IV)

Since 1969, the DPCRR has recorded electronic data on all psychiatric inpatient diagnoses; since 1995, all psychiatric outpatient treatment and emergency room contacts have been added. There has been mandatory reporting to the registry on all psychiatric admissions for both psychiatric departments since 1970.[145,146] Included in the registry are one primary diagnosis and additional secondary diagnoses, based on ICD-8 and ICD-10, and dates of admission and discharge. Of note, ICD-9 was not implemented in Denmark. In the transition from the ICD-8 to ICD-10, diagnostic categories were tripled in number.[145]

4.2.6. The Danish National Prescription Registry (Study IV)

Since 1994, the Danish National Prescription Registry, previously the Register of Medicinal Product Statistics, has collected data on all reimbursed prescription drugs dispensed by community pharmacies in Denmark. These data include information on type of drug (according to the Anatomical Therapeutic Chemical (ATC) classification system) and date of drug dispensation.[147]

4.3. Study design

Using the Danish population-based registries, we conducted one validation study (study I) and three cohort studies (studies II–IV).[148] The study period was based on data availability in the registries.

Table 2. Overview of studies I–IV

	Study I	Study II	Study III	Study IV
Objective	Examine the quality of ICD-8 and ICD-10 codes in the DNPR	Examine an association between IRDS and epilepsy	Examine an association between IRDS and CP	Examine an association between IRDS and ADHD
Design	Population-based prevalence study	Population-based cohort study	Population-based cohort study	Population-based cohort study
Data sources	DCRS, DNPR, medical records	DCRS, DMBR, DNPR	DCRS, DMBR, DNPR, DNCPR	DCRS, DMBR, DNPR, DPCRR, Danish National Prescription Registry
Study period and area	Northern Denmark, 1977–2008	Nationwide: 1978–2009	Nationwide: 1997–2007	Nationwide: 1990–2009
Study population	All live-born infants	All live-born born in 32–36 WOG	All live-born born in 32–36 WOG	All live-born born in 32–36 WOG
Exposure	ICD-8 and ICD-10 discharge diagnosis codes for IRDS	ICD-8 and ICD-10 discharge diagnosis codes for IRDS	ICD-10 discharge diagnosis codes for IRDS	ICD-10 discharge diagnosis codes for IRDS
Outcomes or reference standard	Medical record review (reference standard)	Epilepsy	CP (overall), GMFCS, and DQ	ADHD and redeemed prescription for ADHD medication
Covariables	Sex, ICD periods, type of diagnosis, gestational age	Gestational age, sex, birth year, 5-minute Apgar score, multiplicity maternal age and smoking status during pregnancy, major malformation, BPD, ICH/IVH, NEC, PDA, perinatal breathing disorders, CHD, and infections	Gestational age, sex, birth year, 5-minute Apgar score, multiplicity maternal age and smoking status during pregnancy, major malformation, BPD, ICH/IVH, NEC, PDA, perinatal breathing disorders, CHD, and infections	Gestational age, sex, birth year, 5-minute Apgar score, multiplicity maternal age and smoking status during pregnancy, major malformation, BPD, ICH/IVH, NEC, PDA, perinatal breathing disorders, CHD, and infections
Statistical analyses	PPV	Cumulative incidence proportion (death included as a competing risk); Cox proportional hazard regression	Cumulative incidence proportion (death included as a competing risk); Cox proportional hazard regression	Cumulative incidence proportion (death included as a competing risk); Cox proportional hazard regression
Confounder control	Stratification	Restriction, stratification, and multivariate adjustment	Restriction, stratification, and multivariate adjustment	Restriction, stratification, and multivariate adjustment
Subgroup analyses		Dividing the IRDS group into IRDS and no ICH/IVH and IRDS and presence of ICH/IVH	Dividing the IRDS group into IRDS and no ICH/IVH and IRDS and presence of ICH/IVH	
Sensitivity analyses		Change in exposure to include only children with IRDS and no other additional diagnoses that could mimic the appearance of IRDS	Change in exposure to include only children with IRDS and no other additional diagnoses that could mimic the appearance of IRDS	

Abbreviations: ADHD=attention deficit–hyperactivity disorder; BPD=bronchopulmonary dysplasia; CHD=congenital heart disease; CP=cerebral palsy; DCRS=Danish Civil Registration System; DMBR=Danish Medical Birth Registry; DNCPR=Danish National Cerebral Palsy Registry; DNPR=Danish National Patients Registry; DQ=developmental quotient; GMFCS=Gross Motor Function Classification System; ICD=International Classification of Diseases; ICH/IVH=intracerebral/intraventricular hemorrhage; IRDS=infant respiratory distress syndrome; NEC=necrotizing enterocolitis; PDA=patent ductus arteriosus; PPV=positive predictive value.

4.4. Study population

For study I, we identified patients diagnosed with IRDS from January 1, 1977, to December 31, 2008, regardless of type of diagnosis (primary or secondary). There are approximately 500,000 residents currently in the northern part of Denmark, corresponding to about 11% of the entire Danish population. In studies II–IV, we used the DMBR to identify all live-born infants born between 32 and 36 weeks of gestation. For study II, we included children with IRDS in the study period from January 1, 1978, to December 31, 2009 (approximately 1,900,000 infants). The study periods for studies III and IV were based on the available date information of the outcome; thus, in study III, we included children with IRDS between January 1, 1997, and December 31, 2007 (approximately 710,000 infants), and for study IV, we included children with IRDS between January 1, 1990, and December 31, 2009 (based on approximately 1,300,000 infants).

4.5. Infant respiratory distress syndrome

All four studies defined IRDS as the exposure of interest. We used the DNPR to identify all children with a primary or secondary diagnosis of IRDS using the following ICD-8 code, 776.19 (hyaline membrane disease), up to 1993 and ICD-10 code DP22.0 (idiopathic respiratory distress syndrome) thereafter.

Of note, in study I, we randomly selected three children with a primary or secondary IRDS diagnosis each birth year from 1977 to 2008, giving a total of 93 children with an IRDS diagnosis code.

4.6. Positive predictive value of IRDS

In study I, we calculated the PPV of IRDS as an indirect measure of the specificity in the DNPR. The PPV is a measure of validity: it estimates the proportion of coded children with IRDS who truly have the disease. To estimate the degree of correctly diagnosed children with IRDS, we need a reference standard. In our study, we used medical records as the reference standard to confirm or reject the IRDS coding in the DNPR based on ICD-8 and ICD-10 codes. The clinical symptoms of IRDS were defined as tachypnea (>60 breaths per minute), retractions or nasal flaring, grunting, and central cyanosis. For the primary analysis, IRDS was confirmed when at least two of the four clinical symptoms had been present for more than 30 minutes. In the secondary analysis, IRDS was defined as the presence of at least two of the four clinical symptoms together with positive findings of IRDS on an x-ray. Positive findings were defined as air bronchograms in addition to a reticulogranular ground-glass appearance.

If the above-mentioned terms were not specifically mentioned or if no information was available on whether or not an x-ray was taken, the IRDS diagnosis was ruled out. Of note, we collected additional information on sex, gestational age, and CPAP, among others. Treatment with CPAP needed to be provided by pediatric departments and for more than 30 minutes.

4.7. Outcomes of studies II–IV

4.7.1. Epilepsy

The outcome in study II was defined by the first-time occurrence of a primary or secondary diagnosis of epilepsy. This identification was regardless of type of admission, including emergency room visits, hospital admissions, and hospital outpatient visits. Using the DNPR, we identified epilepsy by the ICD-8 codes 345.00–345.99 and ICD-10 codes DG40.0–DG41.9 (Paper II, Appendix A). Both status epilepticus and epilepsy, including subtypes, were included. In 15% of new-onset children diagnosed with epilepsy, physicians and/or parents postpone or refrain from treatment with antiepileptic medicine. For that reason, we did not include prescription records of antiepileptic medication when we identified children with epilepsy.[149]

4.7.2. Cerebral palsy (CP)

In study III, we defined CP from the DCPR as our main outcome as the first-time occurrence of the diagnosis. In addition, we obtained three other outcomes for a sub-analysis that took the severity of CP into consideration in different ways because the disorder includes multiple and varying types of impairment. There were several subtypes of unilateral and bilateral spastic CP, DQ (<50, 50–85, and >85), and motor deficit degree (GMFCS levels 1–2, 3, and 4–5); the last outcome was valid only until birth year 2003.

4.7.3. Attention deficit–hyperactivity disorder (ADHD)

In study IV, we defined the outcome as the first-time occurrence of a primary or secondary diagnosis of ADHD, regardless of type of admission, including emergency room visits, hospital admissions, and hospital outpatient visits. Using the DPCRR, we included ADHD (hyperkinetic type) with the ICD-10 code DF90.0 (Paper IV, Appendix A).

In Denmark, a substantial part of ADHD treatment is carried out by psychiatric specialists in private practices and by general practitioners. Thus, we defined a separate outcome, in which we tracked dates of redeemed prescriptions filled out for ADHD medication between January 1, 1996, and December 31, 2014 (Paper IV, Appendix A). Compared to the ADHD diagnosis in the DPCRR, we expected this outcome to be more sensitive, albeit potentially less specific.

4.8. Covariates

We retrieved information on multiple covariates to characterize the study population, adjust for potential confounders, and examine effect measure modification. Descriptive data, including sex and date of birth, were retrieved from the DCRS.[72,140]

4.8.1. Pre- and perinatal covariates

From the DMBR, we obtained information on multiplicity (singleton/twins), 5-minute Apgar score, and gestational age. Moderately late preterm birth was defined as birth between 32 and 33 weeks of gestation, and late preterm children as birth between 34 and 36 weeks of gestation. Furthermore, maternal age at delivery and self-reported smoking status (since 1991) were retrieved from DMBR.[73,74]

4.8.2. Congenital malformations and other medical/neonatal morbidities

According to the guidelines from the European Surveillance of Congenital Anomalies (called EUROCAT), we included only major malformations identified in the DNPR. Isolated minor defects such as torticollis, subluxation or unstable hip, or cryptorchidism were disregarded (Paper II, Appendix A).[150] We identified several complications of IRDS in the DNPR, such as ICH/IVH, PVL, patent ductus arteriosus, necrotizing enterocolitis, and bronchopulmonary dysplasia (Paper II, Appendix A).[141,144]

For a sensitivity analysis, we extracted information from the DNPR on other medical/neonatal morbidities with clinical symptoms potentially overlapping with the clinical symptoms of IRDS. These included perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections (Paper II, Appendix A).[141,144]

4.8.3. Parental psychiatric morbidity

From the DPCRR, we extracted information on parental psychiatric morbidity, defined by any primary or secondary psychiatric diagnosis code. We included both in- and outpatient visits to the psychiatric departments (Paper IV, Appendix A).

4.9. Statistical analysis

For studies II and III, follow-up started on the date of birth as recorded in the DCRS. In study IV, time since date of birth was considered as the underlying time scale, and children were considered at risk on January 1, 1996, or on the date of birth, if date of birth happened after January 1, 1996.

In studies II–IV, we presented tables of the summary statistics, including the distribution of children with and without IRDS based on demographics, pre- and perinatal characteristics, and neonatal/medical morbidities.[151]

4.9.1. Positive predictive value of IRDS

In study I, we computed the PPV of IRDS in the DNPR using the medical record as the reference standard. We estimated the PPV as the proportion of children registered with a primary or secondary IRDS diagnosis (ICD-8 or ICD-10) in the DNPR for which the medical record review could confirm the

finding. Thus, the numerator included all children with a confirmed IRDS diagnosis in the medical record, and the denominator was all children with a registered diagnosis code in the DNPR.

The analysis was stratified by type of diagnosis (primary or secondary), by period of ICD (ICD-8 and ICD-10), and by gestational age (<28, 28–31, 32–36, and ≥37 weeks of gestation). For all PPVs, we computed 95% CIs.[152]

4.9.2. Absolute risks

For studies II–IV, we estimated the cumulative incidence proportions addressing competing risk from death for our three neurodevelopmental outcomes. These analyses estimated the absolute risks: the proportion of study subjects who experienced the outcome of interest during a specific period of time (t_0-t). Competing risks such as death will prevent the outcome of interest from happening. If competing risk had not been taken into consideration, e.g., by censoring at occurrence of deaths with a Kaplan–Meier approach, we would have overestimated the absolute risk of the outcomes under study.[153] In studies II and IV, we estimated the 15-year cumulative incidence proportion of epilepsy and ADHD, and in study III, we estimated the 8-year cumulative incidence proportion of CP.

4.9.3. Cox proportional hazard regression analysis

Time-to-event analyses are favorable when looking at long-term outcomes because children with and without IRDS can be compared independently of their potential differences in follow-up time (e.g., because of death or emigration). Cox proportional hazards regression was developed for time-to-event analysis[154] and allows estimation of the relative risk while adjusting for multiple potential confounders. The output of the regression analysis, the hazard ratio (HR), is an estimate of relative risk, but only under certain assumptions: the HR must be constant throughout the follow-up period; that is, hazards must be proportional, which can be graphically verified by log(-log) plots. We computed crude and adjusted HRs and 95% CIs for the outcomes of interest.

In studies II and III, we followed the children with and without IRDS until initial diagnosis of the outcome of interest (epilepsy and CP), death, emigration, 15 years of age, or end of study period (December 31, 2014). We used Cox regression to estimate risks of epilepsy and CP before 15 years for children with IRDS compared with those without. Analyses were adjusted for gestational age, birth year, sex, major malformations, multiplicity, and maternal age.

In study IV, we followed children until the initial diagnosis of ADHD (the date of a filled prescription for ADHD medication, or a combination of the two outcomes), death, emigration, 15 years of age, or end of study period (December 31, 2014). We included the same potential confounders in the regression model as in studies II and III and also added parental psychiatric morbidity.

In all three follow-up studies, we stratified the estimates by several covariates to examine whether the effect of IRDS on the outcome of interest, as estimated by HRs, varied across subgroups (i.e., effect measure modification). Common to all three studies were stratification by gestational age (32, 33, 34, 35, and 36 weeks of gestation), gender, multiplicity (singleton/twins), major malformations, 5-minute Apgar score (0–6, 7–8, 9–10), and maternal age (less than 35 years or 35 years and above). In study II, birth year was stratified into the following subcategories: 1978–1985, 1986–1993, 1994–2002, and 2003–2009; in study III, the same covariate was stratified by different subcategories: 1997–1999, 2000–2002, 2003–2005, and 2006–2007; and in study IV, the subcategories were as follows: 1990–1994, 1995–2000, 2001–2004, and 2005–2009.

4.10. Subgroup analysis

Intracerebral/intraventricular hemorrhage is an important risk factor for CP and epilepsy; it is also a serious complication of IRDS. Thus, ICH/IVH would be defined as an intermediate step in the causal pathway between IRDS and CP or epilepsy. As such, we wanted to see if the observed association was mediated only through ICH/IVH or if an association would still be present in the children with IRDS who were not subsequently diagnosed with ICH/IVH. Subcategorization divided the exposure group into two distinct cohorts: children with IRDS and IVH/ICH within 30 days of birth and children with IRDS and no IVH/ICH. Analyses were repeated comparing each group to the comparison cohort. We used time-to-event analysis and started follow-up at 30 days of birth (using a delayed entry approach).

4.11. Sensitivity analysis

Sensitivity analyses were performed in studies II and III to assess the robustness of our results. Sensitivity analysis accounts for the uncertainty of a given estimate, given the potential unreliability of a particular variable within the analysis. Analysis of this type was necessary in these studies because non-IRDS could be misdiagnosed as IRDS due to an overlap of clinical symptoms with other disorders. These disorders included perinatal breathing disorders other than IRDS, congenital heart diseases, and bacterial and viral infections. Thus, we repeated our analysis to examine the effect of IRDS on the outcome of interest when the definition of IRDS was altered to address this potential misclassification. We restricted the analysis only to children with IRDS who had *none of these* perinatal disorders occurring within 4 days of birth.

4.12. Additional information

All data analyses were performed using STATA statistical software package, version 13.1 (StataCorp LP, College Station, TX, USA). All studies were approved by the Danish Protection Agency (record numbers:

2002-41-1820 (study I) and 2014-41-3183 (studies II–IV)). Informed consent was not required because all studies were register-based and thus we had no contact with the members of the study population.

6. Results

6.1. General characteristics of the study population

The study population of interest in all three follow-up studies (studies II–IV) comprised approximately 54–60% males. Children with IRDS had lower 5-minute Apgar scores and were more often diagnosed with a major malformation compared to the comparison cohort. In addition, the children with IRDS had a higher frequency of medical morbidities, including ICH/IVH, as well as perinatal breathing disorders other than IRDS, congenital heart diseases, and bacterial and viral infections, occurring within 4 days of birth.

6.2. Study I – PPV of IRDS

Using the DNPR, we identified the corresponding medical record of 90 of the 96 (94%) selected patients with a diagnosis of IRDS. Of those, 52 (58%) were males. For 88 IRDS patients, the gestational age was documented in the medical record, of which 65 (74%) infants were born before 37 weeks of gestation and 23 (26%) as term infants (37 weeks of gestation or later).

We confirmed that 73 of the 90 patients had a coding for IRDS diagnosis on the medical record that corresponded to the DNPR. Overall, we found a PPV of 81% (95% CI: 72%–88%) (Table 3). In the subanalysis, in which IRDS was defined as a confirmed x-ray in addition to the previous definition of two or more clinical symptoms of IRDS, we confirmed the diagnosis for a total of 52 IRDS patients, which yielded a PPV of 58% (95% CI: 48%–68%).

In the DNPR, a primary diagnosis of IRDS was reported for 20 (22%) patients, of whom 14 children had a confirmed IRDS diagnosis in the medical record. This result corresponded to a PPV of 70% (95% CI: 48%–86%). A secondary diagnosis of IRDS was coded in 70 (78%) patients, of whom 59 were confirmed with IRDS. This led to a PPV of 84% (95% CI: 75%–91%). Among males, we found a PPV of 75% (95% CI: 62%–85%), and a PPV of 89% (95% CI: 77%–96%) in females. In the ICD-8 period (1997–1993), we found a PPV of 87% (95% CI: 75%–94%), and in the ICD-10 period (1994–2008), we found a PPV of 75% (95% CI: 61%–86%). When we stratified by gestational age, for infants born at 37 weeks of gestation or later, the PPV was 61% (95% CI: 41%–79%); PPV was 92% (95% CI: 77%-98%) in preterm infants born at gestational weeks 28–31 (Table 3).

Treatment with CPAP for more than 30 minutes was reported in 82 (91%) of the patients coded with a diagnosis of IRDS, and 71 (79%) of the 90 medical records explicitly mentioned the IRDS diagnosis.

Table 3. (Paper I, Table 1)[155] – Positive predictive value (PPV) of the respiratory distress syndrome diagnosis in the Danish National Patient Registry in 90 patients born in 1977–2008

	Confirmations (N=90)	**PPV % (95% CI[a])**
Diagnostic criteria		
≥2 clinical symptoms[b]	73/90	81% (72%–88%)
≥2 clinical symptoms AND x-ray confirmation	52/90	58% (48%–68%)
Primary or secondary diagnosis		
Primary discharge diagnosis	14/20	70% (48%–86%)
Secondary discharge diagnosis	59/70	84% (75%–91%)
ICD[c] version period		
ICD-8 (1977–1993)	40/46	87% (75%–94%)
ICD-10 (1994–2008)	33/44	75% (61%–86%)
Gender		
Male	52/90	75% (62%–85%)
Female	38/90	89% (77%–96%)
Gestational age (completed weeks)		
37 weeks of gestation or more	14/23	61% (41%–79%)
32–36 weeks of gestation	31/35	89% (75%–96%)
28–31 weeks of gestation	23/25	92% (77%–98%)
Less than 28 weeks of gestation	4/5	80% (37%–98%)

[a]Confidence interval
[b]Clinical symptoms: tachypnea, retractions, grunting, and cyanosis
[c]ICD = International Classification of Diseases

6.4. Study II – Epilepsy

In study II, we identified 95,026 children born between 1978 and 2009, of whom 6,426 (6.8%) were diagnosed with IRDS. The prevalence of IRDS was 22% among children born at gestational week 32 and 2% for those born at 36 weeks of gestation. Compared to children without IRDS, children with IRDS were more frequently born in the earlier birth years (26% in 1978–1985).

In children with IRDS, the overall cumulative incidence of epilepsy up to age 15 was 3.4%, and in children without IRDS, the cumulative incidence was 2.1% (Figure 5). The overall crude HR for epilepsy in children with IRDS was 1.7 (95% CI: 1.4–1.9) compared to children without IRDS. When we adjusted for sex, birth year, gestational age, multiplicity, major malformations, and maternal age at delivery, the HR was 1.4 (95% CI: 1.2–1.6) (Table 4).

In the stratified analysis, we found an increased risk of epilepsy in children with IRDS across all gestational weeks compared to children without IRDS. We found no substantial variation across categories of birth year, sex, and 5-minute Apgar score. To estimate whether the association between IRDS and epilepsy was mediated through ICH/IVH, we did a subgroup analysis and found an adjusted HR of 5.7 (95% CI: 3.8–8.6) in children with IRDS who experienced an ICH/IVH event within 30 days of birth. The adjusted HR in children with IRDS who did not have ICH/IVH within 30 days of birth was 1.2 (95% CI: 1.0–1.4) (Table 4).

We repeated the analysis after restricting the exposed children with IRDS to include only IRDS with *no* other simultaneous morbidities that had overlapping symptoms with IRDS, occurring within 4 days of birth, including perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections, and the overall adjusted HR was 1.1 (95% CI: 0.9–1.4) (data not shown).

Figure 5. (Paper II, Figure A) Cumulative incidence of epilepsy in 95,026 children with and without IRDS Denmark born 1978–2009.

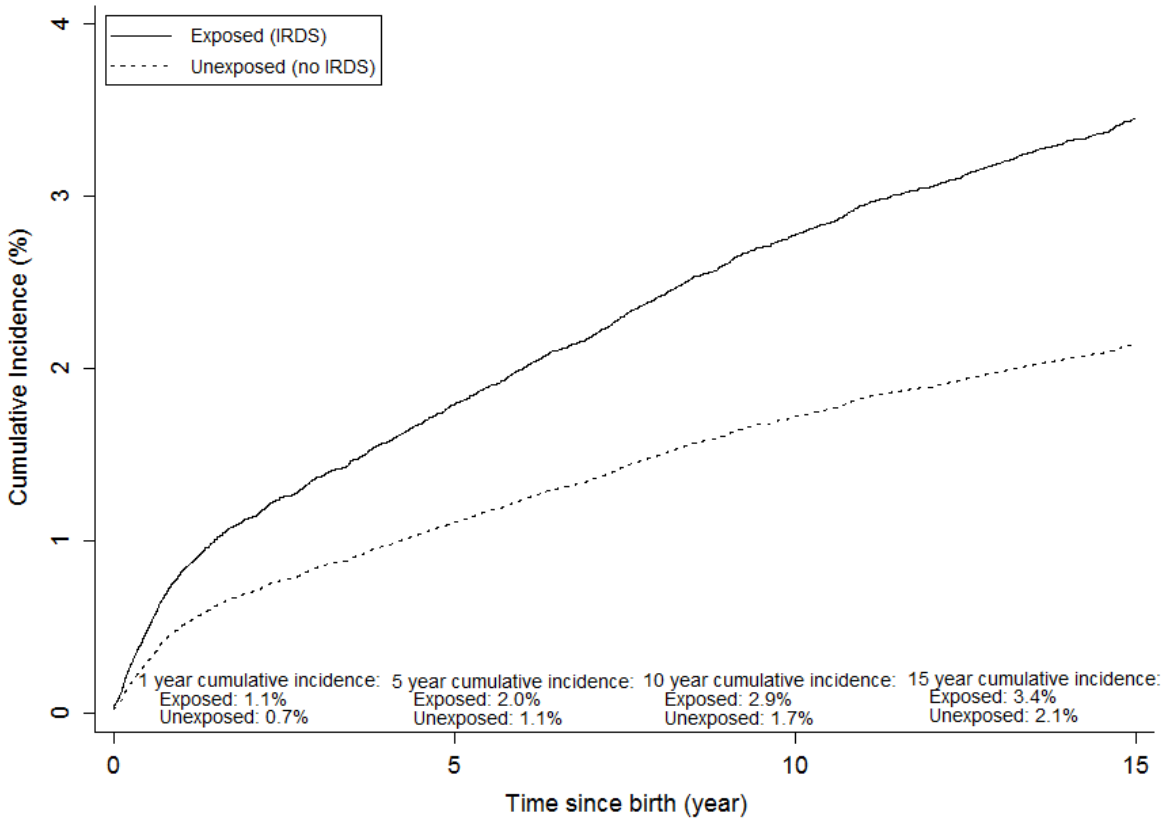


Table 4. (Paper II, Table 2) Hazard ratios for epilepsy among 95,026 children with and without IRDS born 1978–2009

	Number of children with epilepsy		15-year cumulative incidence, % (95% CI)*			
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude HR (95% CI)	Adjusted HR† (95% CI)
Overall	**237**	**2089**	**3.4 (2.9–3.9)**	**2.1 (2.0–2.3)**	**1.7 (1.4–1.9)**	**1.4 (1.2–1.6)**
Gestational age						
32 weeks of gestation	55	155	3.7 (2.8–4.8)	2.7 (2.3–3.2)	1.4 (1.0–2.0)	1.3 (1.0–1.9)
33 weeks of gestation	55	221	3.5 (2.5–4.6)	2.7 (2.3–3.1)	1.3 (0.9–1.8)	1.3 (0.9–1.8)
34 weeks of gestation	55	333	3.9 (2.9–5.0)	2.4 (2.1–2.7)	1.7 (1.3–2.3)	1.6 (1.2–2.2)
35 weeks of gestation	38	478	2.9 (2.0–4.0)	2.0 (1.8–2.2)	1.5 (1.0–2.2)	1.3 (0.9–1.9)
36 weeks of gestation	34	902	2.6 (1.7–3.8)	2.0 (1.9–2.2)	1.4 (0.9–2.1)	1.2 (0.8–1.9)
Year of birth						
1978–1985	84	552	2.6 (1.7–3.8)	2.6 (2.4–2.9)	1.5 (1.0–1.9)	1.3 (0.9–1.7)
1986–1993	82	643	4.6 (3.6–5.7)	2.4 (2.2–2.7)	2.0 (1.5–2.5)	1.7 (1.3–2.2)
1994–2001	36	532	2.6 (1.9–3.6)	1.9 (1.7–2.1)	1.4 (1.0–2.0)	1.2 (0.9–1.8)
2002–2009	35	362	–	–	1.5 (1.1–2.1)	1.2 (0.8–1.7)
Sex						
Female	101	1031	3.2 (2.5–3.9)	2.2 (2.0–2.3)	1.5 (1.2–1.9)	1.2 (1.0–1.5)
Male	131	1058	3.6 (3.0–4.3)	2.1 (2.0–2.3)	1.8 (1.5–2.2)	1.5 (1.2–1.8)
Apgar score at 5 minutes						
Low (0–6)	18	95	4.5 (2.7–7.0)	3.7 (3.0–4.6)	1.1 (0.6–1.8)	1.1 (0.6–1.9)
Intermediate (7–8)	38	172	3.6 (2.5–4.9)	3.0 (2.5–3.5)	1.2 (0.8–1.8)	1.0 (0.7–1.6)
Normal (9–10)	170	1774	3.2 (2.8–3.8)	2.0 (1.9–2.1)	1.7 (1.4–2.0)	1.4 (1.2–1.7)
Missing	11	48	3.4 (1.5–6.5)	2.8 (2.0–3.7)	1.1 (0.5–2.5)	0.9 (0.4–2.1)
Multiplicity						
Singleton	205	1759	3.7 (3.1–4.2)	2.2 (2.1–2.4)	1.7 (1.5–2.0)	1.4 (1.2–1.7)
Twin	32	330	2.3 (1.5–3.3)	1.8 (1.6–2.0)	1.3 (0.9–2.0)	1.0 (0.7–1.6)
Maternal age						
<35 years	2125	1822	3.5 (3.0–4.0)	2.2 (2.1–2.3)	1.7 (1.4–2.0)	1.4 (1.2–1.6)
35 years or older	25	267	2.6 (1.7–3.8)	1.9 (1.7–2.2)	1.5 (0.9–2.3)	1.4 (0.9–2.1)

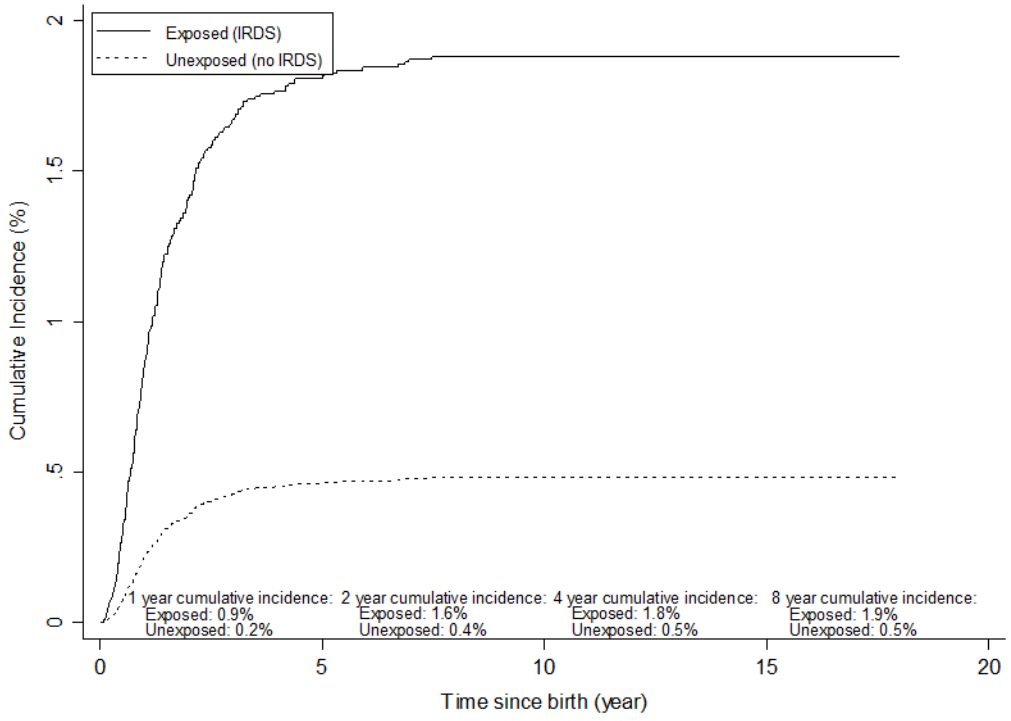
*Death is considered/included as a competing risk.

†Adjusted for sex, twin birth, maternal age, infant's birth year, gestational age, and major malformations

6.5. Study III – CP

The total study population in study II included 39,420 children born between 1997 and 2007, of whom 2,255 (5.7%) were diagnosed with IRDS. The cumulative incidence of CP in children with IRDS was 1.9 (95% CI: 1.4–2.5) up to 8 years of age and 0.5 (95% CI: 0.4–0.6) in children without IRDS (Figure 5). In children with IRDS, we found an overall crude HR for CP of 4.0 (95% CI: 2.9–5.6) compared to children without IRDS. The HR was 2.0 (95% CI: 1.4–2.9) after adjusting for sex, birth year, gestational age, multiplicity, major malformations, and maternal age at delivery (Table 5).

Figure 5. (Paper III, Figure 1) Cumulative incidence of cerebral palsy in 39,420 children with and without IRDS in Denmark, born 1997–2007.



In the analysis with stratification by gestational age, we found an increased risk of CP in children with IRDS in all strata of gestational age compared to the comparison cohort. Although the estimates are less precise, we found no substantial variation in the association between IRDS and CP across categories of birth year, sex, multiplicity, 5-minute Apgar score, and maternal age at delivery (Table 5). The adjusted HR of CP in children with IRDS complicated by an event of ICH/IVH was 12 (95% CI: 4.5–34), and in children with IRDS without a following ICH/IVH event, the adjusted HR was 1.8 (95% CI: 1.3–2.7).

After restricting the exposed group only to a diagnosis of IRDS and *no* other relevant diagnoses occurring within 4 days of birth, including perinatal breathing disorders other than IRDS, congenital heart diseases, and bacterial and viral infections, we found the overall adjusted HR to be 2.1 (95% CI: 1.4–3.1).

Unilateral and bilateral spastic CP were the most common subtypes of CP (data not shown). We found a HR for unilateral spastic CP of 1.5 (95% CI: 0.8–2.9), and for bilateral spastic CP, HR was 2.2 (95% CI: 1.4–3.4) in children diagnosed with IRDS compared to children without. The HR for CP with a normal DQ (above 85) was 1.9 (95% CI: 1.1–3.4); for a DQ between 50 and 85, the HR was 1.7 (95% CI: 0.9–3.1), and for a DQ below 50, the HR for children with IRDS was 2.9 (95% CI: 1.4–6.1). The HR for a mild degree of motor deficit (GMFCS 1–2) was 2.2 (95% CI: 1.3–3.9), and for a severe degree of motor deficit (GMFCS 4–5), the HR was 2.5 (95% CI: 1.3–4.7) (Table 6).

Table 5. (Paper III, Table 2) Hazard ratios for cerebral palsy (CP) by age 8 among children with and without IRDS born during 32–36 weeks of gestation between 1997 and 2007 in Denmark (N=39,410)

	Number of children with CP		**8-year cumulative incidence, % (95% CI)***			
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude HR (95% CI)	Adjusted HR† (95% CI)
Overall	**42**	**178**	**1.9 (1.4–2.5)**	**0.5 (0.4–0.6)**	**4.0 (2.9–5.6)**	**2.0 (1.4–2.9)**
Gestational age						
32 weeks of gestation	21	31	3.5 (2.2–5.2)	1.5 (1.1–2.1)	2.3 (1.3–4.0)	2.4 (1.4–4.2)
33 weeks of gestation	11	44	2.0 (1.1–3.5)	1.3 (1.0–1.7)	1.6 (0.8–3.1)	1.6 (0.8–3.1)
34 weeks of gestation	7	30	1.4 (0.6–2.7)	0.5 (0.4–0.8)	2.5 (1.1–5.8)	2.5 (1.1–5.8)
[35–36] weeks of gestation	3	73	0.5 (0.1–1.4)	0.3 (0.2–0.4)	1.9 (0.6–6.1)	1.7 (0.5–5.5)
Year of birth						
[1997–2002]	28	105	2.5 (1.7–3.5)	0.5 (0.4–0.6)	4.8 (3.2–7.3)	2.4 (1.5–3.7)
[2003–2007]	14	73	1.3 (0.7–2.1)	0.4 (0.3–0.5)	3.1 (1.7–5.4)	1.4 (0.8–2.6)
Gender						
Female	14	76	1.6 (0.9–2.6)	0.4 (0.4–0.6)	3.6 (2.1–6.4)	1.7 (0.9–3.1)
Male	28	102	2.1 (1.4–3.0)	0.5 (0.4–0.6)	4.2 (2.7–6.3)	2.2 (1.4–3.4)
Apgar score at 5 minutes						
Low (0–6)	4	10	3.7 (1.2–8.5)	1.6 (0.8–2.8)	2.1 (0.7–6.8)	2.2 (0.7–7.7)
Intermediate (7–8)	7	31	2.6 (1.2–5.0)	1.7 (1.2–2.4)	1.6 (0.7–3.5)	1.2 (0.5–2.8)
Normal (9–10)	28	131	1.6 (1.1–2.2)	0.4 (0.3–0.5)	4.1 (2.7–6.2)	1.9 (1.2–2.9)
Missing	3	6	5.3 (1.4–13)	0.8 (0.4–1.8)	6.6 (1.6–26)	6.0 (1.0–35)
Multiplicity						
Singleton	29	129	1.8 (1.2–2.5)	0.5 (0.4–0.6)	3.9 (2.6–5.8)	2.0 (1.3–3.1)
Twin	13	49	2.1 (1.2–3.5)	0.5 (0.4–0.7)	4.3 (2.3–7.9)	1.9 (1.0–3.6)
Maternal age						
Younger than 35 years	31	138	1.7 (1.2–2.4)	0.5 (0.4–0.5)	3.9 (2.6–5.7)	1.9 (1.3–2.9)
35 years or older	11	40	2.5 (1.3–4.3)	0.6 (0.4–0.8)	4.4 (2.3–8.6)	2.3 (1.1–4.8)

*Death is considered/included as a competing risk.

†Adjusted for sex, gestational age, infant's birth year, multiplicity, major malformations, and maternal age

Table 6. (Paper III, Table 3) Characteristics of 148 infants with CP born during 32–36 weeks of gestation with and without IRDS, born 1997–2007

	Number of children with CP			
	Children with IRDS	Children without IRDS	**Crude HR (95% CI*)**	**Adjusted HR (95% CI)**
Subtype				
Unilateral spastic CP	12	74	2.7 (1.5–5.0)	1.5 (0.8–2.9)
Bilateral spastic CP	26	87	5.1 (3.3–7.9)	2.2 (1.4–3.4)
Motor Deficit [1997–2003]				
GMFCS† 1–2	16	71	4.0 (2.3–6.8)	2.2 (1.3–3.9)
GMFCS 3	1	4	4.4 (0.5–39)	2.2 (0.2–21)
GMFCS 4–5	4	70	6.1 (3.3–11)	2.5 (1.3–4.7)
Developmental Quotient (DQ)				
DQ <50	11	33	5.6 (2.8–11)	2.9 (1.4–6.1)
DQ 50–85	14	60	3.9 (2.2–7.0)	1.7 (0.9–3.1)
DQ >85	17	80	3.6 (2.1–6.1)	1.9 (1.1–3.4)

*Confidence interval
†Gross Motor Function Classification Skills

6.6. Study IV – ADHD

In study IV, we identified altogether 67,736 moderately late and late preterm children of whom 3,845 (5.7%) had IRDS. The overall cumulative risk of a psychiatric hospital contact for IRDS patients up to 15 years of age was 2.7%, and in children with IRDS who had a redeemed prescription for ADHD medication, the cumulative incidence was 3.8%. The cumulative incidence for both main outcomes was higher in males together with an increase over birth years both in children with IRDS and the comparison cohort. (Figures 7 and 8).

Among children with IRDS, the overall adjusted HR for psychiatric admission or an outpatient contact for ADHD was 1.0 (95% CI: 0.8–1.3). The overall HR for a redeemed prescription for ADHD medication was 1.1 (95% CI: 0.9–1.3) for children with IRDS compared to children without IRDS. We found no statistical differences in HRs across strata after stratifying on several covariates, indicating no effect modification (Tables 7 and 8). When we combined a diagnosis of ADHD with a redeemed prescription for ADHD, the HR did not change substantially [0.9 (95% CI: 0.7–1.3)].

Figure 7. (Paper IV, Figure A) Cumulative incidence of an ADHD diagnosis in 67,736 children with and without IRDS in Denmark, born 1990–2009.

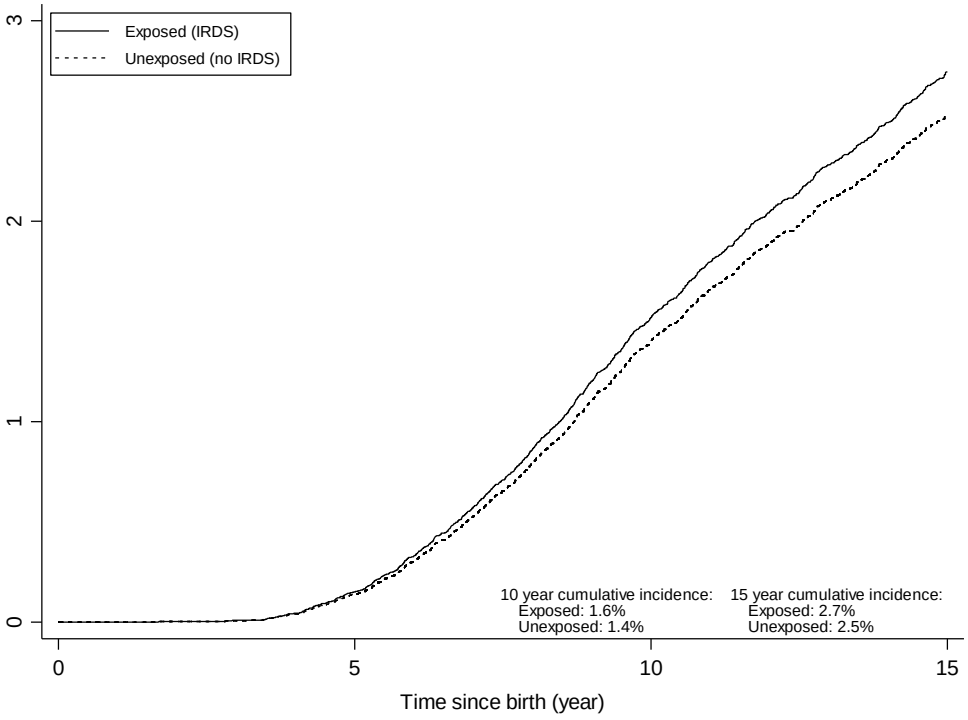


Figure 8. (Paper IV, Figure B) Cumulative incidence of a redeemed prescription for ADHD medication in 67,736 children with and without IRDS in Denmark, born 1990–2009.

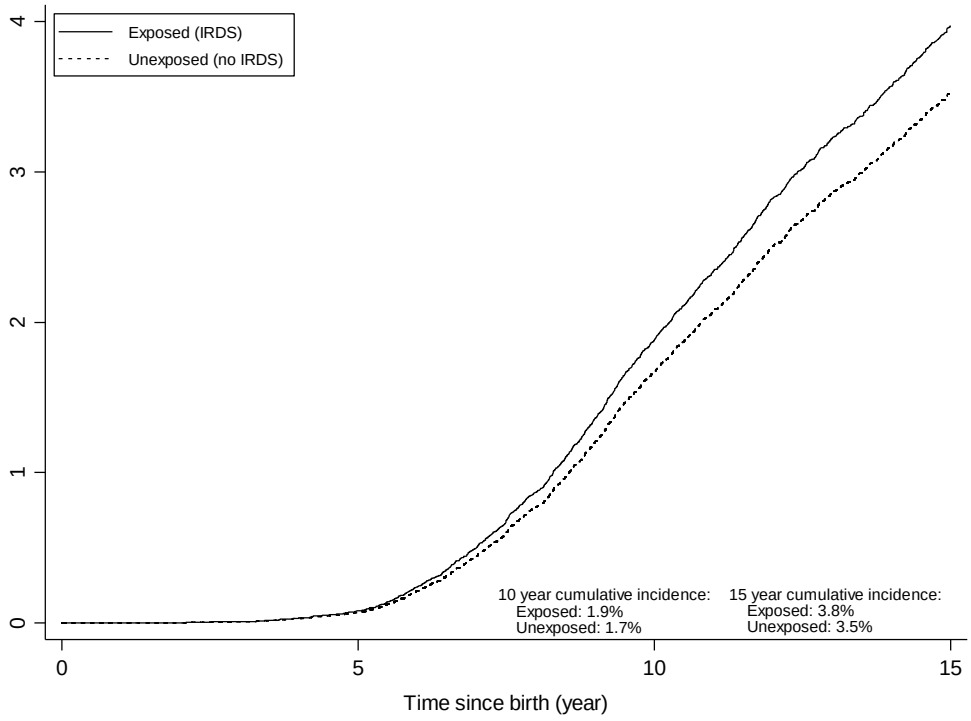


Table 7. (Paper IV, Table 2) Hazard ratios for ADHD among 67,736 children with and without IRDS, Denmark, born 1990–2009

	Number of children with ADHD		15-year cumulative incidence, % (95% CI)*			
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude HR (95% CI)	Adjusted HR† (95% CI)
Overall	**92**	**1,575**	**2.7 (2.1–3.4)**	**2.5 (2.4–2.7)**	**1.1 (0.9–1.4)**	**1.0 (0.8–1.3)**
Gestational age						
32 weeks of gestation	22	91	2.6 (1.5–4.2)	2.9 (2.3–3.6)	0.9 (0.5–1.6)	0.9 (0.5–1.6)
33 weeks of gestation	18	144	2.3 (1.3–3.7)	2.7 (2.2–3.2)	0.9 (0.5–1.5)	0.8 (0.5–1.4)
34 weeks of gestation	19	247	2.6 (1.5–4.1)	2.7 (2.3–3.1)	0.9 (0.6–1.5)	0.9 (0.5–1.5)
35 weeks of gestation	17	386	2.8 (1.6–4.6)	2.3 (2.1–2.6)	1.2 (0.7–2.2)	1.2 (0.7–2.1)
36 weeks of gestation	16	707	4.1 (2.2–6.8)	2.5 (2.3–2.7)	1.7 (0.9–3.0)	1.6 (0.9–2.8)
Year of birth						
1990–1994	25	381	1.5 (0.8–2.5)	1.0 (0.9–1.2)	1.5 (0.8–2.7)	1.2 (0.6–2.3)
1995–1999	27	515	2.7 (1.7–4.0)	2.5 (2.3–2.8)	1.1 (0.7–1.7)	1.1 (0.7–1.6)
2000–2005	25	494	3.3 (1.9–5.2)	3.5 (3.1–4.0)	0.9 (0.6–1.3)	0.8 (0.5–1.2)
2005–2009	15	185	–	–	1.4 (0.8–2.3)	1.3 (0.7–2.2)
Gender						
Female	29	496	1.7 (1.1–2.7)	1.5 (1.3–1.6)	1.2 (0.7–1.9)	1.1 (0.7–1.7)
Male	63	1079	3.5 (2.6–4.5)	3.5 (3.3–3.7)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
Apgar score at 5 minutes						
Low (0–6)	3	36	1.7 (0.5–4.5)	2.4 (1.7–3.4)	0.6 (0.2–2.1)	0.6 (0.2–2.2)
Intermediate (7–8)	14	95	3.0 (1.6–5.2)	2.3 (1.8–3.0)	1.3 (0.7–2.4)	1.4 (0.7–2.7)
Normal (9–10)	72	1402	2.7 (2.0–3.5)	2.5 (2.4–2.7)	1.1 (0.8–1.4)	1.0 (0.7–1.3)
Missing	3	42	4.3 (1.1–11)	4.9 (3.4–6.8)	1.2 (0.4–3.8)	1.0 (0.3–3.3)
Multiplicity						
Singleton	73	1291	2.6 (2.0–3.4)	2.6 (2.5–2.8)	1.0 (0.8–1.4)	1.0 (0.7–1.3)
Twin	19	284	3.2 (1.9–5.1)	2.2 (1.9–2.5)	1.3 (0.8–2.1)	1.1 (0.7–1.8)
Maternal age						
<35 years	81	1372	2.8 (2.2–3.6)	2.6 (2.4–2.8)	1.1 (0.9–1.4)	1.0 (0.8–1.3)
35 years or older	11	203	2.2 (1.1–4.0)	2.2 (1.8–2.5)	1.1 (0.6–2.1)	1.1 (0.6–2.1)

*Death is included as a competing risk.

†Adjusted for gender, multiplicity, birth year, maternal age at delivery, gestational age, major malformations, and parental psychiatric diseases

Table 8. (Paper IV, Table 3) Hazard ratios for ADHD medication among 67,743 children with and without IRDS, born 1990–2009

	Number of children with ADHD		15-year cumulative incidence, % (95% CI)*			
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude HR (95% CI)	Adjusted HR† (95% CI)
Overall	**130**	**2171**	**3.8 (3.1–4.6)**	**3.5 (3.2–4.7)**	**1.1 (0.9–1.4)**	**1.1 (0.9–1.3)**
Gestational age						
32 weeks of gestation	37	137	4.1 (2.7–5.9)	3.9 (3.2–4.7)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
33 weeks of gestation	26	186	3.1 (2.0–4.7)	3.4 (2.8–4.0)	1.0 (0.6–1.5)	0.9 (0.6–1.4)
34 weeks of gestation	30	328	3.9 (2.5–5.7)	3.6 (3.2–4.1)	1.1 (0.7–1.7)	1.1 (0.7–1.6)
35 weeks of gestation	21	548	3.3 (1.9–8.2)	3.6 (3.3–4.0)	1.0 (0.6–1.6)	1.0 (0.6–1.6)
36 weeks of gestation	16	972	5.2 (3.0–8.2)	3.4 (3.2–3.7)	1.6 (1.0–2.7)	1.6 (0.9–2.6)
Year of birth						
1990–1994	43	654	2.5 (1.6–3.8)	1.8 (1.6–2.0)	1.4 (0.9–2.3)	1.3 (0.8–2.1)
1995–1999	32	788	3.3 (2.2–4.7)	4.0 (3.7–4.3)	0.8 (0.6–1.2)	0.8 (0.6–1.2)
2000–2005	42	583	4.5 (3.2–6.0)	4.4 (3.9–4.9)	1.2 (0.9–1.7)	1.1 (0.8–1.6)
2005–2009	13	146	–	–	1.4 (0.8–2.5)	1.2 (0.7–2.2)
Gender						
Female	39	755	2.2 (1.5–3.2)	2.3 (2.1–2.5)	1.1 (0.7–1.6)	1.0 (0.7–1.5)
Male	91	1416	5.1 (4.0–6.3)	4.7 (4.4–4.9)	1.1 (0.9–1.4)	1.1 (0.8–1.4)
Apgar score at 5 minutes						
Low (0–6)	9	53	3.6 (1.5–7.3)	3.0 (2.2–4.1)	1.0 (0.4–2.5)	1.3 (0.5–3.3)
Intermediate (7–8)	17	139	3.6 (2.0–6.0)	4.0 (3.3–4.9)	0.9 (0.5–1.6)	1.0 (0.6–1.8)
Normal (9–10)	100	1935	3.8 (3.0–4.7)	3.5 (3.3–3.7)	1.2 (0.9–1.5)	1.1 (0.8–1.3)
Missing	4	44	5.0 (1.3–13)	5.7 (4.1–7.8)	1.1 (0.3–3.6)	0.7 (0.2–2.5)
Multiplicity						
Singleton	105	1782	3.9 (3.1–4.8)	3.7 (3.5–3.9)	1.1 (0.9–1.4)	1.1 (0.9–1.4)
Twin	25	389	3.7 (2.3–5.5)	2.9 (2.6–3.3)	1.2 (0.8–1.9)	1.1 (0.7–1.7)
Maternal age						
<35 years	113	1915	3.9 (3.1–4.8)	3.6 (3.5–3.8)	1.1 (0.9–1.4)	1.1 (0.8–1.3)
35 years or older	17	256	3.3 (1.9–5.4)	2.8 (2.5–3.2)	1.3 (0.7–2.2)	1.1 (0.6–2.0)

*Death is included as a competing risk.

†Adjusted for gender, multiplicity, birth year, maternal age at delivery, gestational age, major malformations, and parental psychiatric diseases

7. Discussion

7.1. Main conclusions

Study I (PPV of IRDS)

We found a PPV of 81% (95% CI: 72%–88%) of the IRDS diagnoses coded in the DNPR, using the medical record as the reference standard. When we stratified by gestational age between weeks 32 and 36, we found a PPV of 89% (95% CI: 75%–96%). Based on these findings, we conclude that data on IRDS in DNPR can be used for epidemiological studies, especially in preterm children. We based our criteria on clinical symptoms because x-rays were not necessarily used in the milder cases of IRDS. Also, radiological findings are not reported in the DNPR, and the potential impact of misclassification should be considered when using data on the IRDS diagnosis in the DNPR.

Study II (Epilepsy)

We found an increased risk of epilepsy by age 15 in children born between 32 and 36 weeks of gestation and with IRDS compared to children without IRDS. An almost six-fold increased epilepsy risk was seen in children with IRDS and the presence of ICH/IVH. An increased risk was also present in infants with IRDS and no ICH/IVH.

Study III (CP)

Children with IRDS had a two-fold elevated risk of CP. As expected, this association was stronger among children with IVH (adjusted HR of 12); however, our findings still showed almost two-fold risk among children with IRDS that was not complicated by ICH/IVH or periventricular leukomalacia.

Study IV (ADHD)

We found no association between IRDS and ADHD up to age 15 years of age. This estimate did not depend on either of our two definitions of the outcome of a hospitalization for ADHD or a redeemed prescription for ADHD medication.

7.2. Methodological considerations

When interpreting the findings in observational cohort studies, it is essential to assess to what extent the internal validity holds with regard to 1) systemic error, which includes selection bias, information bias, and confounding; and 2) random error (or chance), which affects the precision of the estimates.[156] In our results section, we reported 95% CIs to describe the precision of our estimates. A narrow 95% CI increases the precision of the estimate.

7.3. Selection bias

Selection bias is a systematic error potentially occurring during the selection of subjects into the study cohorts, or during the study period in terms of loss to follow-up.[156] Selection bias is present if there are differential levels of participation among those with and without the exposure or outcome of interest.

In our population-based studies, selection bias is reduced to a minimum through the use of nationwide medical registries that use prospectively collected data.[157,158] Furthermore, these databases are maintained under the Danish tax-supported healthcare system, which gives Danish citizens free and equal access to all hospitals in Denmark.[140] Because the DCRS is updated daily, these studies have virtually complete follow-up accounting for death and emigration, resulting in accurate censoring.[72]

7.4. Information bias

Information bias is a result of measurement error.[156] The two general types of misclassification are non-differential and differential misclassification. Non-differential misclassification of, e.g., the exposure will occur when the misclassification of study variables defining exposure is independent of the outcome. Generally, in the context of two levels of exposure, such as IRDS versus no IRDS, non-differential misclassification will bias the estimates towards an attenuated association. However, if these variables are not independent, the direction of the bias can go either way. This could happen if, for example, the doctor who misdiagnosed the exposure under study (IRDS) is the same one who sees the patient for the outcome under study (e.g., ADHD), which the physician also misdiagnoses. In the studies in this thesis, interdependence of misclassification of IRDS and the neurodevelopmental outcomes under study is unlikely because of, among other factors, the different subspecialties of the coding physicians involved (neonatologists, neurologists, and psychiatrics).[156]

7.4.1. Misclassification of IRDS

In our studies, misclassification of the exposure would mean that some of the children diagnosed with IRDS did in fact not have the disorder, or conversely, that some of the children in the comparison cohort actually had IRDS but were not coded with the disorder.

In all three cohort studies, children with IRDS were defined as our exposure. There is no laboratory test to measure the amount of surfactant in children with IRDS, which makes this disorder difficult to diagnose and grade. Diagnosis is based purely on clinical symptoms and an x-ray. However, x-rays were not routinely performed in children with mild IRDS. In study I, we found a PPV of 89% (95% CI: 75–96) in children with IRDS born between 32 and 36 weeks of gestation. This result means that 21% of the children did not have IRDS; however, because this diagnosis was recorded before our outcomes of interest (epilepsy, CP, and ADHD), it seems very unlikely that the misclassification of IRDS depends on the outcome. Thus, this misclassification would be defined as non-differential, which means that the relative estimates would be biased towards the null hypothesis.

Some of the children coded with IRDS had other simultaneous medical conditions (with overlapping clinical symptoms) that might have been some of the misclassified conditions. To anticipate this possible misclassification, we performed a sensitivity analysis, restricting our exposure of children with IRDS to have only IRDS and no other medical complications occurring within 4 days of birth. These other complications included perinatal breathing disorders other that IRDS, congenital heart diseases, and viral and bacterial infections. This restriction left the estimates in studies II and III virtually unchanged.

7.4.2. Misclassification of the outcome

Epilepsy was the outcome in study II. Two previous Danish studies validated the epilepsy diagnosis in the DNPR between 1977 and 2002 and found a PPV between 75%–81% using medical record review as a standard reference.[88,89] We found it unlikely for any misclassification of epilepsy to be associated with the presence of IRDS at birth. Thus, any bias of the association between IRDS and epilepsy would probably have been underestimated.

In study III, we examined CP as an outcome. Previously, a Danish study reported a completeness of 85% by comparing the DCPR to the DNPR.[90] A PPV was not reported; however, to be included in the DCPR clinical database, children had to fulfill specific inclusion criteria. These criteria are thoroughly assessed through medical records review by a child neurologist at the age of 4–5 years of age, when the diagnosis is more certain. For this reason, we expect the PPV of CP to be close to 100%. As in study II, we believe non-differential bias to be the result of a possible misclassification of CP, as it seems unlikely for CP to be associated with the presence of IRDS at birth.

In study IV, we defined ADHD in two different ways. We found no previous studies that have validated the ADHD diagnosis although, based on other psychiatric diagnoses that have been validated in the DPCRR with high PPVs, we do expect a valid PPV for ADHD. These other psychiatric diagnoses include among others, autism spectrum disorder, schizophrenia, and depression, with a PPV ranging between 75% and 94%.[159-161] A non-negligible proportion of children with ADHD are treated by

psychiatric and pediatric specialists in private practices. To overcome this factor, we tracked dates of filled prescriptions for ADHD medication as a separate outcome. The outcome would be more sensitive although also less specific compared to the hospital ADHD diagnosis code. However, we found similar estimates in both of our outcomes (a hospital diagnosis of ADHD or a filled prescription for ADHD medication). Overall, we did not believe this potential non-differential misclassification to be the reason for the null association found in this study.

7.4.3. Misclassification of gestational age

In the early years of the DMBR, weeks of gestation was based on weeks since the date of conception (defined by the first day of the last menstrual period). Later, prenatal ultrasound measurement also was included as a valid measure for the gestational age. However, in the DMBR, it is not possible to distinguish between the methods of measurement used to determine gestational age. A previous study found the DMBR to overestimate gestational age by one week compared to the information in the medical record.[73] It could be posited that midwives or physicians would be more likely to estimate children diagnosed with IRDS after birth in the earlier weeks of gestation because of their decreased health status/neonatal morbidities. In this scenario, we would compare our exposed children with IRDS to a comparison cohort that would in general be one week older. We do not expect this scenario to be the case, however, because we believe that gestational age was determined before IRDS was identified and thus not dependent on our study outcomes. In the end, if this scenario were a factor, the result would be a non-differential misclassification. After stratifying by birth year, we found no differences in the estimates, indicating that implementation of ultrasound measurement did not affect or dilute the association.

7.5. Confounding

Confounding is, in simple terms, a mixing of effects and implies that the effect of the IRDS is confused with – or masked by – the effect of another covariate, such as gestational age, which leads to bias.[156] It takes three properties to be a confounder.

1. The confounder variable must be associated with the exposure (imbalanced across categories of exposure); e.g., low gestational age must be associated with IRDS.
2. The confounder must be related with the disease in the unexposed children (either as an independent cause or a proxy/predictor for the cause, but not as an effect of the disease). Thus, low gestational age must affect or predict the risk of CP in the comparison cohort (children without IRDS), and low gestational age cannot be an effect of CP.
3. The confounder must not be a part of the causal pathway between the exposure and outcome,[156] such as, e.g., gestational age.

There are several opportunities to control for confounding, which can be addressed in the study design and in the analysis stage. In the study design, we chose to restrict the cohort to moderately late and late preterm infants born between 32 and 36 weeks of gestation because this cohort has an adequate proportion of both exposed and unexposed children.

To minimize confounding in our analyses, we performed stratification (studies I–IV), multivariate adjustments (studies II–IV), and sensitivity analyses (studies II–III) to provide the cleanest possible effect between IRDS and our selected neurodevelopmental outcomes. Generally, we found associations between IRDS and epilepsy and CP; however, we cannot rule out the presence of residual or unmeasured confounding. As an example of residual confounding, we subcategorized birth years; instead, we could have made more narrow categorization intervals. We could also have included birth years as a continuous variable, but doing so would have required other assumptions.

As an example of potentially unmeasured confounding, we did not have information on prenatal care, such as treatment with corticosteroids. Treatment with corticosteroids is associated with reduced prevalence of IRDS because it induces maturation of the lungs, including surfactant maturation. In addition, previous studies have found an increased risk of, e.g., CP in children treated with corticosteroids both prenatally and during early childhood.[65,66] However, we believe that this cannot explain our findings, because more children treated with corticosteroids would then be located in the comparison cohort, which would then bias our estimates towards the null hypothesis.

A postnatal event like ICH/IVH has the potential to be categorized as an intermediate step in the prognosis of IRDS to epilepsy. Thus, we did not include this covariate in our adjusted model. However, because ICH/IVH is an important complication of IRDS and a well-known risk factor for epilepsy and CP, we wondered if the association between IRDS and epilepsy (or CP) may be mediated entirely through ICH/IVH. When we did a subgroup analysis of children with IRDS who later had an ICH/IVH event, we found an almost six-fold increased risk of epilepsy and a 12-fold increased risk of CP. Interestingly, we still saw an increased risk, though diminished, of epilepsy and CP in children diagnosed with IRDS who did not experience an ICH/IVH event. Therefore, although IRDS may heighten the risk of epilepsy and CP because of an impact on ICH/IVH events, it is still possible that IRDS directly influences epilepsy and CP risk.

7.6. Comparing to the existing literature

7.6.1. Study I (PPV of IRDS)

We found no other studies that investigated the PPV of IRDS. However, other neonatal diagnoses, such as congenital cardiac malformations, have been validated in the DNPR. Jepsen et al.[162] found an overall PPV of 89% (95% CI: 86%–92%) between 1994 to 2002, and Agergaard et al.[163] found a PPV of 90% (95%

CI: 89%–91%) between 2000 and 2008. While these studies regularly report a higher PPV than the estimate reported in our study, the methodology of validation in our study is consistent with other studies using the DNPR. Therefore, the PPV reported in our study is as accurate as possible, given current methods of validation.

Positive predictive value can change depending on the criteria used in validation. We found a lower PPV of IRDS in the ICD-10 period compared to the earlier ICD-8 period, although we found the estimates from both periods to be statistically imprecise. The lower PPV of IRDS in the ICD-10 period may reflect a coding practice that was less optimal, or it could reflect better documentation of the clinical symptoms in medical records in the earlier period. Infant respiratory distress syndrome was defined as the presence of two of four clinical symptoms in the medical record, but clinical symptoms of IRDS may not always have been mentioned in the medical record. Furthermore, IRDS is a diagnosis of exclusion, which means that if diseases like necrotizing enterocolitis or congenital heart disease were not diagnosed by the clinicians, the PPV may have been overestimated. In the main criteria, we did not include the x-ray diagnosis because patients with mild IRDS may not have this diagnostic test performed. Moreover, results of the x-ray diagnosis were not available in the registries.

In conclusion, no previous study has provided the PPV for the diagnosis of IRDS in the DNPR. Therefore, we find it reasonable to use the diagnosis of IRDS in the DNPR in future studies, especially for children born between 32 and 36 weeks of gestation; however, validity of the IRDS diagnosis should be taken into consideration when conducting observational studies on IRDS diagnosis based on the DNPR.

7.6.2. Study II (Epilepsy)

A Canadian cohort study conducted by Whitehead[131] in 2006 examined neonatal and pregnancy-related predictors of epilepsy during childhood. That study found a relative risk of epilepsy in children with mild IRDS of 2.0 (95% CI: 1.1–3.7) and in children with severe IRDS of 4.5 (95% CI: 3.0–6.7), compared to children with no IRDS. Their estimates relied on univariate analysis, where they did not account for potential confounding factors, such as gestational age. In the multivariate model, there was no association between IRDS and epilepsy; the reason may be inclusion of covariates that either were interacting with each other or acting as intermediate steps on the pathway from IRDS to epilepsy, and thus did not fulfill the criteria of a confounder.[131]

Other studies have previously examined the long-term risks of other neurodevelopmental disorders in children born preterm in terms of psychomotor development and school readiness.[16,40] In 2000, McGrath et al.[79] indicated that neurological status varied over time, dependent on neonatal morbidities; furthermore, these changes affected both cognitive outcomes and school achievement (in reading and math). The researchers additionally indicated that other neonatal disorders of similar severity

can be classified with normal neurology at an early age and may later present with abnormal neurology. However, the exposure group in this study consisted of a mix of sick preterm infants with various neonatal morbidities/complications, such as IRDS, BPD, sepsis, and mild IVH (grades 1 and 2). In addition, the assessment of neurologic outcomes included multiple outcomes collected into one group, including seizures.[79] Thus, it is not possible to elucidate an association between seizures and IRDS. To address this issue and elucidate the potential association, we combined the outcome in our study to include both status epilepticus and epilepsy, which is well-described and reliable diagnoses.

In summary, our findings were in accordance with previous studies, which indicated an increased risk of neurodevelopmental impairments among preterm children with neonatal complications. We added to this knowledge with findings suggesting an association between IRDS and epilepsy. The mechanisms remain elusive, thus larger randomized trials are needed to establish whether the association is causal.

7.6.3. Study III (CP)

Previous studies have reported modest associations between potential causes or predictors of CP, with variation in study design and setting. Blair et al. (1993)[122] took on a case-control study in Australia and found an OR for CP of 2.3 (95% CI: 1.3–4.3) in children with IRDS born after 20 weeks of gestation; however, that study included only cases with their first time-dependent covariate in a step-wise multivariate model, which left out children who may have, e.g., a second neonatal covariate, such as IRDS. Another Australian case-control study (n=1,020), conducted by Dite et al. (1998),[133] reported an OR for CP in children with IRDS born at any gestational age of 9.4 (95% CI: 1.8–48), based on univariate analysis. In the multivariate analysis, they included potential interacting covariates as well as variables that would be considered intermediate steps on the causal pathway from IRDS and CP. In general, these studies have found a wide range of positive associations; however, no absolute measures were present. Furthermore, all studies were hampered by small study size samples, and most were based solely on univariate analysis with no adjusting covariates included.[132,133,138] These differences in methodology of design and analysis may potentially explain the differences between the estimates in our study and those determined in other studies.

Although in our study we found an elevated risk of CP in all preterm gestational age groups diagnosed with IRDS, a Finnish cohort study by Hirvonen et al. (2014)[134] found no association between IRDS and CP in children born at 32–33 weeks of gestation [OR 1.05 (95% CI: 0.7–1.7)]. Moreover, they found a protective effect of IRDS against CP in infants born at 34–36 weeks of gestation [OR 0.34 (95% CI: 0.2–0.7)]. However, that study included a high number of covariates and did not adjust the statistical significance of the model to address this issue; thus, the covariates could enter the model by chance, and based on this, we could not evaluate the difference in findings between their study and ours. There could

have been inclusion of potentially associated covariates in their analysis model that could have biased the estimate, although that is only speculation; it could, however, explain the different estimates between their study and ours.

Study sample size affects the precision of the estimates. Cerebral palsy is a rare condition, which regularly limits study size. Moreover, because we chose to restrict our cohort to children born at 32–36 weeks of gestation, it became even more important to have a large study population. Therefore, to increase the study sample size, it was possible only to present overall estimates in regard to the outcomes of CP subtypes, DQ, and the level of motor deficit.

In summary, in line with several previous case-control studies and cohort studies, we found an association between IRDS and CP in moderately late and late preterm infants. Although our study may be among the largest to have investigated this association, we are still uncertain about the underlying causes of the increased CP risk.

7.6.4. Study IV (ADHD)

In a nested case-control study on children born at gestational ages 28–42 weeks, Getahun et al.[102] (2012) reported an increased risk of ADHD in children with ischemic-hypoxic conditions, such as IRDS (n=308,634). The researchers reported an overall OR for ADHD of 1.4 (95% CI: 1.0–2.0) in children with IRDS born between 28 and 36 weeks of gestation. The diagnosis of ADHD was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and their inclusion criteria for ADHD were slightly different compared to our study. In their study, the diagnosis of ADHD required a minimum of two hospital visits that indicated a diagnosis of ADHD through coding, or one ADHD-diagnosed visit and at least two prescriptions filled for ADHD medication. When we used the same ADHD combination as an outcome in our study, we still found a lower HR, though with overlapping 95% CIs.

As previously mentioned, ADHD may co-occur with other neurodevelopmental disorders, such as CP.[125] However, a previous study reported that only one in five children with CP had been seen by a child psychiatrist because neurological issues are attributed to the presence of CP.[164] Thus, children with CP had a decreased risk of being diagnosed with ADHD. Given the relationship between IRDS and CP, as described in Study III, some of these children may also have an undiagnosed ADHD. However, CP is a very rare disease, so the proportion of children with IRDS, CP and undiagnosed ADHD would represent only a small proportion of our cohort; thus, this minimal population would probably not have much influence on our estimates.

Several issues should be considered when interpreting our findings. First, definitions of ADHD vary when using the ICD-10 coding system and the DSM-5.[85] Children with ADHD in our study were

diagnosed based on the ICD-10 diagnosis code DF90.0, which includes only the hyperkinetic disorder. The diagnostic criteria for ADHD in ICD-10 are stricter than those in the DSM-5, which does not require concurrent existence of ADHD characteristics: hyperactivity, inattention, and impulsivity.[85] Based on the DSM-5 criteria, an ADHD diagnosis would have been 3–4 times more prevalent in our study than the prevalence we identified. However, we do not expect this to affect the relative estimates of our study.

In summary, compared to a previous cohort study that suggested an association between IRDS and ADHD, we found no such association. There was a null association regardless of whether we defined ADHD on a redeemed prescription for ADHD medication or on a diagnosis of ADHD during psychiatric admission or outpatient visit. Of note, the results of both studies had overlapping confidence intervals.

9. Perspectives

The long-term neurodevelopmental prognosis of IRDS indicates that children are at heightened risk for epilepsy and CP but are at no increased risk for ADHD. However, despite these additions to the knowledge surrounding IRDS, investigation to further elucidate the prognosis of IRDS is still necessary.

Even though our studies are among the largest to examine a potential association between IRDS and the selected neurodevelopmental disorders by using data from nationwide databases on preterm infants, they still do not clarify the specific causes of the increased risk of poorer neurodevelopmental outcomes. Infant respiratory distress syndrome potentially could be a surrogate for other unknown medical conditions or may be one of several other interacting factors. An early recognition of a predictive sign of a future risk of CP could still be helpful when planning follow-up and/or intervention strategies.

In Denmark, we had the opportunity to set up a population-based cohort study based on national administrative registries with almost complete follow-up. Our studies found a PPV for IRDS of 89% in children born between 32 and 36 weeks of gestation. It could be interesting to see what happens to the PPV if we include only children diagnosed with IRDS and no other simultaneous disorders that could potentially lead to a misclassification of IRDS, as we did in the sensitivity analyses in studies II and III. It would also be interesting to see what would happen to the PPV if a diagnosis of the performed procedures, such as x-rays, were attached to this information in the databases; however, these kinds of data are not yet available in the registries.

The recording of surfactant treatment is incentivized via reimbursement to the department if given to infants born before 32 weeks of gestation; this factor should lead to an increase in coding due to the monetary incentive, but the validity of these codes is unknown and needs to be determined prior to additional studies. Use of surfactant might also serve as a proxy for severity of IRDS, but this idea requires confirmation because surfactant is also used in the treatment of other disorders.

Finally, it would be interesting to see the association of IRDS and a combined neurodevelopmental outcome, including both epilepsy and CP, which often co-occur. Such a study could give insight into the impact of IRDS on neurodevelopmental status as a whole. Moreover, to elucidate the mechanism of pathophysiology, stratification could be performed to group neurodevelopmental disorders into the hypothesized biological mechanisms, patterns of symptoms, and overarching category of neuropsychiatric disorder.

10. Summary

Infant respiratory distress syndrome (IRDS) is among the most common respiratory diseases observed in preterm infants and is associated with considerable morbidity and mortality. The overall prevalence of IRDS is about 0.3%; however, prevalence increases with decreasing gestational age. Children born in gestational weeks 32–36 have a prevalence up to 20–30%.

Valid data on IRDS are important in clinical and epidemiologic research. In study I, we estimated the positive predictive value (PPV) of an IRDS diagnosis in the Danish National Patient Registry (DNPR) by a randomized extract of data on three patients per year who had an IRDS diagnosis. We identified 90 of 96 medical records (94%). A confirmed diagnosis required that two of four predefined clinical symptoms be described in the medical record, which was also defined as the reference standard. Overall, the PPV was 81% (95% CI: 72%–88%). When stratifying on gestational age, the PPV decreased in children born at week 37 and above. Therefore, the DNPR can be used for observational studies on IRDS, but the potential impact of misclassification of the IRDS diagnosis should be taken into consideration.

In study II, we used nationwide medical registries to identify a cohort of 95,026 moderately late and late preterm infants born at 32–36 weeks of gestation, of whom 6,426 (6.8%) had IRDS. Up until age 15, we found a cumulative incidence of epilepsy of 3.4% in children with IRDS and 2.1% in children without IRDS. Comparing children with and without IRDS, we found an adjusted hazard ratio (HR) for epilepsy of 1.4 (95% CI: 1.2–1.6). The HR decreased to 1.1 (95% CI: 0.9–1.4) when we restricted to children only with IRDS and no congenital heart disease, no diagnoses of perinatal breathing disorders other than IRDS, and no viral or bacterial infections occurring within 4 days of birth. In moderately late and late preterm children, IRDS was associated with epilepsy up to age 15 years.

In study III, we conducted a population-based cohort study, including 39,420 moderately late and late preterm infants, of whom 2,255 (5.7%) had IRDS. The cumulative incidence of cerebral palsy (CP) up to age 8 years was 1.9% in infants with IRDS and 0.5% in children without IRDS. The overall adjusted HR for CP was 2.0 (95% CI: 1.4–2.9). The adjusted HR for CP increased to 12 (95% CI: 4.5–34) in children with IRDS who experienced a subsequent intracerebral/intraventricular hemorrhage (ICH/IVH) event. The HR for CP declined to 1.8 (95% CI: 1.3–2.7) in infants with IRDS who did not have a subsequent ICH/IVH event. The adjusted HR was 2.1 (95% CI: 1.4–3.1) after restriction to children with no other simultaneous morbidities that may have overlapping symptoms with IRDS, including congenital heart disease, diagnoses of perinatal breathing disorders other than IRDS, and viral or bacterial infections occurring within 4 days of birth. The risk of CP was increased in moderately late and late preterm infants with IRDS compared to infants without IRDS born during the same gestational weeks.

In study IV, we identified in total 67,736 moderately late and late preterm children of whom 3,845 (5.7%) had IRDS. By age 15 years, we found a cumulative risk of ADHD diagnoses (in- or outpatient visit) of 2.7% in children diagnosed with IRDS and 2.5% in children without IRDS. In children who had a redeemed prescription for ADHD medication, we found an overall cumulative incidence of 3.8% in children with IRDS and 3.5% in children without IRDS. The HR for a psychiatric admission or an outpatient contact for ADHD was 1.0 (95% CI: 0.8–1.3) for children with IRDS. The estimated overall adjusted HR for children with IRDS who had a prescription for ADHD medication was 1.1 (95% CI: 0.9–1.3). We found no association between IRDS and ADHD, regardless of whether the outcome was psychiatric admission or an outpatient contact for ADHD, or a redeemed prescription for ADHD medication.

In conclusion, we found an acceptable PPV of IRDS in the DNPR that allowed use of this variable in analysis. Based on this validity, we conducted our three observational cohort studies. We found an association between IRDS and epilepsy and CP; however, there was no association when we changed the outcome to ADHD. Even though these studies preclude evaluation of causal mechanisms, we can conclude that IRDS places individuals at a higher risk of certain neurodevelopmental disorders.

11. Dansk resume

Respiratorisk distress syndrom (RDS) er den hyppigste lungelidelse hos for tidligt fødte børn. Lidelsen optræder hos ca. 0,3 % af alle levendefødte børn i Danmark, men forekomsten stiger jo tidligere barnet fødes og ses hos op til 20–30 % af børn født mellem graviditetsuge 32–36. Tilstanden opstår umiddelbart efter fødslen og skyldes mangel på surfaktant, et protein som produceres i lungerne og hjælper med at holde luftvejene udspilede under vejrtrækning. RDS fører til iltmangel og kan muligvis påvirke centralnervesystemets udvikling i negativ retning. Ubehandlet kan RDS medføre døden. Komplikationerne på kort sigt inkluderer bl.a. kronisk lungesygdom, persisterende ductus arteriosus samt hjerneblødning. Der er kun begrænset viden om senfølgerne af RDS på centralnervesystemets udvikling.

Formålet med denne afhandling var at undersøge, om børn med RDS havde en øget risiko for epilepsi (studie II), spastisk lammelse (studie III) samt attention deficit–hyperactivity disorder (ADHD) (studie IV). Viden om datavaliditeten af RDS-diagnosen i Landspatientregistret var en forudsætning for at kunne udføre disse studier, hvorfor vi undersøgte dette i studie I.

I studie I beregnede vi den positive prædiktive værdi (PPV) af RDS-diagnosen i Landspatientregisteret vha. et randomiseret dataudtræk af patientjournaler på tre patienter per år diagnostiseret med RDS (1977–2008). Klinisk ses RDS ved hurtig vejrtrækning, indtrækninger over brystkassen, vibrering/udspiling af næseborene, 'knirken' og/eller blåfarvning af hud og slimhinder. Beskrivelse af mindst to ud af de fire nævnte fund i patientjournalen blev betragtet som en bekræftelse af RDS-diagnosen. Vi fandt en PPV på 89% hos børn født i graviditetsuge 32–36. Vi konkluderede derfor, at datavaliditeten af RDS-diagnosen i Landspatientregisteret var acceptabel, og dermed kunne LPR bruges til fremtidige observationelle studier, så længe der blev taget højde for en mulig misklassifikation af RDS-diagnosen.

I studie II identificerede vi en studiepopulation på 95.026 børn født i graviditetsuge 32–36 i perioden 1978–2009. Heraf blev 6.426 (6,8%) diagnosticeret med RDS. Vi fandt en kumuleret incidens for epilepsi op til 15-årsalderen på 3,4 % hos børn med RDS og 2,1 % hos børn uden RDS. Sammenlignet med børn uden RDS fandt vi en 40% øget risiko for epilepsi hos børn med RDS. Den øgede risiko faldt til 10 %, hvis vi udelukkende betragtede børn med RDS der ikke på samme tid havde andre diagnoser som f.eks. andre respiratoriske tilstande, infektioner og medfødte hjertesygdomme.

I studie III identificerede vi 39.420 børn født i graviditetsuge 32–36 i perioden 1997–2007. I alt blev 2.255 (5,7 %) diagnosticeret med RDS. Vi fandt en kumuleret incidens for spastisk lammelse op til 8-årsalderen på 1,9 % hos børn med RDS og 0,5 % hos børn uden RDS. Børn med RDS havde 2 gange øget risiko for spastisk lammelse, sammenlignet med børn uden RDS. Risikoen var meget større hos børn med RDS som kort efter fødslen også fik en hjerneblødning. Her var der en 12 gange øget risiko for spastisk

lammelse sammenlignet med børn uden RDS. Hos børn med RDS uden en efterfølgende hjerneblødning var risikoen for spastisk lammelse øget med 80 %, sammenlignet med børn uden RDS.

I studie IV identificerede vi en studiepopulation på 67.736 børn født i graviditetsuge 32–36 i perioden 1990–2009. Heraf havde 3,845 (5,7 %) af børnene RDS. Op til 15-årsalderen fandt vi en kumuleret incidens for hospitalsdiagnosticeret ADHD på 2,7 % hos børn med RDS og 2,5 % hos børn uden RDS. Hos børn med en udskrevet recept på ADHD-medicin fandt vi en kumuleret incidens på 3,8 % hos børn med RDS og 3,5 hos børn uden RDS. Vi fandt ingen øget risiko for ADHD hos børn med RDS sammenlignet med børn uden RDS, hverken for hospitalsdiagnosticeret ADHD eller for indløste recepter på ADHD-medicin.

Vi ønskede med dette projekt at bidrage ny viden om langtidsprognosen hos for tidligt fødte børn med RDS, med fokus på senfølger i nervesystemets. Først fandt vi, at RDS-diagnosen i Landspatientregisteret kunne bruges til at udføre observationelle studier, og dette dannede baggrund for de øvrige tre ph.d.-studier. Vi fandt, at børn født i graviditetsuge 32–36 med RDS havde en øget risiko for senere at udvikle epilepsi og spastisk lammelse, og denne risiko var særligt forhøjet hos børn med RDS som også udviklede en hjerneblødning. Vi fandt dog ingen sammenhæng mellem ADHD og RDS hos børn som blev født i graviditetsuge 32–36.

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14. Appendices

Appendices I–IV provide the full version of papers I–IV

- Appendix I

- Appendix II

- Appendix III

- Appendix IV

Paper I

Clinical Epidemiology

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SHORT REPORT

Positive predictive value of the infant respiratory distress syndrome diagnosis in the Danish National Patient Registry

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Background: Infant respiratory distress syndrome (IRDS) is the most common respiratory disease in preterm infants, and is associated with considerable morbidity and mortality. Valid data on IRDS are important in clinical epidemiological research.

Objectives: The objective of this study was to estimate the positive predictive value (PPV) of the IRDS diagnosis registered in the population-based Danish National Patient Registry according to the *International Classification of Diseases*, 8th and 10th revisions.

Methods: Between January 1, 1977 and December 31, 2008, we randomly selected three patients per year, 96 in total, who were registered with an IRDS diagnosis in the Danish National Patient Registry and living in the northern part of Denmark. Data on the infants included information on the presence of predefined clinical symptoms. We defined IRDS as the presence of at least two of four clinical symptoms (tachypnea, retractions or nasal flaring, grunting, and central cyanosis), which had to be present for more than 30 minutes. Using medical record review as the reference standard, we computed the positive predictive value of the registered IRDS diagnosis including 95% confidence intervals (CIs).

Results: We located the medical record for 90 of the 96 patients (94%), and found an overall PPV of the IRDS diagnosis of 81% (95% CI 72%–88%). This did not vary substantially between primary and secondary diagnoses. The PPV was higher, at 89% (95% CI 80%–95%), for preterm infants born before 37 weeks of gestation.

Conclusion: The PPV of the IRDS diagnosis in the Danish National Patient Registry is reasonable when compared with symptoms described in the corresponding medical records. The Danish National Patient Registry is a useful data source for studies of IRDS, particularly if restricted to preterm infants. Nonetheless, the potential impact of misclassification of the IRDS diagnosis must be considered.

Keywords: epidemiology, data quality, validity, positive predictive value, hospital diagnosis, respiratory distress syndrome

Introduction

Infant respiratory distress syndrome (IRDS) is the most common respiratory disease in preterm infants, and leads to substantial morbidity and mortality.[1,2]

IRDS is caused by lung immaturity and usually develops within minutes of birth. It is defined by tachypnea, retractions or nasal flaring, grunting respiration, and possibly central cyanosis.[3] It occurs in approximately 0.3%–1.2% of live-born infants.[4–6] However, the prevalence of IRDS increases with decreasing gestational age.[4,7] Previous studies have found a prevalence of approximately 90% in premature infants born in gestational week 28.[8]

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Dovepress
http://dx.doi.org/10.2147/CLEP.S44408

Valid data on IRDS are important for clinical epidemiological research. If the coding is accurate, the Danish medical registries provide excellent data to study the long-term prognosis of IRDS, as the registries comprise more than 30 years of medical observations.[9,10]

To our knowledge, no study has examined the validity of the IRDS diagnosis in administrative registries. We therefore conducted the present study with the objective of estimating the positive predictive value (PPV) of the IRDS diagnosis recorded in the population-based Danish National Patient Registry (DNPR) according to the *International Classification of Diseases* (ICD), 8th and 10th revisions, using medical records as reference standard.

Materials and methods

Population

Based on the DNPR, we identified patients diagnosed with IRDS from January 1, 1977 to December 31, 2008 in the northern part of Denmark (corresponding to the former North Jutland County). This part of Denmark has approximately 500,000 inhabitants, equivalent to approximately 11% of the total Danish population. The entire Danish population is provided with unrestricted tax-supported health care.

The Danish National Patient Registry

The DNPR includes data on all non-psychiatric hospital admissions in the country since 1977 and outpatient clinic and emergency room visits since 1995. Data include the patients' civil registration number, which is a unique personal identification number assigned to all Danish residents, date of admission and discharge, surgical procedure(s) performed, one primary diagnosis and up to 19 secondary diagnoses coded by the discharging physician according to the ICD-8 until the end of 1993 and subsequently the ICD-10. The primary diagnosis code registered is the main reason for the hospital contact.

Among all patients with a primary or secondary IRDS diagnosis, we randomly selected three IRDS patients for each calendar year, 96 in total, between 1977 and 2008. The IRDS hospital admissions were identified based on the ICD-8 diagnosis code 776.19 (idiopathic respiratory distress syndrome or hyaline membrane disease) and the ICD-10 diagnosis code P22.0 (idiopathic respiratory distress syndrome).

Medical record review

The medical records of the identified IRDS patients were reviewed and data were entered in EpiData (EpiData Association, Odense, Denmark) by a physician (SKT). Where there was doubt with regard to interpretation of the medical record, another physician (CFC) was consulted. Data entered included presence of predefined clinical symptoms and X-ray findings. We also noted gender, gestational age, treatment with continuous positive airway pressure (CPAP), and whether the IRDS diagnosis was mentioned explicitly in the medical record.

In the primary analysis, we defined IRDS as the presence of at least two of the four clinical symptoms (tachypnea, retractions or nasal flaring, grunting, and central cyanosis), which had to be present for more than 30 minutes. Tachypnea was defined as 60 or more breaths per minute.

In an additional analysis, we defined IRDS as two or more clinical symptoms together with a positive X-ray finding, defined as reticulogranular ground-glass appearance with air bronchograms. If no information was available on whether or not an X-ray had been taken, or if the radiologist had explicitly ruled out signs of IRDS, we classified the individual as not having IRDS. For descriptive purposes, we abstracted data on CPAP treatment, but only if provided by pediatric departments and for more than 30 minutes. Thus, brief CPAP treatment given immediately after birth was not included. Furthermore, we noted if the IRDS diagnosis was mentioned in the medical record as a confirmed diagnosis.

Statistical analysis

We used the medical records as the reference standard when computing the PPV of the IRDS diagnosis. The PPV was defined as the proportion of patients registered with an IRDS diagnosis in the DNPR that was confirmed by medical record review. Thus, the numerator was the number of confirmed IRDS cases according to the medical records, and the denominator was the selected number of patients registered with an IRDS diagnosis in the DNPR. The 95% confidence intervals (CIs) were computed using Jeffrey's method.[11]

We stratified the analyses by primary and secondary diagnoses, by ICD-8 (1977–1993) and ICD-10 (1994–2008) periods, and by gestational age (gestational week <28, 28–31, 32–36, and ≥ 37). The study was approved by the Danish Data Protection Agency.

Results

For 90 of the 96 (94%) selected patients with an IRDS diagnosis in the DNPR, we were able to find the corresponding medical record, of which 52 (58%) were for males and 38 (42%) were for females. Gestational age was reported in the medical record for 88 IRDS patients, of whom 65 (74%)

were preterm infants, and 23 (26%) were born at term (37 weeks of gestation or later).

From the medical record we were able to confirm 73 of the 90 patients coded with an IRDS diagnosis. This gave us an overall PPV of 81% (95% CI 72%–88%) (Table 1). In the additional analysis, with IRDS defined as two or more clinical symptoms of IRDS and a confirmed X-ray (52 IRDS patients), the PPV was 58% (95% CI 48%–68%).

IRDS was registered in the DNPR as the primary diagnosis for 20 (22%) patients, of which 14 were confirmed by the medical record review, corresponding to a PPV of 70% (95% CI 48%–86%). Among 70 (78%) patients registered with IRDS as a secondary diagnosis, 59 were confirmed IRDS patients, corresponding to a PPV of 84% (95% CI 75%–91%). We found a PPV of 87% (95% CI 75%–94%) in the ICD-8 period (1977–1993) and a PPV of 75% (95% CI 61%–86%) in the ICD-10 period (1994–2008). The PPV among males was 75% (95% CI 62%–85%), while it was 89% (95% CI 77%–96%) among females. Stratified by gestational age, we found a PPV ranging from 61% (95% CI 41%–79%) in infants born at 37 weeks of gestation or later, to 92% (95% CI 77%–98%) in infants born between 28 and 31 weeks of gestation (Table 1).

The IRDS diagnosis was explicitly mentioned in 71 (79%) of the 90 medical records, and 82 (91%) of the patients with an IRDS diagnosis were treated with CPAP for more than 30 minutes.

Table 1 Positive predictive value of the infant respiratory distress syndrome diagnosis in the Danish National Patient Registry in 90 patients, 1977–2008

	Confirmations (N = 90)	PPV % (95% CI)
Diagnostic criteria		
Two or more clinical symptoms[a]	73/90	81 (72–88)
Two or more clinical symptoms AND X-ray confirmation	52/90	58 (48–68)
Type of diagnosis		
Primary discharge diagnosis	14/20	70 (48–86)
Secondary discharge diagnosis	59/70	84 (75–91)
Period according to ICD edition		
ICD-8 (1977–1993)	40/46	87 (75–94)
ICD-10 (1994–2008)	33/44	75 (61–86)
Gender		
Male	52/90	75 (62–85)
Female	38/90	89 (77–96)
Gestational age (completed weeks)		
37 weeks of gestation or more	14/23	61 (41–79)
32–36 weeks of gestation	31/35	89 (75–96)
28–31 weeks of gestation	23/25	92 (77–98)
Less than 28 weeks of gestation	4/5	80 (37–98)

Note: [a]Clinical symptoms: tachypnea, retractions, grunting, and cyanosis.
Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*, 8th and 10th revisions; PPV, positive predictive value.

Discussion

In this study, we found reasonable accuracy of the coding for IRDS in the DNPR as confirmed by exact description of the symptoms of IRDS in the medical record. To our knowledge, this is the first study to examine the validity of the DNPR with regards to IRDS. Other studies have estimated the PPV of other neonatal diagnoses in the DNPR, including the diagnoses of congenital cardiac malformations with overlapping time periods, 1994–2002 and 2000–2008.[12,13] They found overall PPVs of 89% (95% CI 86%–92%) and 90% (95% CI 89%–91%),[12,13] which is slightly higher than our PPV, probably because IRDS is a syndrome characterized by the co-occurrence of characteristic symptoms.

We found a slightly lower PPV in the ICD-10 period than in the ICD-8 period. However, these estimates were statistically imprecise. The potential decrease in PPV over time may reflect less optimal coding practices in the later period, but may also be explained by better documentation of symptoms in the medical records of the early period. We defined the IRDS diagnosis as the presence of a minimum of two of four clinical symptoms in the medical record. However, these symptoms may not always be described in the medical records of IRDS patients. Our PPV would potentially be an underestimate. The diagnosis of IRDS is complicated as it is a diagnosis of exclusion. If conditions such as infections or congenital heart disease were overlooked by the clinicians, we may have overestimated the PPV of the IRDS diagnosis. We did not include an X-ray finding of IRDS in our main criteria, because X-rays were not routinely performed in patients with mild IRDS. As expected, we found a higher PPV of the IRDS diagnosis among infants born preterm than among infants born at term. This may be due to the higher prevalence of IRDS among children born preterm.

Our study has some limitations that should be considered when interpreting the results. We only examined one region in Denmark; however, we find it reasonable to believe that the results are representative for the entire country owing to the uniform Danish health care system. Further, we were not able to report on sensitivity, ie, the proportion of all patients with IRDS actually registered in the DNPR, as we only included patients with a DNPR diagnosis of IRDS. However, the completeness of the DNPR has previously been estimated to be approximately 90%.[12,14] Further, we were not able to blind the IRDS diagnosis for the physician who reviewed the

medical records; however, this is unlikely to have had any major influence on our findings.

The PPV of the IRDS diagnosis quantified in our study may be applied in sensitivity analyses in future studies, to examine the potential effect of the misclassification on study results. Alternatively, studies should be restricted to infants born before 37 weeks of gestation. Both the primary and the secondary IRDS diagnoses may be used.

Conclusion

We found a reasonable PPV of 81% (95% CI 72%–88%) of the IRDS diagnosis in the DNPR, when compared with symptoms described in the infants' medical record. The DNPR is a useful data source for studies of IRDS, particularly if restricted to preterm infants. Nonetheless, the potential impact of misclassification of the IRDS diagnosis should be considered.

Disclosure

The authors report no conflict of interest in the study.

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Paper II

Respiratory Distress Syndrome in Preterm Infants and Risk of Epilepsy in a Danish Cohort

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Short Title: Infant Respiratory Distress Syndrome and Epilepsy

Key words: Epidemiology, cohort study, epilepsy, infant respiratory distress syndrome, neurodevelopmental outcome

Abbreviations: CI—confidence interval; CPR—Civil Personal Registration; CRS—Civil Registration System; DNPR—Danish National Patient Registry; HR—hazard ratio; ICD-8—International Classification of Diseases, Eighth Edition; ICD-10—International Classification of Diseases, Tenth Edition; ICH/IVH—intracerebral hemorrhage/intraventricular hemorrhage; IRDS—Infant respiratory distress syndrome

Word count: abstract 239 + article 1,942

Abstract

Aim: Infant respiratory distress syndrome (IRDS) may be complicated by intracerebral hemorrhage, a known trigger of epilepsy. However, few data exist on long term epilepsy risk following IRDS. We therefore examined the association between IRDS in preterm infants and childhood epilepsy.

Methods: We conducted a population-based cohort study using individual-level data linkage among nationwide registries. All infants born at 32-36 weeks of gestation in 1978-2009 were identified in the Medical Birth Registry. We identified children with IRDS and those with epilepsy using the Danish National Patient Registry.

We computed the cumulative incidence of epilepsy with follow-up from birth until epilepsy, emigration, death, age 15, or December 31, 2014. We used Cox's regression analysis to compute hazard ratios comparing children with and without IRDS, adjusting for sex, birth year, gestational age, multiplicity, major malformations, and maternal age.

Results: We identified 95,026 infants, of whom 6,426 (6.8%) had IRDS. The cumulative incidence of epilepsy was 3.4% by age 15 in children with IRDS and 2.1% in children without IRDS. The adjusted hazard ratio of epilepsy among children with IRDS compared to those without was 1.4 (95% confidence interval: 1.2–1.6). When we restricted the IRDS cohort to children with no simultaneous morbidities that had clinical symptoms overlapping with IRDS, the overall adjusted HR was 1.1 (95% CI: 0.9–1.4).

Interpretation: In children born preterm at 32-36 weeks' gestation IRDS was associated with increased risk of childhood epilepsy. Potential mechanisms are discussed.

Introduction

Infant respiratory distress syndrome (IRDS) is a common respiratory disorder among preterm infants,[1, 2] caused by lung immaturity and surfactant deficiency.[3] The IRDS prevalence at birth decreases with increasing gestational age. Thus, IRDS occurs in 28%–37% of infants born at 32 gestational weeks, decreasing to fewer than 17% of those born beyond 33 weeks of gestation.[4-10] Despite antenatal corticosteroids and other preventive measures directed at fetuses at risk of IRDS over the last three decades, the prevalence of IRDS at birth has not decreased, mainly due to the increased proportions of infants born preterm.[2] Complications of IRDS include intracerebral hemorrhage/intraventricular haemorrhage (ICH/IVH).[1, 11-14]

Epilepsy is among the most common serious brain disorders, accounting for 0.5% of the global burden of diseases.[15-17] The etiology of this disorder is largely unknown. Triggers of epilepsy include insults to the central nervous system, such as ICH/IVH and hypoxic ischemic damage.[18, 19]

A study on pregnancy-related and neonatal predictors of childhood epilepsy,[20] reported estimates on mild and severe IRDS. However, the analyses potentially included intermediate steps in the causal pathway from IRDS to epilepsy, which hampered interpretation. We therefore conducted a population-based cohort study to estimate the association between IRDS and childhood epilepsy while accounting for gestational age and other risk factors for neurodevelopmental impairment.

Methods

Study design and setting

This population-based cohort study was based on data from nationwide medical registries in Denmark. The Danish National Health Service provides free tax-supported health care to all Danish residents.[21] We used the Danish Medical Birth Registry, which has recorded all births in Denmark since 1973, to identify our study

cohort of all infants born alive in Denmark from January 1, 1978 to December 31, 2009 (approximately 1.9 million infants).[22, 23] Based on the unique Civil Personal Registration (CPR) number assigned to all Danish residents at birth or upon immigration, the Danish Civil Registration System has kept electronic records of date of birth, date of emigration, and date of death for the Danish population since 1968. The CPR number is used in all public Danish registries, allowing linkage of data among registries.[24]

Infant respiratory distress syndrome

We used the Danish National Patient Registry (DNPR) to identify all children diagnosed with IRDS (diagnostic codes provided in Appendix A) during the study period. The DNPR contains data on all non-psychiatric hospital admissions in Denmark since 1977 and on outpatient clinic and emergency room visits since 1995.[25, 26] Data include dates of admission and discharge, surgical procedures performed, and one primary diagnosis and up to 19 secondary diagnoses coded by the discharging physician according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993 and the *Tenth Revision* (ICD-10) thereafter. We restricted our cohort to moderately late and late preterm infants born between at 32–36 gestational weeks, as recorded in the Danish Birth Registry.

Epilepsy

Children with a first diagnosis of epilepsy (primary or secondary diagnosis) during a hospital admission, emergency room visit, or hospital outpatient visit were identified from the DNPR. Both epilepsy, including multiple subtypes, and status epilepticus were captured. (Appendix A) Prescription records were not used to identify childhood epilepsy, because physicians refrain from or postpone antiepileptic drug treatment in about 15% of new-onset childhood cases.[27]

Covariates

Additional covariates obtained from the Danish Medical Birth Registry included gestational age, birth year, 5-minute Apgar score, multiplicity, maternal age, and maternal smoking status during pregnancy (available since 2004).[23] Information on major malformations and other medical complications such as bronchopulmonary dysplasia, ICH/IVH, necrotizing enterocolitis, and patent ductus arteriosus were retrieved from the DNPR. Furthermore, we identified neonatal morbidities occurring within 4 days of birth with clinical symptoms potentially overlapping with those of IRDS. These included perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections. (Appendix A)

Data analysis

We defined IRDS as a primary or secondary diagnosis of this condition recorded in the DNRP. We followed children with IRDS from date of birth until a hospital-based inpatient or outpatient diagnosis of epilepsy, emigration, death, age 15 years, or the end of the study period (December 31, 2014), whichever came first. We computed the cumulative incidence of epilepsy before age 15, accounting for competing risk of death.[28]

We used Cox's proportional hazard regression analysis to compute crude and adjusted hazard ratios (HR) of time from birth to first epilepsy diagnosis, comparing children with and without IRDS. We adjusted for the following potential confounders: gestational age (32, 33, 34, 35, and 36 weeks of gestation), year of birth in four groups (1978-1985, 1986-1993, 1994-2002, and 2003-2009), sex, major malformations, multiplicity (singleton and twins), and maternal age (less than 35 years of age, and 35 years of age or older). Assumptions of proportional hazards were all verified graphically.

We stratified our analysis on gestational age, year of birth, sex, 5-minute Apgar score, multiplicity, and maternal age. Intracerebral/intraventricular haemorrhage is a known complication to IRDS and may be a potential mediating factor for epilepsy. To examine this further, we did a sub-group analysis dividing the IRDS cohort into children with IRDS and ICH/IVH within 30 days of birth and children with IRDS and no ICH/IVH. In this

analysis we started follow-up for epilepsy on day 30 counted from birth (delayed entry). For all results, 95% confidence intervals (95% CI) were calculated.

In a sensitivity analysis, we restricted our IRDS cohort to only include children who had no simultaneous diagnoses of perinatal breathing disorders other than IRDS, no congenital heart diseases, and no viral and bacterial infections occurring within 4 days of birth as children with these neonatal morbidities could be misclassified as having IRDS.

All analyses were performed using the STATA 13.1 package (StataCorp LP, College Station, TX, USA). The study was approved by the Danish Protection Agency (record number: 2014-41-3183) and did not require informed consent.

Results

The total study population included 95,026 children. Of these, 6,426 (6.8%) were diagnosed with IRDS (54% boys). The prevalence of IRDS was 22% among children born during 32 weeks of gestation and 2% among children born during gestational week 36. More children with IRDS than comparison cohort members were born during the earliest birth period (26% in 1978-1985). Children with IRDS had a higher frequency of neonatal morbidities that had clinical symptoms overlapping with IRDS including perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections occurring within 4 days of birth (29%). Intracerebral hemorrhage/intraventricular haemorrhages were also more common in the IRDS cohort (3%). (Table 1)

A total of 2,326 children were diagnosed with epilepsy. The cumulative incidence of epilepsy up to age 15 was 3.4% in children with IRDS and 2.1% in children without IRDS. (Figure A) The overall crude HR for epilepsy in children with IRDS compared to children without IRDS was 1.7 (95% CI: 1.4–1.9). After adjusting for

gestational age, birth year, sex, multiplicity, major malformations, and maternal age, the HR was 1.4 (95% CI: 1.2–1.6). (Table 2)

When we stratified the analysis by weeks of gestation, we found an increased risk of epilepsy in children with IRDS compared to children without IRDS in all gestational weeks. No substantial variation was found across categories of sex, year of birth, and 5-minute Apgar score. In a sub-group analysis, we found an adjusted HR of 5.7 (95% CI: 3.8–8.6) in children with IRDS that experienced an event of ICH/IVH within 30 days of birth and an adjusted HR of 1.2 (95% CI: 1.0–1.4) in children with IRDS that did not experience an event of ICH/IVH within 30 days of birth. When we restricted the IRDS cohort to children with no other simultaneous morbidities that had clinical symptoms overlapping with IRDS, the overall adjusted HR was 1.1 (95% CI: 0.9–1.4).

Discussion

To our knowledge, this is the first study specifically to examine the risk of epilepsy among children with IRDS. We found an approximately 40% increased risk of epilepsy by age 15 among children with IRDS born at 32–36 gestational weeks, compared to children without IRDS born at the same gestational weeks. Similar to a previous report,[4-10] we found that the prevalence of IRDS decreased from 22% among infants born during 32 weeks of gestation to 2% among infants born during 36 gestational weeks.

Several studies have examined long-term risks of adverse neurodevelopmental outcomes in preterm children in terms of school readiness and psychomotor development.[29, 30] An American follow-up study (2000) found an increased risk of neurodevelopmental impairments among preterm children with neonatal/medical complications, including IRDS.[31] However, they did not estimate the association with IRDS as such. A Canadian cohort study (2006) examined pregnancy-related and neonatal predictors of childhood epilepsy. It reported a relative risk of childhood epilepsy of 2.0 (95% CI: 1.1–3.7) for children with mild IRDS and 4.5 (95% CI: 3.0–6.7) for children with severe IRDS, compared with children without IRDS;[20] however, these estimates were

based on a univariate analysis without adjusting for gestational age and other potential confounding factors. The association was not present in the multivariate model. However, this model potentially included intermediate steps in the causal pathway from IRDS to epilepsy, which may have explained the lacking association.

The following limitations should be considered when interpreting the results. Use of population-based registries and the complete follow-up facilitated by the Danish Civil Registration System minimized the risk of selection bias. Still, the validity of our results depends on accurate diagnostic coding of epilepsy. The positive predictive value for this condition is reported to be 81% (95% CI: 75%–87%) in DNPR data.[34] As misclassification of epilepsy is unlikely to be associated with occurrence of IRDS at birth, any bias probably led to an underestimation of the association between IRDS and epilepsy.

Overall, it is difficult to make a clear and consistent diagnosis of IRDS, as the diagnosis relies on clinical signs, often supplemented by x-ray findings.[35, 36] Surfactant cannot be measured directly. However, we previously reported an overall positive predictive value of 81% (95% CI: 72%–88%) of IRDS diagnoses recorded in the DNPR from 1977 to 2009.[35] In this validation study the IRDS reference standard was defined exclusively by four clinical symptoms described in the medical records, as x-rays were not used frequently early in the study period. Pathology in other organ systems can sometimes manifest as respiratory distress and thereby lead to misdiagnosis. We conducted a sensitivity analysis restricted to children with IRDS who had no morbidities, occurring within 4 days of birth, that may have mimicked IRDS and thereby led to initial misclassification of these diagnosed as IRDS. This attenuated the association, although the change of the estimate was not statistically significant.

A study limitation was the lack of readily available data on IRDS treatment. Over the years, different treatment strategies have been used in an attempt to optimize outcomes for children with IRDS. In analyses stratified by calendar time, there was no substantial variation of the HRs. Another limitation was our inability to take into account the severity of IRDS. We did stratify the analyses by gestational age, as severe IRDS is more prevalent

in earlier gestational weeks. This analysis did not show any variation according to gestational age. Furthermore, although we adjusted for several risk factors for epilepsy, we cannot rule out additional unknown and residual confounding.

We found a particularly increased epilepsy risk in children with IRDS that experienced an ICH/IVH. Of note, we also found an increased risk in children that did not experience an ICH/IVH, implying that the increased risk of epilepsy is not only mediated through this factor.

Conclusion

Although causal mechanisms remain elusive, IRDS was associated with increased risk of childhood epilepsy in moderately late and late preterm infants.

Funding: This study was supported by grants from the Clinical Epidemiological Research Foundation ('Klinisk Epidemiologisk Forskningsfond'), Denmark and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck and the Novo Nordisk Foundations. The authors have no financial relationships relevant to this article to disclosure. The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies and agencies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. All authors declare no conflicts of interest.

Contributor's Statement: Sandra Kruchov Thygesen (SKT) and Henrik Toft Sørensen (HTS) conceptualized and designed the study, acquired the data, carried out the analyses, drafted the initial manuscript (SKT), reviewed and revised the manuscript, and approved the final manuscript as submitted. Morten Olsen, John Rosendahl Østergaard, and Victor W. Henderson designed the study, supervised the data interpretation, critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted. Lars Pedersen (LP) helped to acquire the data and extract the raw data, critically supervised/reviewed the data analyses and reviewed the data interpretation, revised the manuscript, and approved the final manuscript as submitted. SKT and LP had complete access to the study data that support the publication.

Competing risk declaration: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not needed.

Data sharing: No additional data available.

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Figure A. Cumulative incidence of epilepsy in 95,026 children with and without IRDS in Denmark during 1978-2009.

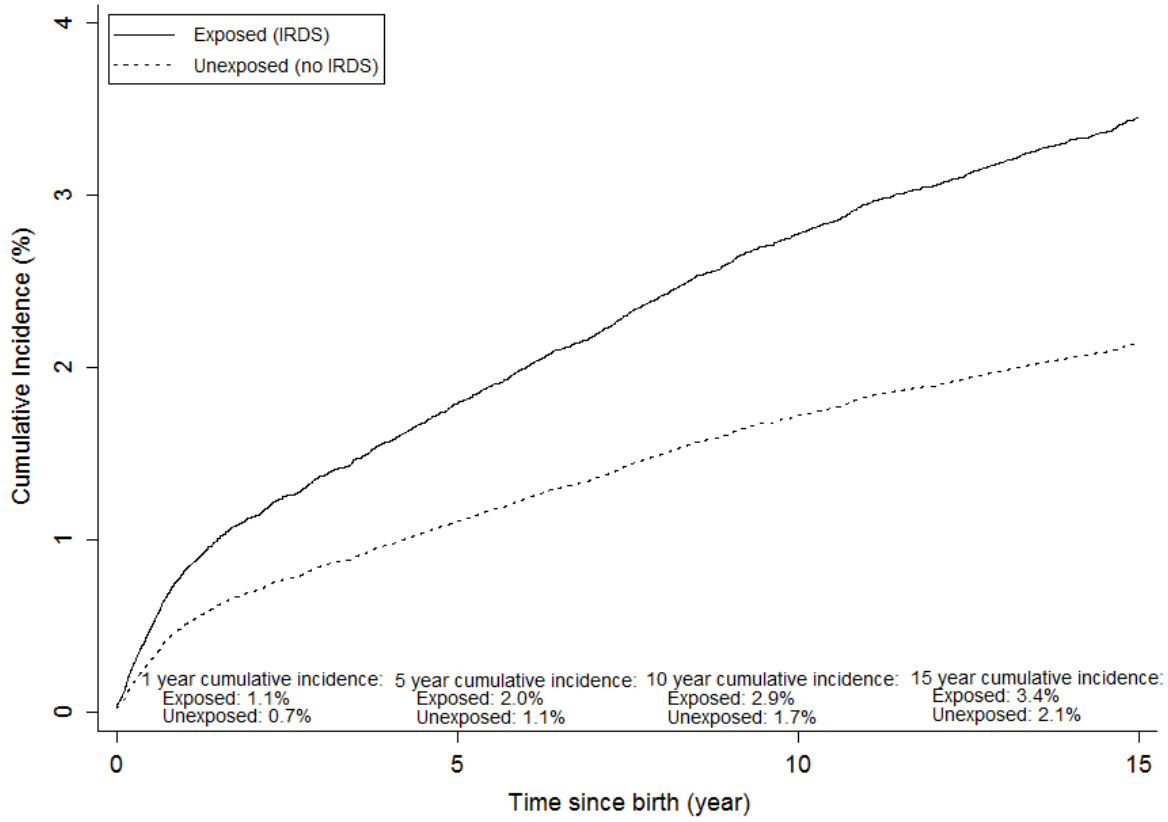

Table 1. Characteristics of 95,026 moderately late and late preterm infants with and without IRDS, Denmark, 1978-2009.

	IRDS, n (%)	No IRDS, n (%)
All	**6,426 (100)**	**88,600 (100)**
Gestational age (week of gestation)		
32	1,465 (22.8)	5,054 (5,7)
33	1,431 (22.3)	7,587 (8.6)
34	1,431 (22.3)	13,179 (14.8)
35	1,146 (17.8)	21,354 (24.1)
36	957 (14.8)	41,426 (46.8)
Birth year		
1978-1985	1,683 (26.2)	14,812 (16.7)
1986-1993	1,538 (23.9)	20,597 (23.3)
1994-2001	1,374 (21.4)	25,934 (29.3)
2002-2009	1,831 (28.5)	27,257 (30.7)
Sex		
Female	2,929 (45.6)	42,662 (48.2)
Male	3,497 (54.4)	45,938 (51.9)
Apgar score at 5 minutes		
Very low (0-3)	90 (1.4)	809 (0.9)
Low (4-6)	283 (4.4)	1,441 (1.6)
Intermediate (7-8)	992 (15.4)	5,199 (5.9)
Normal (9-10)	4,822 (75.0)	79,512 (89.7)
Missing	239 (3.7)	1,639 (1.9)
Multiplicity		
Singleton	5,148 (80.1)	69,959 (79.0)
Twin	1,278 (19.9)	18,641 (21.0)
Major malformation (within the first year)	591 (9.2)	6,013 (6.8)
Mother's age at delivery		
<35 years	5,516 (85.9)	75,661 (85.4)
35 years or older	910 (14.2)	12,938 (14.6)

Mother's smoking status (available since 1991)		
Non Smoker/former smoker	2,723 (73.5)	42,267 (68.2)
Smoker	722 (19.5)	15,946 (25.8)
Missing	261 (7.0)	3,723 (6.0)
Bronchopulmonary dysplasia (BPD) (available since 1994)	28 (0.9)	20 (0.0)
Intracranial/intraventricular hemorrhage (ICH/IVH) (<30 days of birth)	213 (3.3)	533 (0.6)
Necrotizing enterocolitis (NEC) (<30 days of birth)	37 (0.6)	99 (0.1)
Patent ductus arteriosus (PDA) (<30 days of birth)	219 (3.4)	609 (0.7)
Other diseases*	1,829 (28.5)	13,819 (15.6)

*Other diseases whose symptoms may overlap with those of IRDS, occurring within 4 days of birth (perinatal breathing disorders, congenital heart diseases, and viral and bacterial infections).

Table 2. Hazard ratios for epilepsy among 95,026 children with and without infant respiratory distress syndrome (IRDS), 1978-2009.

	Number of children with epilepsy		15-year cumulative incidence, % (95% confidence intervals (CI))*			
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude hazard ratio (95% CI)	Adjusted hazard ratio† (95% CI)
Overall	**237**	**2,089**	**3.4 (2.9-3.9)**	**2.1 (2.0-2.3)**	**1.7 (1.4-1.9)**	**1.4 (1.2-1.6)**
Gestational age						
32 weeks of gestation	55	155	3.7 (2.8-4.8)	2.7 (2.3-3.2)	1.4 (1.0-2.0)	1.3 (1.0-1.9)
33 weeks of gestation	55	221	3.5 (2.5-4.6)	2.7 (2.3-3.1)	1.3 (0.9-1.8)	1.3 (0.9-1.8)
34 weeks of gestation	55	333	3.9 (2.9-5.0)	2.4 (2.1-2.7)	1.7 (1.3-2.3)	1.6 (1.2-2.2)
35 weeks of gestation	38	478	2.9 (2.0-4.0)	2.0 (1.8-2.2)	1.5 (1.0-2.2)	1.3 (0.9-1.9)
36 weeks of gestation	34	902	2.6 (1.7-3.8)	2.0 (1.9-2.2)	1.4 (0.9-2.1)	1.2 (0.8-1.9)
Year of birth						
1978-1985	84	552	2.6 (1.7-3.8)	2.6 (2.4-2.9)	1.5 (1.0-1.9)	1.3 (0.9-1.7)
1986-1993	82	643	4.6 (3.6-5.7)	2.4 (2.2-2.7)	2.0 (1.5-2.5)	1.7 (1.3-2.2)
1994-2001	36	532	2.6 (1.9-3.6)	1.9 (1.7-2.1)	1.4 (1.0-2.0)	1.2 (0.9-1.8)
2002-2009	35	362	-	-	1.5 (1.1-2.1)	1.2 (0.8-1.7)
Sex						
Female	101	1,031	3.2 (2.5-3.9)	2.2 (2.0-2.3)	1.5 (1.2-1.9)	1.2 (1.0-1.5)
Male	131	1,058	3.6 (3.0-4.3)	2.1 (2.0-2.3)	1.8 (1.5-2.2)	1.5 (1.2-1.8)
Apgar score at 5 minutes						
Low (0-6)	18	95	4.5 (2.7-7.0)	3.7 (3.0-4.6)	1.1 (0.6-1.8)	1.1 (0.6-1.9)
Intermediate (7-8)	38	172	3.6 (2.5-4.9)	3.0 (2.5-3.5)	1.2 (0.8-1.8)	1.0 (0.7-1.6)
Normal (9-10)	170	1,774	3.2 (2.8-3.8)	2.0 (1.9-2.1)	1.7 (1.4-2.0)	1.4 (1.2-1.7)
Missing	11	48	3.4 (1.5-6.5)	2.8 (2.0-3.7)	1.1 (0.5-2.5)	0.9 (0.4-2.1)
Multiplicity						
Singleton	205	1,759	3.7 (3.1-4.2)	2.2 (2.1-2.4)	1.7 (1.5-2.0)	1.4 (1.2-1.7)
Twin	32	330	2.3 (1.5-3.3)	1.8 (1.6-2.0)	1.3 (0.9-2.0)	1.0 (0.7-1.6)

Maternal age						
<35 years of age	2125	1,822	3.5 (3.0-4.0)	2.2 (2.1-2.3)	1.7 (1.4-2.0)	1.4 (1.2-1.6)
35 years of age or older	25	267	2.6 (1.7-3.8)	1.9 (1.7-2.2)	1.5 (0.9-2.3)	1.4 (0.9-2.1)

*Death is considered/included as a competing risk

†Adjusted for sex, twin birth, maternal age, infant's birth year, gestational age, and major malformations.

Appendix A. *ICD-8 and ICD-10* diagnosis codes used in the study.

	ICD-8 diagnosis codes (1978-1993)	ICD-10 diagnosis codes (1994-present)
Idiopathic respiratory distress syndrome/hyaline membrane disease	776.19	P22.0
Epilepsy and status epilepticus	345.00-345.99	G40.0-41.9
Major malformations <1 year	740.99-744.85, 744.87-745.09, 745.20-750.09, 750.20-750.99, 751.10-752.09, 752.20-752.39, 752.50-753.25, 753.28-753.99, 754.08-755.10, 755.12-753.12, 756.18, 756.39-756.80, 756.82-757.09, 757.20-759.99	Q00-99
Bronchopulmonary dysplasia	NA	DP271
Intraventricular hemorrhage or	764.00-764.09, 772.00, 772.01, 772.08	DB100-DP109
cerebral leukomalaci <30 days	772.09, 778.09, 778.28, 778.29	DP52 + DP912
Necrotizing enterocolitis <30 days	569.13, 561.01	DP77
Patent ductus arteriosus <30 days	747.09	DQ250
Perinatal breathing disorders and cardiovascular diseases		
-respiratory distress	776.28, 776.29	DP221, DP228, DP229
-pneumonia	471.00, 471.01, 471.08, 471.09, 480.99, 481.00, 481.01, 481.08, 481.09, 482.09, 482.19, 482.29, 482.39, 482.90, 482.99, 483.00, 483.08, 483.09, 484.99, 485.99, 486.99, 519.23	DP23, DJ12-DJ18
-aspiration	776.09	DP24
-emphysema	492.00, 492.01, 492.08, 492.09, 776.20, 776.21	DP25
-hemorrhage in the lungs		DP26
-other perinatal breathing disorders	519.09, 748.49, 748.59, 748.69, 776.92	DP28
-cardiovascular diseases	401.99	DP29
Congenital viral infection	761.29, 761.39, 741.49	DP35
Bacterial infection in newborns	389.9	DP36
Infection in the central nervous system (CNS)	027.01, 036.09, 036.12, 036.10, 036.18, 036.19, 036.89, 036.99, 045.09, 045.19, 045.99, 052.01, 053.02, 054.03, 055.01, 056.01, 072.02, 075.01, 094.90, 320.09, 320.19, 320.80, 320.89, 320.90, 320.91, 320.99, 780.89	DG00-DG09

Paper III

Respiratory distress syndrome in moderately late and late preterm Infants and risk of cerebral palsy

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Keywords: Epidemiology, cohort study, pediatrics, neurology, pulmonary medicine

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Word count: abstract 317 + article 2,510

Number of figures: 1

Number of tables*:* 3

Number of supplementary file: 1 (appendix)

Number of references: 35

Strengths and limitations of this study

- A strength of this study includes the nationwide cohort study design with virtually complete follow-up, minimizing the risk of selection bias.
- To our knowledge, this is the first study to specifically determine the association between infant respiratory distress syndrome and cerebral palsy utilizing multivariate analysis, and as such, the validity of the estimates presented is unknown.
- Even though this study is one of the largest examining a potential association between infant respiratory distress syndrome and cerebral palsy, it still does not clarify the specific causes leading to increased risk of cerebral palsy.

Abstract

Objectives: Infant respiratory distress syndrome (IRDS) is a known risk factor for intracerebral/intraventricular hemorrhage (ICH/IVH) and periventricular leukomalacia. These lesions are known to increase the risk of cerebral palsy (CP). Thus, we wanted to examine the long-term risk of CP following IRDS in moderately late and late preterm infants.

Design: Population-based cohort study.

Setting: All hospitals in Denmark.

Participants: We used nationwide medical registries to identify a cohort of all moderately and late preterm infants (defined as birth during 32-36 full gestational weeks) born in Denmark in 1997-2007 with and without hospital diagnosed IRDS.

Main outcomes measures: We followed study subjects from birth until first diagnosis of CP, emigration, death, or end of follow-up in 2014. We computed the cumulative incidence of CP before age 8 years and used Cox's regression analysis to compute hazard ratios of IRDS, comparing children with IRDS to those without. Hazard ratios were adjusted for multiple covariates.

Results: We identified 39,420 moderately late and late preterm infants, of whom 2,255 (5.7%) had IRDS. The cumulative incidence of CP was 1.9% in infants with IRDS and 0.5% in the comparison cohort. The adjusted hazard ratio of CP was 2.0 [95% confidence interval (CI): 1.4-2.9]. The adjusted HR of CP was 12 (95% CI: 4.5-34) in children with IRDS complicated by ICH/IVH. The hazard ratio of CP in infants with IRDS that was not accompanied by ICH/IVH was 1.8 (95% CI: 1.3–2.7). After restriction to children without diagnoses of perinatal breathing disorders other than IRDS, congenital heart disease and viral or bacterial infections occurring within 4 days of birth, the overall adjusted hazard ratio was 2.1 (95% CI: 1.4-3.1).

Conclusion: The risk of CP was increased in moderately late and late preterm infants with IRDS compared to infants without IRDS born during the same gestational weeks.

Introduction

Increasing preterm birth rates over the last few decades have kept the overall incidence of infant respiratory distress syndrome (IRDS) high.[1-3] Infant respiratory distress syndrome decreases with increasing gestational age and has a prevalence of about 30% after 32 weeks of gestation.[4-6] The condition is caused by lack of surfactant in the lungs, which leads to atelectasis, decreased gas exchange, and hypoxia. Potential complications of IRDS include intracerebral/intraventricular hemorrhage (ICH/IVH) and periventricular leukomalacia (PVL).[7, 8] Studies have reported increased risk of neurodevelopmental impairments, such as neurocognitive and school performance outcomes as well as attention deficit hyperactivity disorder (ADHD) in preterm children with subsequent ischemic-hypoxic conditions, including IRDS.[9, 10]

Cerebral palsy (CP) is the most common cause of severe disabilities in early childhood.[11] The core symptom of CP is disorder of movement and/or posture, but is often accompanied by other neurodevelopmental disorders or sensory problems, such as disturbances of sensation, cognition, communication, perception, behavior and/or seizure disorders.[12] The disorder has a multifactorial and poorly understood etiology. The most important risk factor for CP is preterm birth, observed in about 28%–35% of all children with CP.[13, 14] Major lesions that contribute to CP include ICH/IVH and PVL.[7, 15, 16]

Few data exist on the long term prognosis following IRDS. A few case-control studies have reported indications of an association between IRDS and CP.[17-19] However, these studies are limited by small sample sizes and lack of absolute risk estimates. In the present study, we therefore examined the association between IRDS and CP in a nationwide follow-up study of children born moderately and late preterm.

Methods

Setting and data linkage

We conducted this cohort study using population-based medical databases covering the entire country of Denmark. Linkage between databases was possible through the Civil Registration System (CRS), which has

kept electronic records of birth date, date of emigration, and date of death since 1968.[20] At birth or upon immigration, all Danish residents are assigned a unique Civil Personal Registration (CPR) number that is used in all public Danish registries. The Danish National Health Service provides free tax-supported health care to the country's 5.6 million citizens.

Study Cohort

Our cohort was identified using the Danish Medical Birth Registry, which contains information on all births in Denmark since 1973. We identified all infants born alive in Denmark from January 1, 1997 to December 31, 2007 (approximately 710,000 infants)[21, 22] and then restricted our cohort to moderately late and late preterm infants (defined as birth between 32 and 36 full weeks). Adequate representation of children both with and without IRDS is available during these gestational weeks.

Infant respiratory distress syndrome

We identified all children diagnosed with IRDS (exposed children) in the Danish National Patient Registry (DNPR). The DNPR contains data on all non-psychiatric hospital admissions in the country since 1977 and on outpatient clinic and emergency room visits since 1995.[23, 24] Data include dates of admission and discharge, surgical procedure(s) performed, and one primary diagnosis and up to 19 secondary diagnoses coded by the discharging physician according to the *International Classification of Diseases, Eighth Edition* (ICD-8) until the end of 1993 and the *Tenth Edition* (ICD-10) thereafter.

Cerebral palsy

Children diagnosed with CP were identified from the Danish National Cerebral Palsy Registry (DNCPR). Prerequisites for inclusion in this Registry are a prenatal or perinatal aetiology (events occurring within 28 days of birth.

All children included in the Registry had their diagnosis externally validated by a child neurologist at the age of 4-5 years, based on review of clinical findings recorded in the medical files. While the Registry includes data on prenatally and perinatally acquired cases of CP since 1950, it became nationwide only in 1995.

NCRP is assumed to cover > 85 % of the children with CP in Denmark.[25] Registry data include subtype and degree of CP,[11] developmental quotient (DQ: <50, 50-85, >85), motor handicap measured by the Gross Motor Function Classification System (GMFCS, 0-4) (though only complete until birth year 2003), accompanying neurological diseases, and orthopedic surgeries. Results of ultrasound and CT scans of the brain and evaluation of timing of brain damage are available.[25] The GMFCS is a tool used to measure gross motor skills in children with CP. The classification system ranges from level 1 (walking with no support) up to level 5 (immobile/impaired in all areas of motor function).[26] We obtained the following study outcomes from the Registry: overall diagnosis of CP, subtypes of unilateral and bilateral spastic CP, motor handicap degree (GMFCS levels 1-2, 3, and 4-5), and DQ (<50, 50-85, and >85).

Covariates

We obtained information from the Danish Medical Birth Registry for the entire cohort on gestational age at birth, 5-minute Apgar score, multiplicity, maternal age, and self-reported maternal smoking during pregnancy.[22] We used data from the DNPR to ascertain the distribution of complications in children with and without IRDS, including bronchopulmonary dysplasia, ICH/IVH, necrotizing enterocolitis, and patent ductus arteriosus (Appendix A). Congenital malformations are associated with increased risk of CP and also may be associated with IRDS. We therefore ascertained from the DNPR all diagnoses of congenital malformations detected during the first year of life.

A subgroup of children may have had other conditions within 4 days of birth whose symptoms potentially overlapped with IRDS, leading to misdiagnosis of IRDS. These diseases include perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections. We identified these conditions from the DNPR. (Appendix A)

Statistical analysis

We followed all children in the study cohort from date of birth until the date of the first diagnosis of CP, emigration, death, or December 31, 2014, whichever came first. We computed the cumulative incidence of CP before 8 years of age with death as a competing risk.[27] In a sub-analysis, sub-types of CP were analyzed

as separate outcomes (unilateral and bilateral spastic CP), as well as motor handicap degree (GMFCS 1-2, 3, and 4-5) (until birth year 2003), and developmental quotient (<50,50-85, and >85).

We used Cox proportional hazard regression to estimate unadjusted and adjusted hazard ratios (HRs) for CP among children with IRDS compared to children without IRDS. The analyses were adjusted for gestational age (32, 33, 34, 35, and 36 weeks of gestation), birth year (1997-1999, 2000-2002, 2003-2005, and 2006-2007), gender, multiplicity (singleton/twins), major malformations, and maternal age (<35 and ≥35 years of age). The assumptions of proportional hazards were all verified graphically. We considered a low 5-minute Apgar score as a causal intermediate step between IRDS and CP, and thus did not include this covariate as a confounder in the adjusted analyses. However, we did include 5-minute Apgar score in the regression model in a sub-analysis.

We stratified the analyses on gestational age (birth at 32, 33, 34, and 35-36 full weeks), birth year (1997-2002, 2003-2007), gender, multiplicity, 5-minute Apgar score (0-6, 7-8, 9-10, missing), and maternal age (<35 and ≥35 years of age) and calculated 95% confidence intervals (CIs). Intracerebral/intraventricular hemorrhage is a known complication of IRDS and an important risk factor for CP. We therefore repeated the analyses for children with IRDS *and* IVH/ICH within 30 days of birth and children with IRDS *and no* IVH/ICH.

Perinatal diseases may be misinterpreted as IRDS because of overlapping clinical symptoms. Such perinatal disorders include perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections. Thus, in a sensitivity analysis, we restricted the IRDS cohort to new-borns *with no* other perinatal disorders occurring within 4 days of birth.

All analyses were performed using the STATA 13.1 package (StataCorp LP, College Station, TX, USA). The study was approved by the Danish Protection Agency (record number: 2014-41-3183) and did not require informed consent.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

From the Danish Medical Birth Registry, we identified 39,420 children born moderately and late preterm between 1997 and 2007. Of these, 2,255 (5.7%) were diagnosed with IRDS. Intracerebral/intraventricular haemorrhage (2%) was more common in the IRDS cohort compared to comparison cohort (0.3%). Having another perinatal disorder occurring within four days of birth, including perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infection were more prevalent in the children with IRDS (30%) compared to children without IRDS (18%). (Table 1)

The cumulative incidence of CP before 8 years of age was 1.9 (95% CI: 1.4-2.5) in children with IRDS and 0.5 (95% CI: 0.4-0.6) in children without IRDS. The overall crude HR for CP in children with IRDS compared to children without IRDS was 4.0 (95% CI: 2.9-5.6). After adjusting for gestational age, birth year, gender, multiplicity, major malformations, and maternal age, the HR was 2.0 (95% CI: 1.4-2.9). (Table 2)

When we stratified the analysis by gestational age, we found an increased risk of CP across all strata in children with IRDS compared to children without IRDS. As well, we found no substantial variation in the increased risk of CP in children with IRDS across categories of gender, year of birth, multiplicity, 5-minute Apgar score, and maternal age, although these estimates were less precise. The adjusted HR of CP was 12 (95% CI: 4.5-34) in children with IRDS complicated by ICH/IVH and 1.8 (95% CI: 1.3-2.7) in children with IRDS without ICH/IVH as a complication.

Including 5-minute Apgar score as a potential confounder in the regression model did not change our estimates substantially. When restricting to children diagnosed with IRDS *and no* other relevant diagnoses occurring within 4 days of birth (i.e. perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections), the overall adjusted HR was 2.1 (95% CI: 1.4-3.1).

The most common subtype of CP was unilateral and bilateral spastic CP. (Data not shown) For children diagnosed with IRDS, we found a HR of 1.5 (95% CI: 0.8-2.9) for unilateral spastic CP and 2.2 (95% CI: 1.4-3.4) for bilateral spastic CP. The HR was 1.9 (95% CI: 1.1-3.4) for CP with a normal DQ (above 85), 1.7 (95% CI: 0.9-3.1) for a DQ between 50 and 85, and 2.9 (95% CI: 1.4-6.1) for a DQ below 50. (Table 3)

In children with IRDS born during 1997-2003, the HR was 2.2 (95% CI: 1.3-3.9) for a mild degree of motor handicap (GMFCS 1-2) and 2.5 (95% CI: 1.3-4.7) for a severe degree of motor handicap (GMFCS 4-5). (Table 3)

Discussion

We found an increased risk of CP associated with IRDS in children born moderately late and late preterm. To our knowledge, this is the first study to examine the risk of CP following IRDS.

Other studies have shown increased risk of neurodevelopmental impairments, defined by psychomotor development and school readiness, in preterm children with IRDS.[9, 10, 28, 29] Studies have looked at possible causes or predictors of cerebral palsy in different settings and found modest associations. In an Australian case-control study, Blair et al. reported an odds ratio of CP of 2.3 (95% CI: 1.3-4.3); and in another case-control study from Western Australia, Dite et al. found an odds ratio of 9.4 (95% CI: 1.8-48) in children diagnosed with IRDS. However; even though they reported increased risk estimates of CP in children with IRDS, the estimates were based on univariate analyses in relatively small study populations. Thus, potential confounders were not taken into consideration and no absolute measures were available.[17-19] In a cohort study, Hirvonen et al. found a negative association between IRDS and CP in late preterm infants. However,

apparently the multivariate model included intermediate steps between IRDS and CP in terms of mechanical ventilator treatment and intracranial hemorrhage. Furthermore, the analysis was not based on time-to-event methods, but based on logistic regression.[30] This may have explained the differences between their results and ours.

Through data linkage performed by the Danish Civil Registration System, this population-based study had virtually complete follow-up for death, emigration, and hospital admissions, minimizing the risk of selection bias. We previously reported a positive predictive value of 89% (95% CI: 75%–96%) for children with IRDS born between 32 and 36 weeks of gestation in the DNPR.[31] In this study, IRDS was based exclusively on clinical symptoms, as x-rays were only used infrequently early in the study period. Thus, in a sensitivity analysis, we redefined our exposure of children with IRDS to only those having IRDS with no other perinatal disorders occurring within 4 days of birth. Our estimates were virtually unchanged in this analysis. Because the Cerebral Palsy Registry is a clinical database based on specific inclusion criteria including thorough medical record review of all children with CP in Denmark, we expect the positive predictive value of the CP diagnosis to be close to 100%. A previous validation study of the NCPR through the DNPR reported its completeness to be 85%.[25] As any misclassification is not likely associated with IRDS, such non-differential bias would eventually lead to an underestimation of the association between IRDS and CP.

One of the strongest risk factors for development of CP is known to be low gestational age,[32, 33] which is also the strongest risk factor for IRDS. For this reason, we stratified our analyses on gestational age to ensure that any increased risk of CP in children with IRDS was not masked by this association. After taking this precaution, we still found an increased risk of CP among children born during gestational weeks 32 to 34. Only a few children diagnosed with CP were born during 35 and 36 weeks of gestation, which made calculations of the HR imprecise.

To study a rather seldom disease like CP large study populations are required, especially when the study sample is restricted to children born at 32-36 gestational weeks. For this reason, we only were able to present

overall estimates in our analyses of subtypes of CP, degree of motor handicap, and DQ. These estimates were all increased throughout all levels of CP severity.

Even though this study is among the largest studies examining a potential association between IRDS and CP by using data from nationwide databases on preterm infants, it still does not clarify the specific causes of the increased risk of CP. We found a twelve-fold increase of CP in children with IRDS and ICH/IVH compared to our control population. This suggests an important role of ICH/IVH in the pathogenesis.[15, 34, 35]

Infant respiratory distress syndrome potentially could be a surrogate for another unknown medical condition. However, recognition of an early predictor of increased future CP risk could still be helpful when planning follow-up and/or intervention strategies in children born preterm.

Conclusion

We found that the risk of CP was twice as high in moderately late and late preterm infants with IRDS compared to infants without IRDS born during the same gestational weeks. Although a twelve-fold increased risk of CP was found in children with IRDS and ICH/IVH, the increased risk was also present in infants without ICH/IVH.

Contributor's Statement: SKT conceptualized and designed the study, acquired the data, carried out the analyses, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. MO, JRO, and HTS conceptualized and designed the study, supervised the data interpretation, critically reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as submitted. MO helped to acquire the data and extract the raw data, critically supervised/reviewed the data analyses and reviewed the data interpretation, revised the manuscript, and approved the final manuscript as submitted.

Funding: This study was supported by grants from the Clinical Epidemiological Research Foundation ('Klinisk Epidemiologisk Forskningsfond'), Denmark (HTS), and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck and the Novo Nordisk Foundations (HTS). The funding agencies had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; or the decision to submit the article for publication.

Competing risk declaration: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work

Ethical approval: Not needed.

Author Statement: All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: SKT affirms that the study hypothesis arose before inspection of the data and that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

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Figure 1. Cumulative incidence of cerebral palsy in 39,420 children with and without IRDS in Denmark, born 1997–2007.

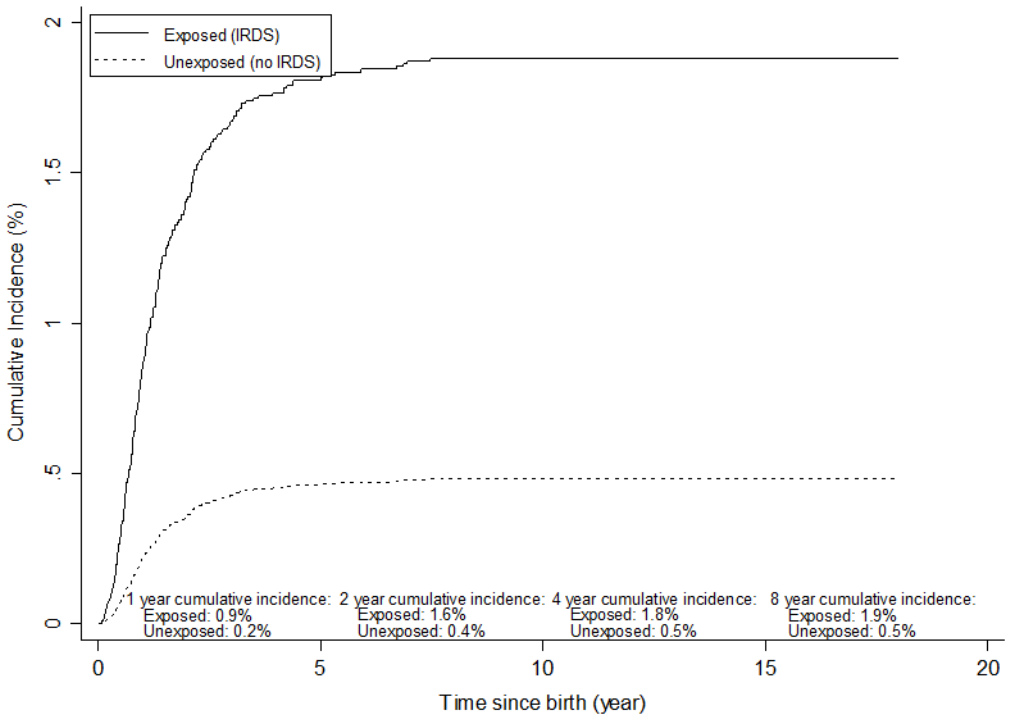

Table 1. Characteristics of 39,420 infants born during 32–36 weeks of gestation with and without infant respiratory distress syndrome (IRDS), between January 1, 1997 and December 31, 2007 in Denmark.

	IRDS, n (%)	No IRDS, n (%)
All	**2,255 (100.0)**	**37,165 (100.0)**
Gestational age (week of gestation)		
32	602 (26.7)	2,058 (5.5)
33	545 (24.2)	3,313 (8.9)
34	526 (23.3)	5,652 (15.2)
35	346 (15.3)	9,156 (24.6)
36	236 (10.5)	16,986 (45.7)
Birth year		
1997-1999	534 (23.7)	9,379 (25.2)
2000-2002	602 (26.7)	10,443 (28.1)
2003-2005	696 (30.9)	10,433 (28.1)
2006-2007	423 (18.8)	6,910 (18.6)
Gender		
Female	897 (39.8)	17,184 (46.2)
Male	1,358 (60.2)	19.981 (53.8)
Apgar score at 5 minutes		
Low (0-6)	111 (4.9)	646 (1.7)
Intermediate (7-8)	271 (12.0)	1,824 (4.9)
Normal (9-10)	1,816 (80.5)	33,974 (91.4)
Missing	57 (2.5)	721 (1.9)
Multiplicity		
Singleton	1,644 (72.9)	27,438 (73.8)
Twin	611 (27.1)	9,727 (26.2)
Epilepsy	53 (2.4)	590 (1.6)
Major malformation (<1 year)	217 (9.6)	2,525 (6.8)
Morther's age at delivery		
<18 years	5 (0.2)	130 (0.4)
18-34 years	1,807 (80.1)	30,131 (81.1)
≥35 years	443 (19.7)	6,903 (18.6)
Missing	0 (0.0)	1 (0.0)

Maternal smoking status		
Non Smoker/former smoker	1,689 (74.9)	26,487 (71.3)
Smoker	403 (17.9)	8,433 (22.7)
Missing	163 (7.2)	2,245 (6.0)
Bronchopulmonal dysplasia (BPD)	22 (1.0)	16 (0.1)
Intracerebral/intraventricular hemorrhage (ICH/IVH) (<30 days)	46 (2.0)	121 (0.3)
Necrotizing enterocolitis (NEC) (<30 days)	20 (0.9)	59 (0.2)
Patent ductus arteriosus (PDA) (<30 days)	77 (3.4)	239 (0.6)
Other diseases*	682 (30.2)	6,641 (17.9)

*Other diseases whose symptoms may overlap with those of IRDS, occurring within 4 days of birth (perinatal breathing disorders other than IRDS, congenital heart diseases, and viral an7d bacterial infections).

Table 2. Hazard ratios of cerebral palsy (CP) by age 8 among children with and without infant respiratory distress syndrome (IRDS) born during 32–36 weeks of gestation between 1997 and 2007 in Denmark. (N=39,410)

	Number of children with CP		8-year cumulative incidence, % (95% confidence interval (CI))			
	Children with IRDS	Children without IRDS	Children with IRDS	Children without IRDS	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
Overall	**42**	**178**	**1.9 (1.4-2.5)**	**0.5 (0.4-0.6)**	**4.0 (2.9-5.6)**	**2.0 (1.4-2.9)**
Gestational age						
32 weeks of gestation	21	31	3.5 (2.2-5.2)	1.5 (1.1-2.1)	2.3 (1.3-4.0)	2.4 (1.4-4.2)
33 weeks of gestation	11	44	2.0 (1.1-3.5)	1.3 (1.0-1.7)	1.6 (0.8-3.1)	1.6 (0.8-3.1)
34 weeks of gestation	7	30	1.4 (0.6-2.7)	0.5 (0.4-0.8)	2.5 (1.1-5.8)	2.5 (1.1-5.8)
[35-36] weeks of gestation	3	73	0.5 (0.1-1.4)	0.3 (0.2-0.4)	1.9 (0.6-6.1)	1.7 (0.5-5.5)
Calendar year						
[1997-2002]	28	105	2.5 (1.7-3.5)	0.5 (0.4-0.6)	4.8 (3.2-7.3)	2.4 (1.5-3.7)
[2003-2007]	14	73	1.3 (0.7-2.1)	0.4 (0.3-0.5)	3.1 (1.7-5.4)	1.4 (0.8-2.6)
Gender						
Female	14	76	1.6 (0.9-2.6)	0.4 (0.4-0.6)	3.6 (2.1-6.4)	1.7 (0.9-3.1)
Male	28	102	2.1 (1.4-3.0)	0.5 (0.4-0.6)	4.2 (2.7-6.3)	2.2 (1.4-3.4)
Apgar score at 5 minutes						
Low (0-6)	4	10	3.7 (1.2-8.5)	1.6 (0.8-2.8)	2.1 (0.7-6.8)	2.2 (0.7-7.7)
Intermediate (7-8)	7	31	2.6 (1.2-5.0)	1.7 (1.2-2.4)	1.6 (0.7-3.5)	1.2 (0.5-2.8)
Normal (9-10)	28	131	1.6 (1.1-2.2)	0.4 (0.3-0.5)	4.1 (2.7-6.2)	1.9 (1.2-2.9)
Missing	3	6	5.3 (1.4-13)	0.8 (0.4-1.8)	6.6 (1.6-26)	6.0 (1.0-35)
Multiplicity						
Singleton	29	129	1.8 (1.2-2.5)	0.5 (0.4-0.6)	3.9 (2.6-5.8)	2.0 (1.3-3.1)
Twin	13	49	2.1 (1.2-3.5)	0.5 (0.4-0.7)	4.3 (2.3-7.9)	1.9 (1.0-3.6)
Maternal age						
Younger than 35 years of age	31	138	1.7 (1.2-2.4)	0.5 (0.4-0.5)	3.9 (2.6-5.7)	1.9 (1.3-2.9)
35 years of age or older	11	40	2.5 (1.3-4.3)	0.6 (0.4-0.8)	4.4 (2.3-8.6)	2.3 (1.1-4.8)

*Adjusted for sex, gestational age, infant's birth year, multiplicity, major malformations, and maternal age.

Table 3. Characteristics of 148 infants with cerebral palsy (CP) born during 32-36 weeks of gestation with and without infant respiratory distress syndrome (IRDS), 1997-2007, Denmark.

	Number of children with CP			
	Children with IRDS	Children without IRDS	**Crude HR (95% CI*)**	**Adjusted HR (95% CI)**
Subtype				
Unilateral spastic CP	12	74	2.7 (1.5–5.0)	1.5 (0.8–2.9)
Bilateral spastic CP	26	87	5.1 (3.3–7.9)	2.2 (1.4–3.4)
Motor Deficit [1997–2003]				
GMFCS† 1–2	16	71	4.0 (2.3–6.8)	2.2 (1.3–3.9)
GMFCS 3	1	4	4.4 (0.5–39)	2.2 (0.2–21)
GMFCS 4–5	4	70	6.1 (3.3–11)	2.5 (1.3–4.7)
Developmental Quotient (DQ)				
DQ <50	11	33	5.6 (2.8–11)	2.9 (1.4–6.1)
DQ 50–85	14	60	3.9 (2.2–7.0)	1.7 (0.9–3.1)
DQ >85	17	80	3.6 (2.1–6.1)	1.9 (1.1–3.4)

*Confidence interval
†Gross Motor Function Classification Skills

Appendix A. ICD-10 diagnoses codes used in the study retrieved from the Danish National Patient Registry.

	ICD-10 diagnosis code (1994-2009)
Idiopathic respiratory distress syndrome/hyaline membrane disease	DP220+DP22A
Cerebral palsy	DG80, DG81, DG82, DG83
Major malformations <1 year	Q00-99
Complications:	
Bronchopulmonary dysplasia <1 year	DP271
Intraventricular hemorrhage or cerebral	DB100-DP109
leukomalaci <30 days	DP52 + DP912
Necrotizing enterocolitis <30 days	DP77
Patent ductus arteriosus <30 days	DQ250
Other diseases (<4 days after birth date):	
Perinatal breathing disorders and cardiovascular diseases	DP221, DP228, DP229, DP23-DP26, DP28-DP29
Congenital virus infection	DP35
Bacterial infection in newborns	DP36
Infection in the central nervous system (CNS)	DG00-DG09
Pneumonia	DJ12-DJ18

Paper IV

Risk of attention deficit–hyperactivity disorder in children with and without a history of infant respiratory distress syndrome

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Short Title: Infant Respiratory Distress Syndrome and ADHD

Abbreviations: ADHD—Attention Deficit Hyperactivity Disorder; CI—confidence interval; DNPR—Danish National Patient Registry; HR—hazard ratio; ICD-8—International Classification of Diseases, Eighth Revision; ICD-10—International Classification of Diseases, Tenth Revision; IRDS—Infant Respiratory Distress Syndrome

Key Words: epidemiology, ADHD, infant respiratory distress syndrome, neurodevelopmental outcome, population-based

Funding Source: This study was supported by grants from the Clinical Epidemiological Research Foundation ('Klinisk Epidemiologisk Forskningsfond'), Denmark, and the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck and the Novo Nordisk Foundations.

Financial Disclosure: The author and co-authors have no financial disclosures.

Conflict of Interest: The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of these studies have any relation to the present study. All authors declare no conflicts of interest.

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Word count: abstract 315 + article 2,379

Abstract

Objectives: Neonatal ischemic-hypoxic conditions are suggested risk factors for attention deficit hyperactivity disorder (ADHD). This study aimed to examine the association between infant respiratory distress syndrome (IRDS) in moderately late and late preterm children and ADHD.

Design: Cohort study.

Setting: All Danish children born moderately late and late preterm (born at 32-36 weeks of gestation) in Denmark during 1990-2009 were included. Using nationwide medical databases, we identified all children with an IRDS diagnosis.

Main outcomes measure: We defined ADHD as a hospital diagnosis of ADHD or a redeemed prescription for an ADHD medication. Children were followed from date of birth or January 1, 1996, whichever came later. Follow-up continued until initial diagnosis of ADHD (or the date of a redeemed prescription for ADHD medication), emigration, death, 15 years of age, or December 31, 2014, whichever came first. Accounting for the competing risk of death, we computed the 15-year cumulative incidence of ADHD. We used Cox regression analysis to compute crude and adjusted hazard ratios of ADHD, comparing children with IRDS to those without this condition. Hazard ratios were adjusted for multiple covariates.

Results: We identified 67,736 moderately late and late preterm children, of whom 3,845 (5.7%) had IRDS. By age 15 years the overall cumulative risk of ADHD diagnoses was 2.7% in children with a history of IRDS. The corresponding cumulative use of ADHD medication was 3.8%. The HR comparing risk of an ADHD diagnosis in children with and without a history of IRDS was 1.0 (95% CI:0.8-1.3). The corresponding HR was 1.1 (95% CI: 0.9-1.3) for a redeemed prescription for ADHD medication.

Conclusion: We found no evidence to suggest an increased risk of ADHD in children diagnosed with IRDS compared to children without IRDS born at the same gestational age. This finding held for the

outcome of a psychiatric hospitalization for ADHD, an outpatient contact for ADHD, or a redeemed prescription for ADHD medication.

Introduction

Infant respiratory distress syndrome (IRDS) is a common neonatal ischemic-hypoxic condition only seen in preterm infants (defined as birth <37 full weeks of gestation).[1,2] The overall prevalence of IRDS is 0.3%–1.2% in live-born infants;[3-5] however, the condition is more common with decreasing gestational age, with prevalence reaching about 30% in infants born at 32 weeks.[3,5,6] Short-term complications of IRDS include intraventricular/intracerebral hemorrhage (IVH/ICH) and periventricular leukomalacia (PVL);[7,8] however, there has been little research on the long term neurodevelopmental impact of IRDS.

Although uncertainty about the etiology of attention deficit hyperactivity disorder (ADHD) remains, ischemic-hypoxic conditions, such as IRDS, birth asphyxia, and preeclampisa have been suggested as contributing to ADHD development.[9-12] Worldwide, ADHD is one of the most common psychiatric disorders in children, with an overall prevalence of about 4%-10%, depending on assessment method and diagnostic conventions.[13] The condition is clinically characterized by symptoms of hyperactivity, impulsivity, and/or inattention. It is often combined with other neurodevelopmental morbidities, such as autism spectrum disorder and specific developmental disorders of language, learning, and motor development, including cerebral palsy.[14,15] About 50% of children with ADHD may have symptoms persisting into adulthood.[16]

A previous study on rats concluded that neonatal hypoxic-ischemic events may contribute to development of ADHD.[12] A case control study among human subjects reported an association between ADHD and hypoxic-ischemic events, which included IRDS as one of the exposure variables. The latter study reported an OR of ADHD of 1.4 (95% CI:1.0-2.0).[9]

We examined whether IRDS was associated with ADHD up to 15 years of age among children born moderately late and late preterm, by using nationwide Danish medical registries allowing virtually complete follow-up.

Methods

Setting and linkage

We conducted this cohort study using population-based databases covering the entire country of Denmark. Linkage between databases was possible through the Civil Registration System (CRS), which has kept electronic records on date of birth, date of emigration, and date of death since 1968.[18] At birth or upon immigration, all Danish residents are assigned a unique Civil Personal Registration (CPR) number by the CRS. The CPR number is used in all public Danish registries. The Danish National Health Service provides free tax-supported health care to the country's 5.6 million residents.

Study cohort

Our study cohort was identified using the Danish Medical Birth Registry, which contains information on all births in Denmark since 1973. We first identified all infants born alive in Denmark from January 1, 1990 to December 31, 2009 (approximately 1,300,000 infants)[19,20] and then restricted our cohort to moderately and late preterm infants born between 32 and 36 weeks of gestation. Adequate proportions of children with and without IRDS are available at these gestational ages.

Infant respiratory distress syndrome

We identified all children in our study cohort who had an IRDS diagnosis in the Danish National Patient Registry (DNPR). The DNPR contains data on all non-psychiatric hospital admissions in Denmark since 1977 and on outpatient clinic and emergency room visits since 1995.[21,22] Data include dates of admission and discharge, surgical procedure(s) performed, and one primary diagnosis and up to 19 secondary diagnoses coded by the discharging physician according to the *International Classification of Diseases, Eighth Edition* (ICD-8) until the end of 1993 and the *Tenth Edition* (ICD-10) thereafter.

Attention deficit hyperactivity disorder

The Danish Psychiatric Central Research Registry (DPCRR) contains electronic data on psychiatric inpatient diagnoses since 1969, and on outpatient diagnoses since 1995. Since 1970, it has been mandatory for all inpatient psychiatric departments and psychiatric hospitals to report psychiatric admissions to the Registry. The records include CPR number, dates of start and end of treatment, one primary diagnosis, and up to 20 secondary diagnoses. The diagnoses were coded according to ICD-8 until December 31, 1993, and according to ICD-10 thereafter.

A substantial portion of Danish psychiatric healthcare is provided in outpatient clinics. Outpatient clinic records were first included in the DPCRR in 1995, but not completely until 1996. For this reason, we began patient follow-up on January 1, 1996. Our main outcome variable—an initial diagnosis of ADHD (primary or secondary)—was obtained from the DPCRR.

Much of the treatment for ADHD in Denmark is provided by general practitioners and psychiatric and pediatric specialists in private practice. Thus, as a separate outcome, we also tracked dates of redeemed prescriptions for ADHD medication for children and adolescents up to age 15 years, recorded in the nationwide prescription database between January 1, 1996 and December 31, 2014. We specifically obtained information on the following medications, classified according to the Anatomical Therapeutic Chemical (ATC) system (Appendix A). Redeemed prescriptions may be a more sensitive outcome measure, but also potentially less specific than an ADHD diagnosis in the DPCRR.

To compare with existing literature, we used the same inclusion criteria. Thus, as an additional outcome, we defined ADHD as either a minimum of two inpatient or outpatient hospital contacts coded with an ADHD diagnosis in the DPCRR, OR one hospital contact coded with an ADHD diagnosis AND at least two prescriptions filled for ADHD medication in the Danish prescription database.

Covariates

For all children in the study cohort, we obtained information from the Danish Birth Registry on gestational age, 5-minute Apgar score, multiplicity, maternal age, and self-reported maternal smoking during pregnancy.[20] In order to examine the distribution of complications in children with and without IRDS, we obtained information on bronchopulmonary dysplasia, ICH/IVH, necrotizing enterocolitis, and patent ductus arteriosus from the DNPR (Appendix A). Parental psychiatric morbidity was defined as any psychiatric diagnosis coded in the DPCRR, based on both inpatient stays and outpatient visits to psychiatric treatment centers.

Statistical analysis

Follow-up started on the date of birth or January 1, 1996, whichever came later. It continued until an initial diagnosis of ADHD (or the date of a redeemed prescription for ADHD medication), emigration, death, 15 years of age, or December 31, 2014, whichever occurred first. We excluded children who were hospitalized for ADHD or who had a redeemed prescription for ADHD medication before January 1, 1996. Using death as a competing risk, we computed the 15-year cumulative incidence of ADHD.[23]

Cox proportional hazard regression analysis was used to compute hazard ratios (HRs) of time to initial diagnosis of ADHD or redemption of a prescription for ADHD medication among children with IRDS compared to children without IRDS. The analyses were adjusted for gestational age (32, 33, 34, 35, and 36 weeks of gestation), birth year (1990-1994, 1995-2000, 2001-2004, and 2005-2009), gender, multiplicity (singleton/twins), major malformations, maternal age (less than 35 years or 35 years and above), and parental history of psychiatric disorders. The assumptions of proportional hazards were all verified graphically. As we considered a low 5-minute Apgar score to be a causal intermediate step between IRDS and ADHD, we did not include this covariate as a confounder in the adjusted analyses. To compare to the existing literature, we defined ADHD as presence of either two hospital contacts coded

with an ADHD diagnosis or one hospital code with an ADHD diagnosis and two prescriptions filled for ADHD medication. We computed both crude and adjusted HRs.

We stratified our analyses on gestational age, birth year, gender, multiplicity, 5-minute Apgar score, and maternal age, and calculated 95% confidence intervals (95% CI) for all estimates.

All analyses were performed using the STATA 13.1 package (StataCorp LP, College Station, TX, USA). The study was approved by the Danish Protection Agency (record number: 2014-41-3183) and did not require informed consent.

Results

We identified a total of 67,736 moderately and late preterm children, of whom 3,845 (5.7%) had IRDS. Compared to children without IRDS, children with IRDS were more likely to be male (57% versus 53%), to be born between 32 and 34 weeks of gestation (72% versus 30%), to have a 5-minute Apgar score of 8 or below (18% versus 8%), and to have a major malformation within the first year of life (10% versus 7%). Medical complications, such as ICH/IVH were present in 2.2% of children with IRDS compared to 0.4% of children without IRDS. (Table 1)

A total of 1,667 children had an ADHD diagnosis and 2,301 children had a redeemed prescription for an ADHD medication. Overall, 915 children had the ADHD outcome defined as a combination of hospital codes for ADHD diagnoses and filled prescriptions of ADHD medication. For IRDS patients up to 15 years of age, the overall cumulative risk of a psychiatric inpatient or outpatient hospital contact was 2.7% (95% CI: 2.1-3.4) (Figure A); for children without IRDS the cumulative incidence was 2.5% (Figure B). The overall cumulative risk for a redeemed prescription of ADHD medication was 3.8 (95% CI: 3.1-4.6) in children with IRDS and 3.5 (95% CI: 3.2-4.7) in children without IRDS. The cumulative incidence was higher in males than in females (Tables 2 and 3).

The overall unadjusted HR for a psychiatric admission for ADHD or an outpatient visit for ADHD among children with IRDS was 1.1 (95% CI: 0.9-1.4). Confounder adjustments did not change the HR [1.0 (95% CI: 0.8-1.3)]. Overall, the unadjusted HR for a redeemed prescription for ADHD medication was 1.1 (95% CI: 0.9-1.4) and after adjustments for potential confounders, the HR was unchanged [1.1 (95% CI: 0.9-1.3)]. We found no differences in HRs across strata after stratifying on several covariates. (Tables 2 and 3). Also, the HR did not change substantially, when defining ADHD as a combination of diagnosis code filled prescriptions for ADHD medication, 0.9 (95% CI: 0.7-1.3).

Discussion

This population-based cohort study, with complete follow-up from birth to age 15 years, yielded no evidence to suggest an association between IRDS and the two separate outcomes, an AHDH diagnosis or a filled prescription for an ADHD medication.

In the nested case-control study based on population-based data from Kaiser Permanente Southern California (KPSC) medical records/hospitals, Getahun *et al.*[9] suggested an increased risk of ADHD (cases=13,613 and controls=68,065) in newborns with ischemic-hypoxic conditions, such as IRDS (n=185). In children with IRDS born between 28-33 weeks of gestation, the authors reported an adjusted OR of ADHD of 1.4 (95% CI: 1.0-2.0) compared to children without IRDS. In children with IRDS born between 34-36 weeks of gestation, they also found an OR of ADHD of 1.4 (95% CI: 1.1-2.0) compared to children without IRDS. Their point estimates were higher than in our study; however, based on overlapping CIs, their estimates were not statistically significant different from ours. Their case-control study defined ADHD based on the *International Classification of Diseases, Ninth Revision*, Clinical Modification (ICD-9-CM), and their inclusion criteria for ADHD were slightly different from our main outcomes in our study. Thus, by using the same inclusion criteria as they did in their case-control study; we found an HR of 0.9 (95% CI: 0.7-1.3). Our point estimate was lower, though based on overlapping CIs

it was not statistically significant. They did, however, not adjust for major malformations or history of parental psychiatric diagnoses, which may partially explain the difference in their point estimate and ours. The Getahun *et al*. study was based on children born to KPSC members (N=464,317) and, among others, still was members after 5 years of age. During this time, as a substantial part (approximately 29%) of the study population left the Kaiser Permanente system. This could lead to a potential selection bias if this group was different with regards to cases and controls.

The strengths of our study include availability of data from population-based registries with complete follow-up for emigration, death, and the outcomes under study. We previously reported a positive predictive value of 89% (95% CI: 75%–96%) for the IRDS diagnosis in the DNPR for children with born moderately late and late preterm.[24]

Our study has several potential limitations. Diagnostic criteria for IRDS were based solely on clinical symptoms, as x-rays were not always used in the early study period. The ADHD diagnosis in the DPCRR has not been validated, to our knowledge. However, we expect a high PPV for ADHD based on other diagnoses in the DPCRR that have been validated, including ASD, schizophrenia, and depression, with PPVs ranging between 75% and 94%.[25-27] Another concern is that a non-negligible proportion of children with ADHD are treated by psychiatric and pediatric specialists in private practices. To overcome this shortcoming, we tracked dates of filled prescriptions for ADHD medication as a separate outcome. This outcome would be more sensitive, though less specific, than an inpatient or outpatient hospital contact coded with a ADHD diagnosis. However, estimates were similar for both of our outcomes (a hospital-based diagnosis of ADHD or a filled prescription for ADHD medication). Overall, we do not believe that potential non-differential misclassification is the reason for the null association we observed.

Attention deficit hyperactivity disorder may co-occur with other neurodevelopmental disorders, such as specific developmental learning disorders, autism spectrum disorder, and cerebral palsy (CP).[14,28] However, a previous study reported that only one in five children diagnosed with CP and symptoms of

ADHD had been seen by a child psychiatrist.[28] This may indicate that children with more severe chronic neurodevelopmental disorders are at decreased risk of being diagnosed with ADHD even if they fulfill the diagnostic criteria. In a previous study, we found an association between IRDS and CP. (study II) Based on this finding, possible misclassification of ADHD may have influenced our estimates towards the null. Still, CP is a very rare disease and thus is unlikely to have had much influence on our estimates.

Several additional issues should be considered when interpreting our findings. The ADHD diagnosis was based on the ICD-10 diagnosis code DF90.0, which includes only the hyperkinetic form of the disorder, requiring presence of all three symptoms: hyperactivity, inattention, and impulsivity.[29] Its diagnostic criteria are stricter than those for an ADHD diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V). Based on the DSM-V criteria, an ADHD diagnosis would have been observed 3-4 times more frequently in our study. Thus, it should be noted that the null association found in our study relates only to ICD-10 diagnostic criteria, relevant to more severe cases of ADHD.[29]

Conclusion

We found no evidence to suggest an increased risk of ADHD in children diagnosed with IRDS compared to children without IRDS born at the same gestational age, regardless of whether the outcome was a psychiatric admission or outpatient contact for ADHD, a redeemed prescription for ADHD medication, or a combination of both.

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Figure A. Cumulative incidence of attention deficit hyperactivity disorder (ADHD) in 67,736 children with and without infant respiratory distress syndrome (IRDS) born in Denmark during 1990-2009.

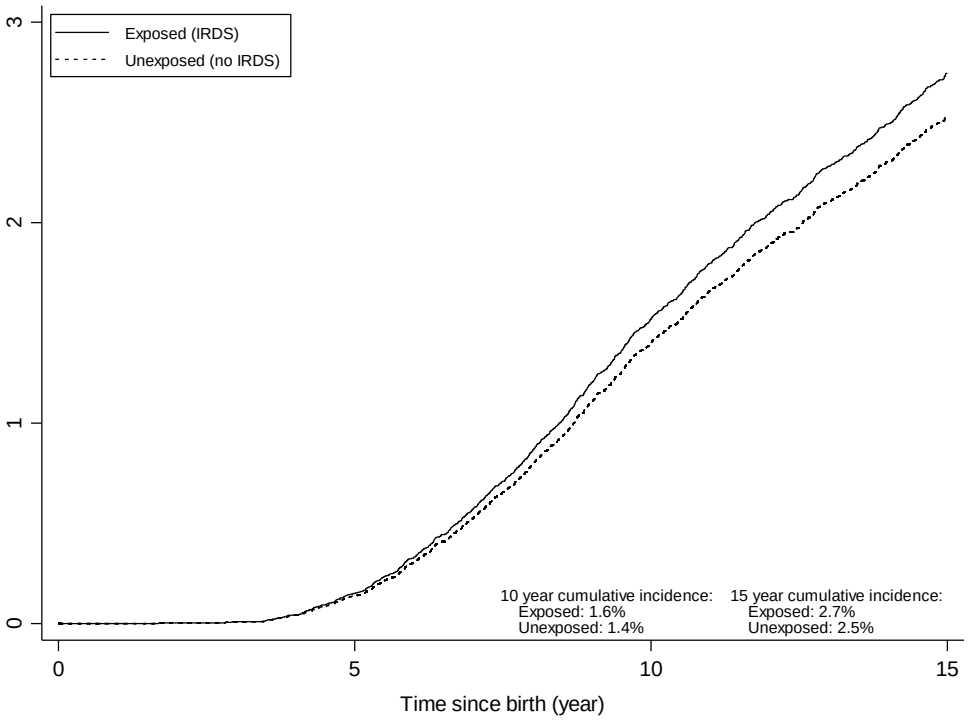

Figure B. Cumulative incidence of redeemed prescriptions for attention deficit hyperactivity disorder (ADHD) medications among 67,743 children with and without infant respiratory distress syndrome (IRDS) born in Denmark during 1990-2009.

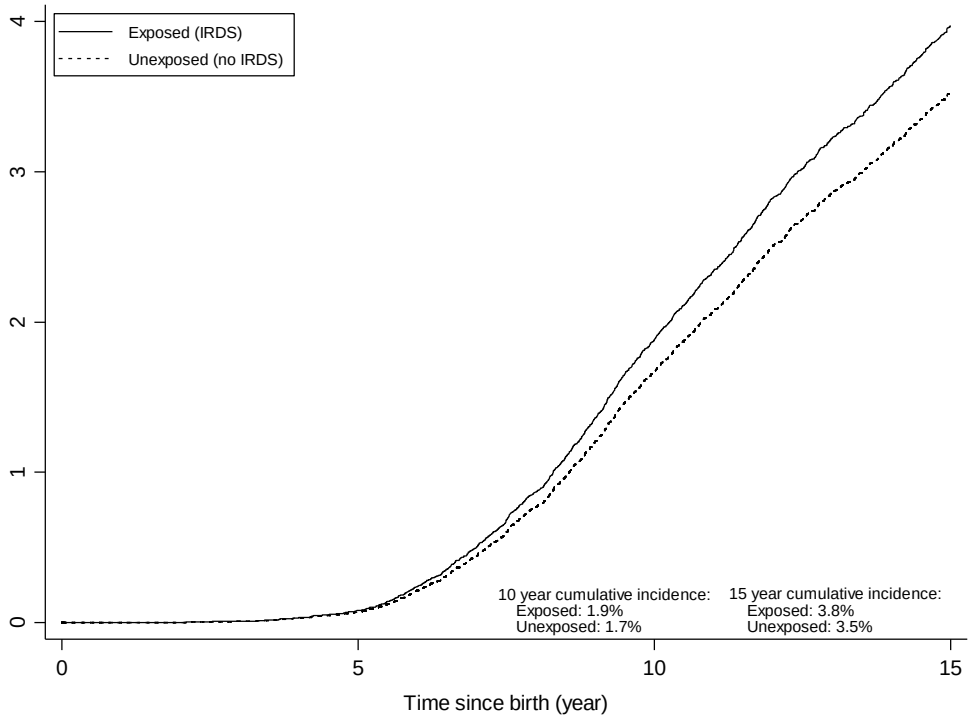

Table 1. Characteristics of 67,736 moderately late and late preterm infants with and without infant respiratory distress syndrome (IRDS), born in Denmark during 1990-2009.

	IRDS, n (%)	No IRDS, n (%)
All	**3,845 (100)**	**63,891 (100)**
Gestational age (week of gestation)		
32	960 (25.0)	3,530 (5.5)
33	924 (24.0)	5,592 (8.8)
34	899 (23.4)	9,689 (15.2)
35	633 (16.5)	15,708 (24.6)
36	429 (11.2)	29,372 (46.0)
Birth year		
1990-1994	767 (20.0)	13,822 (21.6)
1995-1999	850 (22.1)	15,881 (24.9)
2000-2004	1,075 (28.0)	17,462 (27.3)
2005-2009	1,153 (30.0)	16,726 (26.2)
Gender		
Female	1,649 (42.9)	30,289 (47.4)
Male	2,196 (57.1)	33,602 (52,6)
Apgar score at 5 minutes		
Very low (0-3)	60 (1.6)	516 (0.8)
Low (4-6)	147 (3.8)	832 (1.3)
Intermediate (7-8)	501 (13.0)	3,416 (5.4)
Normal (9-10)	3,051 (79.4)	58,208 (91.1)
Missing	86 (2.2)	919 (1.4)
Multiplicity		
Singleton	2,893 (75.2)	48,445 (75.8)
Twin	952 (24.8)	15,446 (24.2)
Major malformation (within the first year)	366 (9.5)	4,220 (6.6)
Mother's age at delivery		
<18 years	9 (0.2)	260 (0.4)
18-34 years	3,157 (82.1)	52,944 (82.9)
>34 years	679 (17.7)	10,681 (16.7)
Missing	0 (0)	6 (0.0)

Mother's smoking status (since 1991)		
Non Smoker/former smoker	2,709 (73.7)	42,011 (68.3)
Smoker	711 (19.3)	15,790 (25.7)
Missing	256 (7.0)	3,687 (6.0)
Maternal psychiatric diagnosis	538 (14.0)	9,131 (14.3)
Paternal psychiatric diagnosis	266 (6.9)	5,440 (8.5)
Bronchopulmonary dysplasia (BPD) (since 1994)	28 (0.9)	20 (0.0)
Intracranial/intraventricular hemorrhage (ICH/IVH) (<30 days)	84 (2.2)	228 (0.4)
Necrotizing enterocolitis (NEC) (<30 days)	32 (0.8)	82 (0.1)
Patent ductus arteriosus (PDA) (<30 days)	138 (3.6)	458 (0.7)
Other diseases*	974 (25.3)	9.562 (15.0)

*Other diseases whose symptoms may overlap with those of IRDS, occurring within 4 days of birth (perinatal breathing disorders other than IRDS, congenital heart diseases, and viral and bacterial infections).

Table 2. Hazard ratios for attention deficit hyperactivity disorder (ADHD) diagnoses among 67,736 children with and without infant respiratory distress syndrome (IRDS), born in Denmark during 1990-2009.

	Number of children with an ADHD diagnosis		15-year cumulative incidence, % (95% confidence interval (CI))*		Hazard ratio, % (95% CI)*	
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude	Adjusted†
Overall	**92**	**1,575**	**2.7 (2.1-3.4)**	**2.5 (2.4-2.7)**	**1.1 (0.9-1.4)**	**1.0 (0.8-1.3)**
Gestational age						
32 weeks of gestation	22	91	2.6 (1.5-4.2)	2.9 (2.3-3.6)	0.9 (0.5-1.6)	0.9 (0.5-1.6)
33 weeks of gestation	18	144	2.3 (1.3-3.7)	2.7 (2.2-3.2)	0.9 (0.5-1.5)	0.8 (0.5-1.4)
34 weeks of gestation	19	247	2.6 (1.5-4.1)	2.7 (2.3-3.1)	0.9 (0.6-1.5)	0.9 (0.5-1.5)
35 weeks of gestation	17	386	2.8 (1.6-4.6)	2.3 (2.1-2.6)	1.2 (0.7-2.2)	1.2 (0.7-2.1)
36 weeks of gestation	16	707	4.1 (2.2-6.8)	2.5 (2.3-2.7)	1.7 (0.9-3.0)	1.6 (0.9-2.8)
Year of birth						
1990-1994	25	381	1.5 (0.8-2.5)	1.0 (0.9-1.2)	1.5 (0.8-2.7)	1.2 (0.6-2.3)
1995-1999	27	515	2.7 (1.7-4.0)	2.5 (2.3-2.8)	1.1 (0.7-1.7)	1.1 (0.7-1.6)
2000-2005	25	494	3.3 (1.9-5.2)	3.5 (3.1-4.0)	0.9 (0.6-1.3)	0.8 (0.5-1.2)
2005-2009	15	185	-	-	1.4 (0.8-2.3)	1.3 (0.7-2.2)
Gender						
Female	29	496	1.7 (1.1-2.7)	1.5 (1.3-1.6)	1.2 (0.7-1.9)	1.1 (0.7-1.7)
Male	63	1,079	3.5 (2.6-4.5)	3.5 (3.3-3.7)	1.0 (0.8-1.4)	1.0 (0.7-1.3)
Apgar score at 5 minutes						
Low (0-6)	3	36	1.7 (0.5-4.5)	2.4 (1.7-3.4)	0.6 (0.2-2.1)	0.6 (0.2-2.2)
Intermediate (7-8)	14	95	3.0 (1.6-5.2)	2.3 (1.8-3.0)	1.3 (0.7-2.4)	1.4 (0.7-2.7)
Normal (9-10)	72	1,402	2.7 (2.0-3.5)	2.5 (2.4-2.7)	1.1 (0.8-1.4)	1.0 (0.7-1.3)
Missing	3	42	4.3 (1.1-11)	4.9 (3.4-6.8)	1.2 (0.4-3.8)	1.0 (0.3-3.3)
Multiplicity						
Singleton	73	1,291	2.6 (2.0-3.4)	2.6 (2.5-2.8)	1.0 (0.8-1.4)	1.0 (0.7-1.3)
Twin	19	284	3.2 (1.9-5.1)	2.2 (1.9-2.5)	1.3 (0.8-2.1)	1.1 (0.7-1.8)

Maternal age						
<35 years of age	81	1,372	2.8 (2.2-3.6)	2.6 (2.4-2.8)	1.1 (0.9-1.4)	1.0 (0.8-1.3)
35 years or older	11	203	2.2 (1.1-4.0)	2.2 (1.8-2.5)	1.1 (0.6-2.1)	1.1 (0.6-2.1)

*Death is included as a competing risk.

†Adjusted for gender, multiplicity, birth year, maternal age at delivery, gestational age, major malformations, and parental psychiatric disorders.

Table 3. Hazard ratios for attention deficit hyperactivity disorder (ADHD) medication (redeemed prescriptions) among 67,743 children with and without infant respiratory distress syndrome (IRDS), born in Denmark during 1990-2009.

	Number of children with a redeemed prescription for ADHD medication		15-year cumulative incidence, % (95% confidence interval (CI))*		Hazard ratio, % (95% CI)*	
	Children with IRDS	Children with no IRDS	Children with IRDS	Children with no IRDS	Crude	Adjusted†
Overall	**130**	**2,171**	**3.8 (3.1-4.6)**	**3.5 (3.2-4.7)**	**1.1 (0.9-1.4)**	**1.1 (0.9-1.3)**
Gestational age						
32 weeks of gestation	37	137	4.1 (2.7-5.9)	3.9 (3.2-4.7)	1.1 (0.7-1.7)	1.1 (0.7-1.7)
33 weeks of gestation	26	186	3.1 (2.0-4.7)	3.4 (2.8-4.0)	1.0 (0.6-1.5)	0.9 (0.6-1.4)
34 weeks of gestation	30	328	3.9 (2.5-5.7)	3.6 (3.2-4.1)	1.1 (0.7-1.7)	1.1 (0.7-1.6)
35 weeks of gestation	21	548	3.3 (1.9-8.2)	3.6 (3.3-4.0)	1.0 (0.6-1.6)	1.0 (0.6-1.6)
36 weeks of gestation	16	972	5.2 (3.0-8.2)	3.4 (3.2-3.7)	1.6 (1.0-2.7)	1.6 (0.9-2.6)
Year of birth						
1990-1994	43	654	2.5 (1.6-3.8)	1.8 (1.6-2.0)	1.4 (0.9-2.3)	1.3 (0.8-2.1)
1995-1999	32	788	3.3 (2.2-4.7)	4.0 (3.7-4.3)	0.8 (0.6-1.2)	0.8 (0.6-1.2)
2000-2005	42	583	4.5 (3.2-6.0)	4.4 (3.9-4.9)	1.2 (0.9-1.7)	1.1 (0.8-1.6)
2005-2009	13	146	-	-	1.4 (0.8-2.5)	1.2 (0.7-2.2)
Gender						
Female	39	755	2.2 (1.5-3.2)	2.3 (2.1-2.5)	1.1 (0.7-1.6)	1.0 (0.7-1.5)
Male	91	1,416	5.1 (4.0-6.3)	4.7 (4.4-4.9)	1.1 (0.9-1.4)	1.1 (0.8-1.4)
Apgar score at 5 minutes						
Low (0-6)	9	53	3.6 (1.5-7.3)	3.0 (2.2-4.1)	1.0 (0.4-2.5)	1.3 (0.5-3.3)
Intermediate (7-8)	17	139	3.6 (2.0-6.0)	4.0 (3.3-4.9)	0.9 (0.5-1.6)	1.0 (0.6-1.8)
Normal (9-10)	100	1,935	3.8 (3.0-4.7)	3.5 (3.3-3.7)	1.2 (0.9-1.5)	1.1 (0.8-1.3)
Missing	4	44	5.0 (1.3-13)	5.7 (4.1-7.8)	1.1 (0.3-3.6)	0.7 (0.2-2.5)

Multiplicity						
Singleton	105	1,782	3.9 (3.1-4.8)	3.7 (3.5-3.9)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
Twin	25	389	3.7 (2.3-5.5)	2.9 (2.6-3.3)	1.2 (0.8-1.9)	1.1 (0.7-1.7)
Maternal age						
<35 years of age	113	1,915	3.9 (3.1-4.8)	3.6 (3.5-3.8)	1.1 (0.9-1.4)	1.1 (0.8-1.3)
35 years or older	17	256	3.3 (1.9-5.4)	2.8 (2.5-3.2)	1.3 (0.7-2.2)	1.1 (0.6-2.0)

*Death is included as a competing risk.

†Adjusted for gender, multiplicity, birth year, maternal age at delivery, gestational age, major malformations, and parental psychiatric disorders.

Appendix A. ICD diagnoses codes and ADHD medication (ATC codes) used in the study retrieved from the Danish National Patient Registry.

	ICD-8 diagnosis code (1970-1993)	ICD-10 diagnosis code (1994-2009)
Idiopathic respiratory distress syndrome/hyaline membrane disease		DP220+DP22A
Attention Deficit Hyperactive Disorder (ADHD)		DF90.0
Major malformations <1 year		Q00-99
Complications:		
Bronchopulmonary dysplasia <1 year		DP271
Intraventricular hemorrhage or cerebral		DB100-DP109
leukomalaci <30 days		DP52 + DP912
Necrotizing enterocolitis <30 days		DP77
Patent ductus arteriosus <30 days		DQ250
Other diseases (<4 days after birth date):		
Perinatal breathing disorders and cardiovascular diseases		DP221, DP228, DP229, DP23-DP26, DP28-DP29
Congenital virus infection		DP35
Bacterial infection in newborns		DP36
Infection in the central nervous system (CNS)		DG00-DG09
Pneumonia		DJ12-DJ18
Parental psychiatric morbidity	29009-31599	DF00-DF99
ADHD medication:		**ATC* code**
Methylphenidate		N06BA04
Atomoxetine		N06BA09
Dexamphetamine		N06BA12

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