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Complete List of Authors:	Thygesen, Sandra; Aarhus Universitetshospital, Department of Clinical Epidemiology Olsen, Morten; Aarhus University, Department of Clinical Epidemiology Ostergaard, John; Aarhus Universitetshospital, Department of Pediatrics Sørensen, Henrik T.; Aarhus University Hospital, Department of Clinical Epidemiology; Stanford University, Departments of Health Research and Policy (Epidemiology)
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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

Affiliations:

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Sandra Kruchov Thygesen
MD

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Morten Olsen
Associate professor

Department of Pediatrics, Aarhus University Hospital, Palle Juul-Jensens Boulevard, 8200 Aarhus N, Denmark
John R Østergaard
Professor

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark and
Departments of Health Research and Policy (Epidemiology), Stanford University, 259 Campus Drive, Stanford, CA 94305, United States
Henrik Toft Sørensen
Professor

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

Corresponding Author: Sandra Kruchov Thygesen, st@clin.au.dk, phone: + 45 8716 8063

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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.

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.

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.

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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 legend:

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.

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) (<1 year)		
Yes	22 (1.0)	16 (0.1)
Intracerebral/intraventricular hemorrhage (ICH/IVH) (<30 days)		
Yes	46 (2.0)	121 (0.3)
Necrotizing enterocolitis (NEC) (<30 days)		
Yes	20 (0.9)	59 (0.2)
Patent ductus arteriosus (PDA) (<30 days)		
Yes	77 (3.4)	239 (0.6)
Other diseases*		
Yes	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 and 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 1992 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)

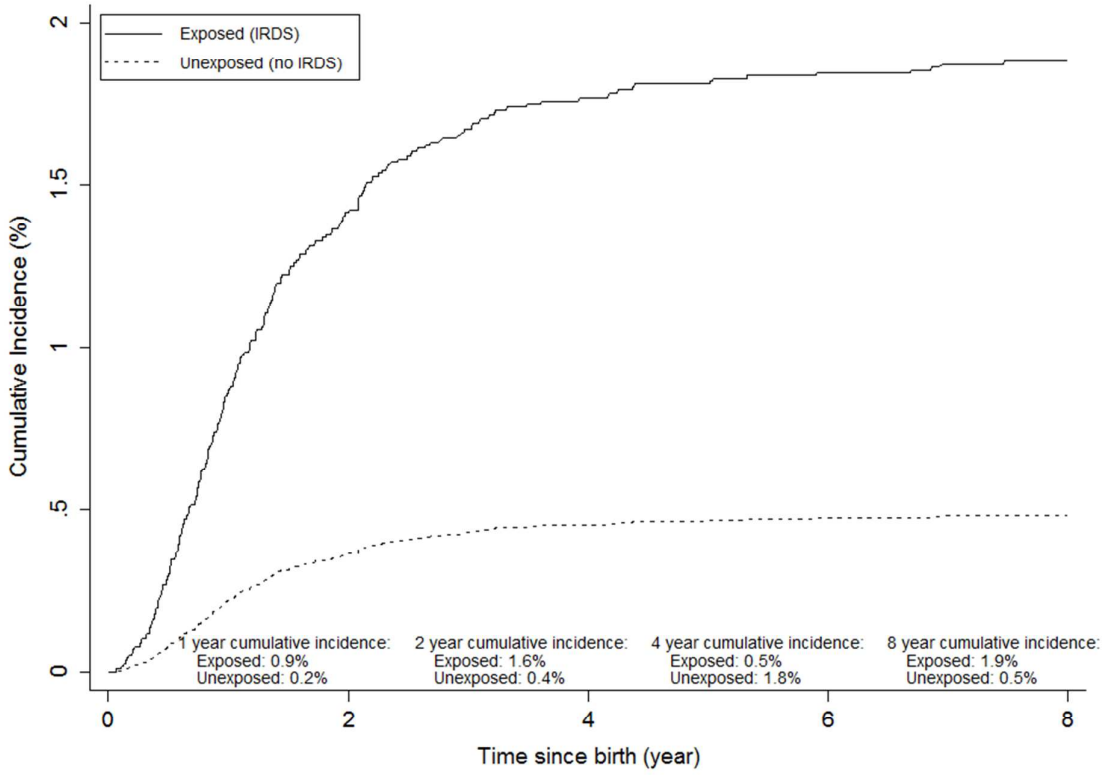
*Adjusted for sex, gestational age, infant's birth year, multiplicity, major malformations, and maternal age.

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 hazard ratio (95% CI*)**	**Adjusted hazard ratio (95% CI)**
Sub-type				
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 Handicap [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

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.



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

STROBE Statement—We hereby confirm that our manuscript, entitled, *"Respiratory distress syndrome in preterm infants and risk of epilepsy"* complies with the STROBE guidelines for the reporting of observational studies. Below we have inserted a "Page number" column to indicate where the STROBE Item number has been incorporated into our paper.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	21-22
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11, 23-24
		(*b*) Report category boundaries when continuous variables were categorized	10-11, 23-24
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 23-24
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14-15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Respiratory distress syndrome in moderately late and late preterm Infants and risk of cerebral palsy: A population-based cohort study

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Respiratory distress syndrome in moderately late and late preterm infants and risk of cerebral palsy: A population-based cohort study

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

Affiliations:

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Sandra Kruchov Thygesen
MD

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Morten Olsen
Associate professor

Department of Pediatrics, Aarhus University Hospital, Palle Juul-Jensens Boulevard, 8200 Aarhus N, Denmark
John R Østergaard
Professor

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark and
Departments of Health Research and Policy (Epidemiology), Stanford University, 259 Campus Drive, Stanford, CA 94305, United States
Henrik Toft Sørensen
Professor

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Corresponding Author: Sandra Kruchov Thygesen, st@clin.au.dk, phone: + 45 8716 8063

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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.

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.

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 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. DNCPR is assumed to cover > 85 % of the children with CP in Denmark.[25] Registry data include subtype and degree of CP,[11] predefined ranges of 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 DQ were mostly based on a clinical evaluation by a neuropediatrician, because the results of the psychological assessments were rarely available in the medical files. 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, selected subtypes of CP, (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, chorioamnionitis, intrauterine growth restriction, abruptio placenta, multiplicity, maternal age, and self-reported maternal smoking during pregnancy.[22] In the early years, 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 measurements were also included as a valid measure for the gestational age. However, in the Danish Medical Birth Registry it is not possible to distinguish between the methods of measurement used to determine gestational age.[21] 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, and may potentially lead 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, the commonest 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) (only valid 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. Chorioamnionitis, intrauterine growth restriction, and abruptio placenta are important risk factors of CP and associated with IRDS through low gestational age. Though, they did not qualify as confounders in the association between IRDS and CP, we did include the three covariates as confounders 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 or coexist with IRDS. 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). According to Danish legislation, registry-based studies do not need permission from an ethical board. 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 (Figure 1). 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 a diagnosis of ICH/IVH as a complication.

Including 5-minute Apgar score as a potential confounder in the regression model did not change our estimates substantially. The same was evident, when we included chorioamnionitis, intrauterine growth restriction, and abruptio placenta as potential confounders in the regression analysis (overall HR of 2.0 (95% CI: 1.4-2.9)). When restricting to children diagnosed with IRDS *and no* other relevant coexisting 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.

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. Because lack of surfactant cannot be measured directly, the diagnosis of IRDS is based on the clinical appearance of the infant; thus, it is not possible to make a clear and consistent diagnostic test. 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. Additionally, 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 DNCPR 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 rare 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 were only able to present overall estimates in our analyses of selected subtypes of CP, degree of motor handicap, and DQ. These estimates were all increased throughout all levels of CP severity. Of note, the

prespecified DQ score category, including scores of 50-85, encompassed both children with normal intelligence as well as delayed children, indicating a diverse group. Thus, not too much emphasis should be given to this group.

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] In moderately late and late preterm infants, CNS imaging is not routinely performed, indicating that some of these children may have an undiagnosed ICH/IVH. Based on this, the proportion of IRDS patients with ICH/IVH may have been underestimated.

Antenatal corticosteroids decrease the risk of IRDS, as well as ICH/IVH. However, recent studies have reported adverse neurodevelopment outcomes in children receiving antenatal steroids.[36] We did not have information of treatment with antenatal corticosteroids, which is a limitation of our study.

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. A twelve-fold

increased risk of CP was found in children with IRDS and ICH/IVH, suggesting an important role of ICH/IVH in the pathogenesis.

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.

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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 legend:

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.

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) (<1 year)		
Yes	22 (1.0)	16 (0.1)
Intracerebral/intraventricular hemorrhage (ICH/IVH) (<30 days)		
Yes	46 (2.0)	121 (0.3)
Necrotizing enterocolitis (NEC) (<30 days)		
Yes	20 (0.9)	59 (0.2)
Patent ductus arteriosus (PDA) (<30 days)		
Yes	77 (3.4)	239 (0.6)
Other diseases*		
Yes	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 and 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 1992 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. Hazard ratios of cerebral palsy (CP) among children with and without infant respiratory distress syndrome (IRDS) born during 32–36 weeks of gestation between 1992 and 2007 in Denmark.

	Number of children with CP			
	Children with IRDS	Children without IRDS	**Crude hazard ratio (95% CI*)**	**Adjusted hazard ratio (95% CI)**
Selected sub-types†				
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 Handicap [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
†Only selected sub-types are included
‡The covariate is only valid in 1997-2003 and had missing information for 2 CP cases
§Gross Motor Function Classification Skills
¶The DQ covariate had missing data for 5 CP cases. Of note, we did complete case analysis

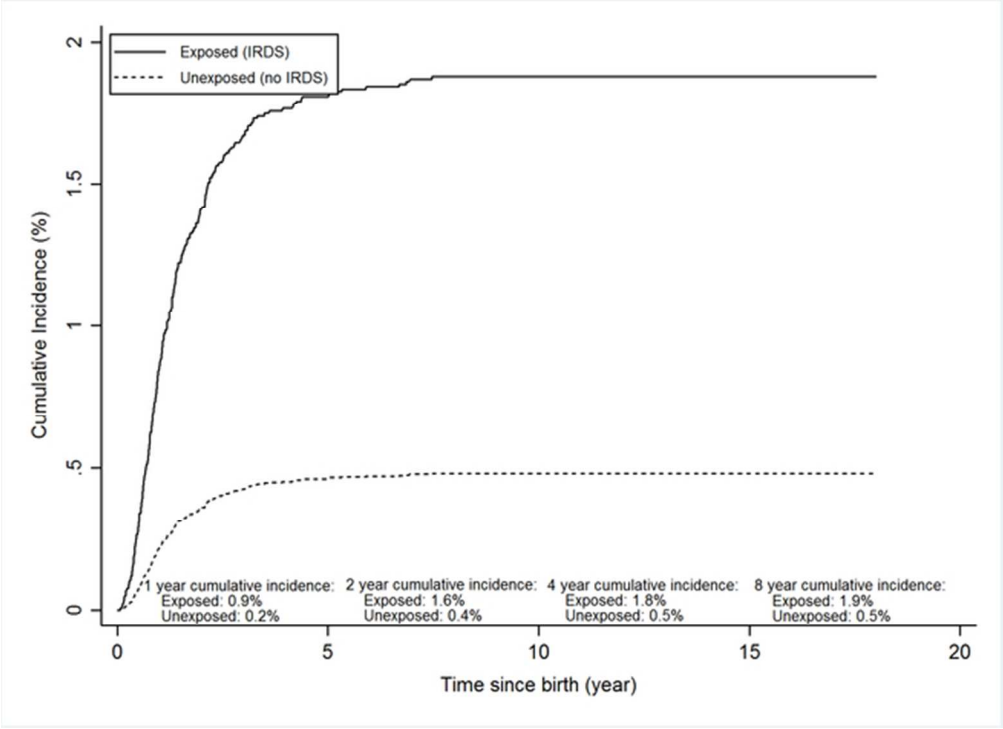

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.
(Figure A)
55x40mm (300 x 300 DPI)

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

STROBE Statement—We hereby confirm that our manuscript, entitled, *"Respiratory distress syndrome in preterm infants and risk of cerebral palsy: A population-based cohort study"* complies with the STROBE guidelines for the reporting of observational studies. Below we have inserted a "Page number" column to indicate where the STROBE Item number has been incorporated into our paper.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	24-25
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11, 26-28
		(*b*) Report category boundaries when continuous variables were categorized	10-11, 24-25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 26-28
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12, 28
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Respiratory distress syndrome in moderately late and late preterm Infants and risk of cerebral palsy: A population-based cohort study

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Respiratory distress syndrome in moderately late and late preterm infants and risk of cerebral palsy: A population-based cohort study

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

Affiliations:

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Sandra Kruchov Thygesen
MD

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Morten Olsen
Associate professor

Department of Pediatrics, Aarhus University Hospital, Palle Juul-Jensens Boulevard, 8200 Aarhus N, Denmark
John R Østergaard
Professor

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark and
Departments of Health Research and Policy (Epidemiology), Stanford University, 259 Campus Drive, Stanford, CA 94305, United States
Henrik Toft Sørensen
Professor

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Corresponding Author: Sandra Kruchov Thygesen, st@clin.au.dk, phone: + 45 8716 8063

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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 a diagnosis of ICH/IVH. 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.

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.

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 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. DNCPR is assumed to cover > 85 % of the children with CP in Denmark.[25] Registry data include subtype and degree of CP,[11] predefined ranges of 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 DQ were mostly based on a clinical evaluation by a neuropediatrician, because the results of the psychological assessments were rarely available in the medical files. 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, selected subtypes of CP, (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, chorioamnionitis, intrauterine growth restriction, abruptio placenta, multiplicity, maternal age, and self-reported maternal smoking during pregnancy.[22] Of note, information on administration of antenatal corticosteroids was not available. In the early years, weeks of gestation was based on the first day of the last menstrual period. Later, prenatal ultrasound measurements were also included as a valid measure for the gestational age. However, in the Danish Medical Birth Registry it is not possible to distinguish between the methods of measurement used to determine gestational age.[21] 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, and may potentially lead 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, the commonest 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) (only valid 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. Chorioamnionitis, intrauterine growth restriction, and abruptio placenta are important independent risk factors of CP. Moreover, these conditions are associated with IRDS, not independently, but through low gestational age. Though, they did not qualify as confounders in the association between IRDS and CP, we did include the three covariates as confounders 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. Of note, ICH/IVH is not performed as a routine in moderately late and late preterm infants, so this proportion of infants only include infants who presented with a clinical presentation and for that reason had indication for at head ultrasound.

Perinatal diseases may be misinterpreted as IRDS because of overlapping clinical symptoms or coexist with IRDS. 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). According to Danish legislation, registry-based studies do not need permission from an ethical board. 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. 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 (Figure 1). 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 a discharge diagnosis of ICH/IVH.

Including 5-minute Apgar score as a potential confounder in the regression model did not change our estimates substantially. The same was evident, when we included chorioamnionitis, intrauterine growth restriction, and abruptio placenta as potential confounders in the regression analysis (overall HR of 2.0 (95% CI: 1.4-2.9)). When restricting to children diagnosed with IRDS *and no* other relevant coexisting 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.

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. Because lack of surfactant cannot be measured directly, the diagnosis of IRDS is based on the clinical appearance of the infant; thus, it is not possible to make a clear and consistent diagnostic test. 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. Additionally, 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 DNCPR 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 rare 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 were only able to present overall estimates in our analyses of selected subtypes of CP, degree of motor handicap, and DQ. These estimates were all increased throughout all levels of CP severity. Of note, the

prespecified DQ score category, including scores of 50-85, encompassed both children with normal intelligence as well as delayed children, indicating a diverse group. Thus, not too much emphasis should be given to this group.

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 a diagnosis of ICH/IVH compared to our control population. This may suggest an important role of ICH/IVH in the pathogenesis, though this is only speculations.[15, 34, 35] In moderately late and late preterm infants, CNS imaging is not routinely performed, indicating that some of these children may have an undiagnosed ICH/IVH. Based on this, the proportion of IRDS patients with ICH/IVH may have been underestimated.

Antenatal corticosteroids decrease the risk of IRDS, as well as ICH/IVH. However, recent studies have reported adverse neurodevelopment outcomes in children receiving antenatal steroids.[36] We did not have information of treatment with antenatal corticosteroids, which is a limitation of our study.

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.

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.

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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 legend:

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.

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) (<1 year)		
Yes	22 (1.0)	16 (0.1)
Intracerebral/intraventricular hemorrhage (ICH/IVH) (<30 days)		
Yes	46 (2.0)	121 (0.3)
Necrotizing enterocolitis (NEC) (<30 days)		
Yes	20 (0.9)	59 (0.2)
Patent ductus arteriosus (PDA) (<30 days)		
Yes	77 (3.4)	239 (0.6)
Other diseases*		
Yes	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 and 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 1992 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. Hazard ratios of cerebral palsy (CP) among children with and without infant respiratory distress syndrome (IRDS) born during 32–36 weeks of gestation between 1992 and 2007 in Denmark.

	Number of children with CP			
	Children with IRDS	Children without IRDS	**Crude hazard ratio (95% CI*)**	**Adjusted hazard ratio (95% CI)**
Selected sub-types†				
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 Handicap [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
†Only selected sub-types are included
‡The covariate is only valid in 1997-2003 and had missing information for 2 CP cases
§Gross Motor Function Classification Skills
¶The DQ covariate had missing data for 5 CP cases. Of note, we did complete case analysis

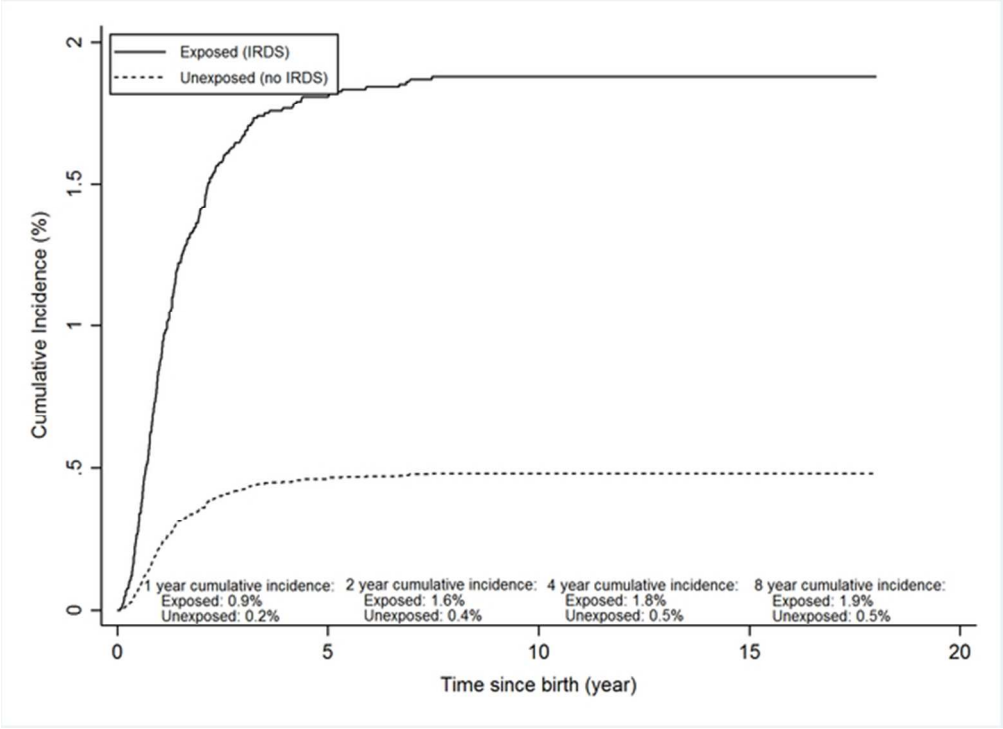

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.
(Figure A)
55x40mm (300 x 300 DPI)

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

STROBE Statement—We hereby confirm that our manuscript, entitled, *"Respiratory distress syndrome in preterm infants and risk of cerebral palsy: A population-based cohort study"* complies with the STROBE guidelines for the reporting of observational studies. Below we have inserted a "Page number" column to indicate where the STROBE Item number has been incorporated into our paper.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	24-25
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11, 26-28
		(*b*) Report category boundaries when continuous variables were categorized	10-11, 24-25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 26-28
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12, 28
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15-16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Respiratory distress syndrome in moderately late and late preterm Infants and risk of cerebral palsy: A population-based cohort study

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Respiratory distress syndrome in moderately late and late preterm infants and risk of cerebral palsy: A population-based cohort study

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

Affiliations:

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Sandra Kruchov Thygesen
MD

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark
Morten Olsen
Associate professor

Department of Pediatrics, Aarhus University Hospital, Palle Juul-Jensens Boulevard, 8200 Aarhus N, Denmark
John R Østergaard
Professor

Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark and
Departments of Health Research and Policy (Epidemiology), Stanford University, 259 Campus Drive, Stanford, CA 94305, United States
Henrik Toft Sørensen
Professor

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Corresponding Author: Sandra Kruchov Thygesen, st@clin.au.dk, phone: + 45 8716 8063

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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 accompanied by a diagnosis of ICH/IVH. 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.

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.

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 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. DNCPR is assumed to cover > 85 % of the children with CP in Denmark.[25] Registry data include subtype and degree of CP,[11] predefined ranges of 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 DQ were mostly based on a clinical evaluation by a neuropediatrician, because the results of the psychological assessments were rarely available in the medical files. 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, selected subtypes of CP, (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, chorioamnionitis, intrauterine growth restriction, abruptio placenta, multiplicity, maternal age, and self-reported maternal smoking during pregnancy.[22] Of note, information on administration of antenatal corticosteroids was not available. In the early years, weeks of gestation was based on the first day of the last menstrual period. Later, prenatal ultrasound measurements were also included as a valid measure for the gestational age. However, in the Danish Medical Birth Registry it is not possible to distinguish between the methods of measurement used to determine gestational age.[21] 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, and may potentially lead 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, the commonest 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) (only valid 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. Chorioamnionitis, intrauterine growth restriction, and abruptio placenta are important independent risk factors of CP. Moreover, these conditions are associated with IRDS, not independently, but through low gestational age. Though, they did not qualify as confounders in the association between IRDS and CP, we did include the three covariates as confounders 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* a diagnosis of ICH/IVH within 30 days of birth compared to children with IRDS *and no* diagnosis of ICH/IVH. Of note, cranial ultrasound is not performed as a routine in moderately late and late preterm infants, so the proportion of infants with a diagnosis of ICH/IVH is based on detection in only infants selected for neuroimaging based on clinical presentation and risk factors.

Perinatal diseases may be misinterpreted as IRDS because of overlapping clinical symptoms or coexist with IRDS. 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). According to Danish legislation, registry-based studies do not need permission from an ethical board. 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. 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 (Figure 1). 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 a discharge diagnosis of ICH/IVH.

Including 5-minute Apgar score as a potential confounder in the regression model did not change our estimates substantially. The same was evident, when we included chorioamnionitis, intrauterine growth restriction, and abruptio placenta as potential confounders in the regression analysis (overall HR of 2.0 (95% CI: 1.4-2.9)). When restricting to children diagnosed with IRDS *and no* other relevant coexisting 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.

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. Because lack of surfactant cannot be measured directly, the diagnosis of IRDS is based on the clinical appearance of the infant; thus, it is not possible to make a clear and consistent diagnostic test. 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. Additionally, 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 DNCPR 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 rare 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 were only able to present overall estimates in our analyses of selected subtypes of CP, degree of motor handicap, and DQ. These estimates were all increased throughout all levels of CP severity. Of note, the

prespecified DQ score category, including scores of 50-85, encompassed both children with normal intelligence as well as delayed children, indicating a diverse group. Thus, not too much emphasis should be given to this group.

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 a diagnosis of ICH/IVH compared to our control population. This may suggest an important role of ICH/IVH in the pathogenesis, though this is only speculations.[15, 34, 35] In moderately late and late preterm infants, neuroimaging is not routinely performed, indicating that some of these children may have an undiagnosed ICH/IVH. Based on this, the proportion of children with ICH/IVH may have been underestimated in both the exposed group as well as the comparison cohort, making the HR imprecise.

Antenatal corticosteroids decrease the risk of IRDS, as well as ICH/IVH. However, recent studies have reported adverse neurodevelopment outcomes in children receiving antenatal steroids.[36] We did not have information of treatment with antenatal corticosteroids, which is a limitation of our study.

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.

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.

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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 legend:

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.

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) (<1 year)		
Yes	22 (1.0)	16 (0.1)
Intracerebral/intraventricular hemorrhage (ICH/IVH) (<30 days) †		
Yes	46 (2.0)	121 (0.3)
Necrotizing enterocolitis (NEC) (<30 days)		
Yes	20 (0.9)	59 (0.2)
Patent ductus arteriosus (PDA) (<30 days)		
Yes	77 (3.4)	239 (0.6)
Other diseases*		
Yes	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 and bacterial infections).
†Information on total number of infants undergoing cranial ultrasound examination is unavailable.

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 1992 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. Hazard ratios of cerebral palsy (CP) among children with and without infant respiratory distress syndrome (IRDS) born during 32–36 weeks of gestation between 1992 and 2007 in Denmark.

	Number of children with CP			
	Children with IRDS	Children without IRDS	**Crude hazard ratio (95% CI*)**	**Adjusted hazard ratio (95% CI)**
Selected sub-types†				
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 Handicap [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
†Only selected sub-types are included
‡The covariate is only valid in 1997-2003 and had missing information for 2 CP cases
§Gross Motor Function Classification Skills
¶The DQ covariate had missing data for 5 CP cases. Of note, we did complete case analysis

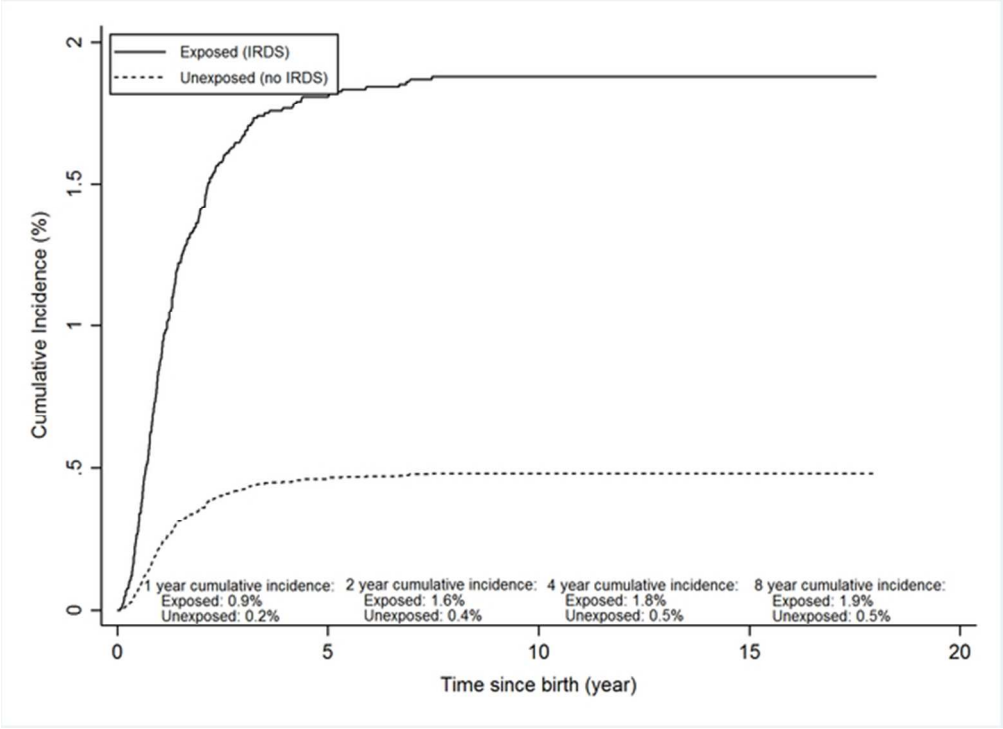

Figure 1. Cumulative incidence of cerebral palsy in 24,728 children with and without infant respiratory distress syndrome (IRDS) in Denmark during 1997-2003.
(Figure A)
55x40mm (300 x 300 DPI)

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

STROBE Statement—We hereby confirm that our manuscript, entitled, *"Respiratory distress syndrome in preterm infants and risk of cerebral palsy: A population-based cohort study"* complies with the STROBE guidelines for the reporting of observational studies. Below we have inserted a "Page number" column to indicate where the STROBE Item number has been incorporated into our paper.

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	6-8
		(*e*) Describe any sensitivity analyses	9

Continued on next page

Results			Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	24-25
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11, 26-28
		(*b*) Report category boundaries when continuous variables were categorized	10-11, 24-25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 26-28
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12, 28
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15-16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.