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Long-term risk of psychiatric disorders in childhood and adolescence following neonatal invasive group B *Streptococcus* disease—A Danish cohort study

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SUMMARY

Objectives: The long-term risk of child and adolescent psychiatric disorders (PDs) after neonatal invasive group B *Streptococcus* disease (iGBS) and the modifying factors are poorly understood.
Methods: A population-based matched cohort study, including 1548 infants with iGBS diagnosed during the first 3 months of life from 1997 through 2020 and follow-up until 2022, based on data from Danish national health and administrative registers. A general population comparison cohort of infants without iGBS was randomly sampled and matched 1:10 by sex, the child's birth year and month, and gestational age (n= 15,345).
Results: The cumulative incidence proportion (CIP) with 95% confidence intervals (CIs) of any PD was 21.1% (95% CI 18.7–23.7) in infants exposed to iGBS (88% sepsis, 12% meningitis) and 16.2% (95% CI 15.5–17.0) in the comparison cohort. The 18-year CIP of PD was higher for infants exposed to iGBS meningitis compared to iGBS sepsis. The adjusted hazard ratio for PD in infants with iGBS was 1.41 (95% CI 1.23–1.62).
Conclusions: iGBS in early infancy is a risk factor for PDs, especially iGBS meningitis. Premature birth, gestational diabetes, and low maternal education increased the risk of any PD further.
Summary: Group B *Streptococcus* (*Streptococcus agalactiae*) remains the leading cause of neonatal, invasive disease and is associated with high mortality and risk of neurodevelopmental impairments. Scarce data exist regarding the long-term risk of psychiatric disorders following invasive group B *Streptococcus* disease in early infancy (iGBS), especially following sepsis. In this Danish national cohort study, we investigated the association of iGBS and the risk of psychiatric disorders until adolescence and early adulthood. We investigated to which extent premature birth, sex (at birth), maternal socioeconomic position or gestational diabetes were modifying the association between iGBS and psychiatric disorders.

Our study found an increased risk of psychiatric disorders persisting into adolescence following iGBS, including both meningitis and sepsis. Specific psychiatric disorders with elevated risk included anxiety, obsessive-compulsive disorder, autism, and attention deficit hyperactivity disorder. Premature birth, maternal gestational diabetes, and low maternal education further increased the risk of any psychiatric disorders, whereas the child's sex did not.

Abbreviations: iGBS, Invasive group B *Streptococcus* disease; ADHD, Attention-deficiency hyperactivity disorder; PD, Psychiatric disorder; SEP, Socio-economic position; CRS, The Danish Civil Registration System; DMBR, The Danish Medical Birth Registry; DNPR, The Danish National Patient Registry; PCRR, Danish Psychiatric Central Research Register; ICD-10, International Classification of Diseases, 10th revision codes; OCD, Obsessive-compulsive disorder; IR, Incidence rate; PY, per 1000 person-years; HR, Hazard ratio; CI, Confidence interval; CIP, Cumulative incidence proportion; IC, Interaction contrast

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Introduction

Neonatal infections contribute substantially to the global disease burden.[1] Invasive group B *Streptococcus* disease (iGBS) continues to be the leading cause of neonatal invasive infections and young infant mortality worldwide[2-5]: approximately 450,000 cases a year of infant iGBS occur within the first 3 months of life globally.[2] Neonatal infections, particularly meningitis, may alter fetal brain development and lead to neuropsychiatric consequences later in childhood.[6,7] Prior research has indicated that iGBS is associated with neurological and neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD), autism, and intellectual/learning disabilities.[8-11] Although several studies have examined neurodevelopmental outcomes after iGBS, assessment methods have differed, follow-up times have been short, and the primary focus has been on meningitis. Therefore, data on long-term outcomes after iGBS, specifically iGBS sepsis, are lacking. Furthermore, data on high-risk subgroups are scarce but will be crucial to enable clinicians and policymakers to identify such subgroups and implement relevant intervention and prevention strategies. Risk of early neurodevelopmental impairment is elevated after iGBS in premature born neonates,[8] boys,[12] and children with mothers of low socioeconomic status[10]; however, the long-term effects in these subgroups remain unexplored. Recent research has suggested that gestational diabetes might mediate increased risk of iGBS disease and subsequent risk of neurodevelopmental impairment in offspring.[13,14] If gestational diabetes modifies the risk of psychiatric disorders (PDs) after iGBS, this subgroup of pregnant women could potentially be targeted for early surveillance of group B *Streptococcus* carriage.

We investigated the risk of PDs in infants diagnosed with iGBS sepsis or meningitis during the first 3 months of life, including any effects of the child's sex (at birth), gestational age, gestational diabetes, and the mother's socioeconomic position (SEP), to identify subgroups with high risk of PDs after iGBS.

Methods

This nationwide, matched cohort study included all children born in Denmark between January 1, 1997, and December 31, 2020, with follow-up until December 31, 2022. Denmark has a free tax-supported health care system,[15] where a unique personal identification number assigned by the Danish Civil Registration System (CRS) to all residents of Denmark at birth or immigration, enables data linkage across the Danish population-based health and administrative registries (details in sTable1).[16]

Data sources

The cohorts were established linking data from the Danish Medical Birth Registry (DMBR)[17] and the CRS. The Danish National Patient Registry (DNPR) and Danish Psychiatric Central Research Register (PCRR) were used to define the date of PD and type of PD diagnosis. Data on maternal income and educational level were collected from the Integrated Database for Labor Market Research and the Educational Attainment Register.[18]

Invasive group B Streptococcus cohort

Exposed infants were defined as those diagnosed with iGBS sepsis or meningitis within the first 3 months of life, registered in the DNPR (inpatients and outpatients' primary and secondary discharge diagnoses) according to International Classification of Diseases, 10th revision (ICD-10) codes (sTable2). The iGBS screening strategy has previously been described.[10] The index date was defined as the date of hospital admission for iGBS.

General population comparison cohort

A general population comparison cohort was randomly selected with replacement and matched to each exposed infant at a ratio as high as 1:10, by sex at birth (sex), birth year and month, and gestational age (< 28 weeks, 28–36 weeks, or ≥ 37 weeks). The index date for the comparison cohort was the same as the corresponding admission date of the child with iGBS. Children in the comparison cohort had no history of iGBS before their index date. Children in the comparison cohort could have had an invasive infection within the first 3 months of life due to another pathogen, but these were not excluded from the analysis.

Child and adolescent psychiatric disorders

The diagnostic classification of PDs was defined by ICD-10 codes for mental, behavioral, and nervous system disorders. These codes were obtained from the DNPR and the PCRR,[19] according to inpatients' and outpatients' primary and secondary discharge diagnoses[20] (sTable2). Psychiatric evaluation and diagnostics in Denmark are performed by medical doctors specialized in psychiatry. More than 90% of all psychiatric patients are either referred by their general practitioner, relatives, or by psychologists and psychiatrists from the primary healthcare sector of Denmark. Data from private clinics (approximately 10% of all psychiatric patients) were not available in this study. The primary outcome of interest was any PD. Secondary outcomes comprised the following PD subgroups: organic mental disorder, use of drugs or alcohol, schizophrenic disorders, affective disorders, nervous and stress-related disorders, behavioral changes associated with psychological disturbances and physical factors, disorders in personality structure, intellectual disabilities, mental developmental disorders, behavioral and emotional disturbances, and other non-specified PDs. Finally, we investigated the risk of the following specific PDs: ADHD, obsessive-compulsive disorder (OCD), anxiety, autism, and eating disorder.

Covariates

Information regarding maternal characteristics, including age, delivery type, education, gestational diabetes, and history of PD, was obtained from the CRS, DNPR, DMBR, and Integrated Database for Labor Market Research and the Educational Attainment Register.[18] Maternal income was retrieved from the income statistics register at Statistics Denmark. Income level was divided into low-, middle-, middle-high, or high-income based on defined quartiles. Educational level was divided into low (primary or lower education), middle (upper secondary or academic professional degree), or high (university education with bachelor's degree or higher).

Data on each infant's sex and date of birth were retrieved from the CRS. Information on birthweight, gestational age, pregnancy type, and delivery type was retrieved from the DMBR. Missing data were retained as a separate category in the analyses.

Statistical analyses

Our cohorts were followed from the index date to the date of any PD, death, emigration, 18 years of age, or the end of the study period (December 31, 2022), whichever occurred first. We censored at 18 years of age, because children younger than 18 years in Denmark are diagnosed and treated in departments of psychiatric child and adolescent disorders. Incidence rates (IRs) per 1000 person-years (PY) were computed for the iGBS and comparison cohorts. Cox proportional hazards regression analysis was used to compute hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). We used a directed acyclic graph to identify possible covariates for adjustment (sFigure1). HRs were adjusted for sex, prematurity, year

of birth, maternal age at delivery, maternal history of PD, and maternal income categories. Analyses were repeated for 0–10 years in the follow-up period. The proportional hazards assumption was assessed graphically with log-minus-log plots, and no major violations were detected.

We calculated the overall cumulative incidence proportion (CIP) as a measure of risk of the first registered PD diagnosis during the total available follow-up time, by using cumulative incidence functions and treating death as competing event.

To identify subgroups with a higher risk of PDs after iGBS, we evaluated the extent to which the child's sex and gestational age, and the mother's gestational diabetes and SEP modified the association between iGBS and PD risk. Effect measure modification relates to the variation in effect measures by strata on another variable.[12] Effect measure modification on an additive scale occurs when differences in rates/risks between exposed (*i.e.*, iGBS exposed) and unexposed (*i.e.*, comparison cohort) groups differ according to the strata of a third variable (*i.e.*, PDs).

We estimated the effect measure modification on an additive scale by calculating the interaction contrast (IC) for PD with the following formula (example shown for sex): IC = incidence $\text{rate}_{\text{iGBS girl}}$ – incidence $\text{rate}_{\text{iGBS boy}}$ – incidence $\text{rate}_{\text{non-iGBS girl}}$ + incidence rate $_{\text{non-iGBS boy}}$. In our calculations, girls with no iGBS, children born at term with no iGBS, women with no gestational diabetes, and mothers with high educational level were used as reference groups. Statistical analyses were performed from September 2023 through August 2024 in STATA version MP 18.0 and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Among the source population of 1626,383 liveborn children (1997–2020), we identified 1548 children with a history of iGBS (87.7% sepsis and 12.3% meningitis) and 15,345 children with no iGBS history (55.6% boys) (Table 1). Approximately 22% of children with iGBS were born premature (< 37 completed weeks' gestation). Members of the iGBS and comparison cohorts were followed for a median of 14.4 years (interquartile range: 8.5–18 years).

Incidence rates and hazard ratios for any psychiatric disorder and psychiatric disorder subgroups

The IR after 18 years' follow-up for any PD was 12.18 per 1000 PY (95% CI 10.62–13.75) among children with iGBS and 8.62 PY (95% CI 8.21–9.03) in the comparison cohort (Table 2). The adjusted HR for any PD during 18 years' follow-up was 1.41 (95% CI 1.23–1.62). The HR of any PD in the first 10 years of follow-up was 1.69 (95% CI 1.41–2.02) (sTable 3). The IR after 18 years' follow-up was 19.00 PY (95% CI 12.88–25.13) for iGBS meningitis and 11.41 PY (95% CI 9.81–13.01) for sepsis. The IRs slightly decreased when follow-up was restricted to 10 years (Table2). The HR for children with meningitis was 2.18 (95% CI 1.54–3.10) after 18 years' follow-up and 2.71 (95% CI 1.75–4.20) after 10 years' follow-up. The HR for children with sepsis was 1.34 (95% CI 1.15–1.55) after 18 years' follow-up and 1.56 (95% CI 1.28–1.91) after 10 years' follow-up.

iGBS was associated with elevated risk of nervous and stress-related disorders (HR 1.43 [95% CI 1.17–1.75]), intellectual disabilities (HR 2.19 [95% CI 1.45–3.29]), mental developmental disorders (HR 1.36 [95% CI 1.02–1.83]), and behavioral and emotional disorders (HR 1.46 [95% CI 1.01–2.10]) (sTable 4).

Cumulative incidence of any psychiatric disorder in the invasive GBS disease cohort and comparison cohort

The CIP of PD after 18 years' follow-up was 21.1% (95% CI 18.7–23.7) in the iGBS cohort and 16.2% (95% CI 15.5–17.0) in the comparison cohort (Fig. 1a). In the iGBS cohort, 250 (16.1%) children had more than one PD, whereas 1943 (12.6%) children in the comparison cohort had more than one PD registered during 18 years' follow-up (sTable 4). The CIP was 30.1% (95% CI 21.5–39.1) in the iGBS meningitis cohort and 17.3% (95% CI 14.9–19.5) in the corresponding comparison cohort (Fig. 1b). The CIP was 20.0% (95% CI 17.5–22.7) in the iGBS sepsis cohort and 16.1% (95% CI 15.4–16.9) in the comparison cohort (Fig. 1c). CIP by sex, gestational age, and maternal educational level is shown in Table 3.

Table 1
Characteristics of neonates with iGBS and matched comparison cohort members.

	iGBS cohort, n (%)	Comparison cohort, n (%)
Total	1548 (100%)	15,345 (100%)
iGBS type		
Meningitis	191 (12.3%)	–
Sepsis	1357 (87.7%)	–
Sex		
Female	687 (44.4%)	6803 (44.3%)
Male	861 (55.6%)	8542 (55.7%)
Gestational age, weeks		
< 28	58 (3.7%)	441 (2.9%)
28–36	272 (17.6%)	2729 (17.8%)
≥37	1218 (78.7%)	12,175 (79.3%)
Year of iGBS diagnosis		
1997–2001	474 (30.6%)	4719 (30.8%)
2002–2006	327 (21.1%)	3239 (21.1%)
2007–2011	326 (22.8%)	3237 (21.1%)
2012–2016	262 (16.9%)	2589 (16.9%)
2017–2020	158 (10.2%)	1561 (10.2%)
Multiplicity	1442 (93.2%)	14,112 (92.0%)
Singleton		
Twins or higher order	106 (6.8%)	1233 (8.0%)
Birth weight, g		
< 2500	256 (16.6%)	2070 (13.5%)
2500–2999	163 (10.6%)	2091 (13.7%)
3000–3499	356 (23.1%)	4349 (28.5%)
3500–3999	448 (29.0%)	4382 (28.7%)
4000–4499	268 (17.4%)	1937 (12.7%)
≥4500	53 (3.4%)	450 (3.0%)
Maternal age, years		
18–24	213 (13.8%)	2039 (13.3%)
25–29	513 (33.1%)	5129 (33.4%)
30–34	532 (34.4%)	5312 (34.6%)
35–39	242 (15.6%)	2399 (15.6%)
≥40	48 (3.1%)	466 (3.0%)
Parity		
1	860 (55.6%)	7164 (46.7%)
≥2	674 (43.5%)	8011 (52.2%)
Missing	14 (0.9%)	170 (1.1%)
Delivery type		
Vaginal	1099 (71.0%)	11,681 (76.1%)
Caesarean delivery	449 (29.0%)	3664 (23.9%)
Apgar score at 5 min		
0–5	49 (3.2%)	211 (1.4%)
6–9	316 (20.4%)	1328 (8.7%)
10	1159 (75.0%)	13,616 (89.1%)
Missing	22 (1.4%)	132 (0.9%)
Maternal psychiatric history	160 (10.3%)	1424 (9.3%)
Gestational diabetes	71 (4.6%)	485 (3.2%)
Maternal income		
Low	408 (26.2%)	3810 (24.8%)
Middle	400 (25.8%)	3790 (24.7%)
Middle-high	368 (23.8%)	3810 (24.8%)
High	356 (23.0%)	3853 (25.1%)
Missing	16 (1.0%)	82 (0.5%)
Maternal education		
Low (primary or lower education)	472 (30.5%)	4925 (32.1%)
Middle (upper secondary or academic professional degree)	772 (49.9%)	7532 (49.1%)
High (university education at bachelor degree or higher)	190 (12.3%)	1920 (12.5%)
Missing	114 (7.4%)	968 (6.3%)

Table 2
Incidence rates and hazard ratios of psychiatric disorders among children with iGBS and in the comparison cohort, Denmark, 1997–2022.

Overall outcome in the given period	iGBS cohort			Comparison cohort			Adjusted[a] HR (95% CI)
	Number of outcome events	Sum of person-years	IR per 1000 person-years (95% CI)	Number of outcome events	Sum of person-years	IR per 1000 person-years (95% CI)	
iGBS total							
0–18 years	232	19,036.64	12.18 (10.62–13.75)	1699	19,7087.9	8.62 (8.21–9.03)	1.41 (1.23–1.62)
0–10 years	137	12,975.5	10.56 (8.79–12.33)	832	13,2986.2	6.26 (5.83–6.68)	1.69 (1.41–2.03)
iGBS meningitis							
0–18 years	37	1946.684	19.00 (12.88–25.13)	198	22,367.69	8.85 (7.62–10.09)	2.18 (1.54–3.10)
0–10 years	25	1402.219	17.83 (10.83–24.82)	104	15,773.31	6.59 (5.33–7.86)	2.71 (1.75–4.20)
iGBS sepsis							
0–18 years	195	17,089.95	11.41 (9.81–13.01)	1501	17,4720.2	8.59 (8.16–9.03)	1.34 (1.15–1.55)
0–10 years	112	11,573.28	9.86 (7.89–11.47)	728	11,7212.9	6.21 (5.76–6.66)	1.56 (1.28–1.91)

[a] HR adjusted by sex, gestational age, year of birth, maternal income, maternal age and maternal psychiatric history.

iGBS exposed children were more likely to develop nervous and stress-related disorders, intellectual disabilities, mental developmental disorders, mental developmental disorders, and behavioral and emotional disturbances than children in the comparison cohort (sTable 4). These subgroups of disorders included anxiety, OCD, autism, and ADHD, but not eating disorders. Results for organic mental disorders, schizophrenic or schizotypal disorders, disorders in personality structure and behavior, and non-specified conditions were based on a few outcomes, thus resulting in imprecise estimates with wide confidence intervals.

Effect measure modification analyses

In all, 134 (18.4%) exposed boys and 98 (16.6%) exposed girls had a diagnosis of any PD after 18 years' follow-up (Table 3). The adjusted HR was 1.37 (95% CI 1.14–1.64) for boys and 1.50 (95% CI 1.22–1.86) for girls (Table 3). The risk of PD was not found to be modified by sex (IC = −0.38 [95% CI −3.85 to 3.08]) (Table 3).

Among premature neonates with iGBS, 63 (15.4%) had any PD, whereas 169 (11.7%) of mature neonates had any PD after 18 years' follow-up. The adjusted HR was 1.37 (95% CI 1.06–1.79) for premature born children and 1.44 (95% CI 1.22–1.69) for mature born children. Premature birth was associated with elevated risk of any PD after iGBS, and the interaction accounted for 6.8% of this effect (IC = 1.12 [95% CI −3.54 to 5.88]).

The CIP was 26.0% (95% CI 21.5–30.7) among exposed neonates whose mothers had a low educational level and 20.0% (95% CI 18.7–21.4) among mothers of a low educational level in the general population comparison cohort. (Table 3). The HR for PD in the low maternal education group was 1.44 (95% CI 1.16–1.78). Low maternal education was associated with greater PD risk than a middle educational level (IC = 1.49 [95% CI −2.64 to 5.62]), and the interaction accounted for 9.3% of this effect.

The CIP was 10.5% (95% CI 5.7–16.8) for exposed neonates whose mothers had a high educational level and 12.8% (95% CI 10.7–15.1) for children in the general comparison cohort whose mothers had a high educational level. High educational level, in comparison to low educational level, accounted for 24.4% of the interaction (IC = 4.38 [95% CI −0.60 to 9.36]).

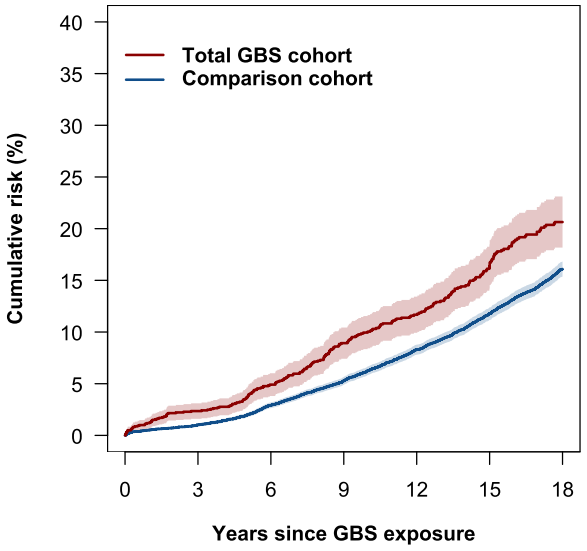
Among women with gestational diabetes who had a child with iGBS, the CIP of any PD was 40.7% (95% CI 23.4–57.4). In comparison, women with gestational diabetes in the comparison cohort had a CIP of any PD of 22% (95% CI 16.5–28.0). Gestational diabetes, with respect to an absence of gestational diabetes, accounted for 24.1% of the interaction (IC = 4.87 [95% CI −0.11 to 9.85]).

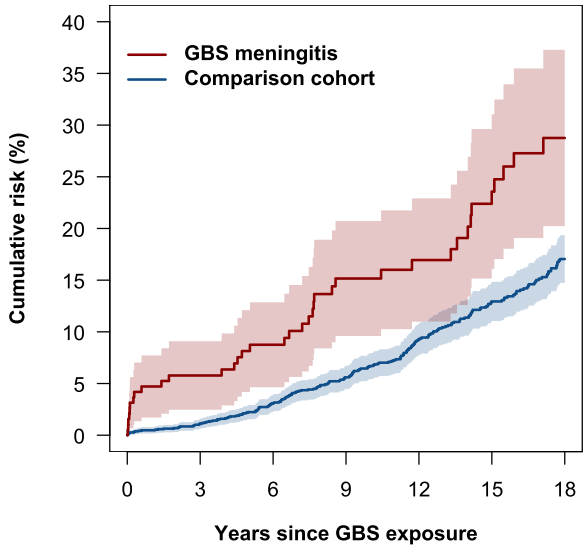
Discussion

The risk of any PD until adolescence was higher among children exposed to neonatal iGBS sepsis or meningitis than among children in the population comparison cohort. Subgroups of PDs where iGBS exposed children showed an increased risk included organic mental disorders; nervous and stress-related disorders; behavioral changes associated with physiological disturbances and physical factors; disorders of personality structure and behavior; intellectual disabilities; mental developmental disorders; and behavioral and emotional disturbances. Specific disorders of elevated risk included OCD, anxiety, autism, and ADHD. Effect measure modification analyses indicated an elevated risk of PDs among exposed children born prematurely, if their mother had gestational diabetes during pregnancy or a low educational level.

Our study contributes to the existing body of literature by including a large population of infants with a history of iGBS and a general population comparison cohort devoid of iGBS. This approach facilitates the evaluation of excess PDs and those attributable to the interactions between iGBS and sex, prematurity, gestational diabetes, or SEP. A novel finding in this study was the elevated long-term risk of PDs after iGBS sepsis, although less pronounced than that after iGBS meningitis. The results address a considerable knowledge gap regarding long-term outcomes following iGBS and offer new insights into the long-term effects of septicemia and the risk of psychiatric outcomes. Previously, neurodevelopmental impairments or -disorders have been assessed as composite outcomes (*i.e.*, mild, moderate or severe impairment),[8] whereas our study evaluated the specific psychiatric disorders separately. We identified associations with disorders typically manifesting in adolescence, such as anxiety. Additionally, we examined the risk of PDs to a sample of the general population where sepsis and meningitis caused by other pathogens can still occur, potentially biasing the findings towards the null.

In this context, our findings align with previous research investigating NDIs following iGBS sepsis and meningitis in both low-middle- and high-income settings in school-aged children. In a Norwegian study, where the health-care setting is very similar to Denmark, an elevated risk of ADHD, pervasive and specific developmental disorders, and neurodevelopmental disorders were found following iGBS (up to 1 year of age).[21] Although we found a less pronounced association between ADHD risk in this study, the association was in the same direction, and discrepancies might be explained by differences in PD diagnostic coding practices, the number of cases in each cohort, or the age at which participants were included in the study. In a multicounty study comprising 5 low- and





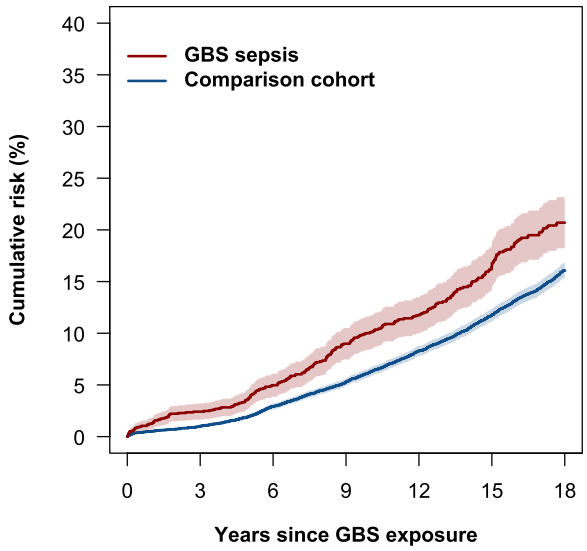


Fig. 1. a: Cumulative incidence of any psychiatric disorder by follow-up time in years. Cumulative risk of any psychiatric disorder during follow-up for the invasive group B *Streptococcus* cohort (red) and comparison cohort (blue). **b:** Cumulative incidence of any psychiatric disorder by follow-up time in years. Cumulative risk of any psychiatric disorder during follow-up for the invasive group B *Streptococcus* meningitis cohort (red) and corresponding comparison cohort (blue). **c:** Cumulative incidence of any psychiatric disorder by follow-up time in years. Cumulative risk of any psychiatric disorder during follow-up for the invasive group B *Streptococcus* sepsis cohort (red) and corresponding comparison cohort (blue).

middle-income countries, an elevated prevalence of overall behavioral problems, as well as heightened anxiety, attention, and conduct problems among iGBS survivors, was reported by the primary caregivers using the Child Behaviour Checklist compared to a matched comparison population devoid of iGBS.[22] Additionally, an increased risk of moderate/severe NDIs among iGBS survivors was found.[11] However, due to the small cohort size of this multicenter study, risk estimates were imprecise. The routinely and prospectively collected data, cross-country aligned psychiatric evaluation and diagnostics, and the size of the exposed cohort is therefore one of the main strength of this study.

The IR of PDs among iGBS exposed girls changed markedly after 10 years' follow-up compared to 18 years' follow-up. Previous research has indicated sex-based differences in neurodevelopmental impairment outcomes, which were observed predominantly in boys as compared to girls.[10,12] The predominance of early-onset disorders in males' contrast with the preponderance of adolescent-onset disorders in females.[23] A population-based study from Denmark revealed that among children with PDs, girls are diagnosed with any PD at later ages than boys.[21] The distinct difference between sexes appears to be influenced not by the exposure itself, but rather by inherent differences in sex and their clinical presentation, help-seeking behaviors, ethnic disparities and socioeconomic status.[24] Supporting these findings a study on rat offspring exposed to GBS in utero, GBS-infected females presented a hyperactive and disinhibited behavior pattern following puberty.[25]

Our findings contribute to the existing body of research indicating that iGBS poses a risk of NDIs in early childhood life, including an increased risk following premature birth.[26-28] Prematurity was found to interact with PD risk after neonatal iGBS, thus increasing the risk of any PD. Although we didn't have the power to divide our cohort of premature born children further, our results indicate that premature birth is not only a risk factor for early neurodevelopmental disorders but also long-term mental health disorders.

Limitations

Inaccurate coding of diagnoses in nationwide registries is an important validity concern: in this study we used discharge diagnostic codes to define iGBS; these codes might have included infants with iGBS not diagnosed by culture, and therefore some overlap between sepsis and meningitis cases may be present. Members of the comparison cohort may have experienced sepsis or meningitis caused by different pathogens. Therefore, further research is needed to evaluate the risk of PDs associated with other pathogens, to accurately characterize the severity of iGBS infections, and to facilitate comprehensive comparisons. Live birth bias could occur and introduce misclassification. Loss in late pregnancy and shortly after birth is multifactorial, and the risk is greatest among the premature born babies. We did not have information on iGBS in intrauterine deaths or stillbirths, allowing us to estimate any difference in the magnitude of live birth bias in this study. Although our findings align

Table 3
Effect modification by sex, prematurity, maternal education, and gestational diabetes of the association between invasive group B *Streptococcus* disease and psychiatric disorders during 18 years' follow-up.

	Comparison cohort Children with/ without psychiatric disorder, N	CIP (%) (95% CI)	IR (95% CI)	iGBS cohort Children with/ without psychiatric disorder, N	CIP (%) (95% CI)	IR (95% CI)	Effect modification on an additive scale[a] (*interaction contrast [95% CI]; AP [%]*)	HR (95% CI) for iGBS within strata
Sex								
Male	1013/7529	16.5 (15.5–17.5)	9.39	134/727	21.3	12.78	−0.38	1.37
Female	686/6117	16.0 (14.9–17.2)	(8.81–9.96)	98/589	(18.0–24.7)	(10.62–14.94)	(−3.85–3.08) NA	(1.14–1.64)
			7.69		21.0 (17.3–25.0)	11.46		1.50
			(7.11–8.27)			(9.19–13.72)		(1.22–1.86)
Gestational age								
< 37 weeks	459/2711	20.9	11.99	63/267	26.2	16.42	1.12	1.37
≥ 37 weeks	1240/10,935	(19.2–22.7)	(10.90–13.09)	169/1049	(20.6–32.2)	(12.36–20.47)	(−3.64–5.88)	(1.06–1.79)
		15.5	7.81		19.8	11.12	6.8%	1.44
		(14.3–15.9)	(7.37–8.24)		17.01–22.6)	(9.44–12.80)		(1.22–1.69)
Maternal education								
Middle	773/6759	14.6	7.73	107/665	19.8	11.04	1.49	1.44
Low	730/4195	(13.7–15.6)	(7.19–8.28)	96/376	(16.4–23.3)	(8.95–13.13)	(−2.64–5.62) 9.3%	(1.18–1.76)
		20.0	11.18		26.0	15.98		1.44
		(18.7–21.4)	(10.37–11.99)		(21.5–30.7)	(12.78–19.17)		(1.16–1.78)
Maternal education								
High	134/1786	12.8	6.13	14/176	10.5	6.55	4.38	1.09 (0.63–1.89)
Low	730/4195	(10.7–15.1)	(5.09–7.17)	96/376	(5.7–16.8)	(3.12–9.98)	(−0.60–9.36) 27.4%	1.44 (1.16–1.780)
		20.0	11.18		26.0	15.98		
		(18.7–21.4)	(10.37–11.99)		(21.5–30.7)	(12.78–19.17)		
Gestational diabetes								
No	1642/13,218	16.1	8.55	217/1260	20.5	11.46	4.87	1.80
Yes	57/428	(15.4–16.8)	(8.13–8.96)	15/56	(18.0–23.1)	(8.49–14.44)	(−0.11–9.85)	(1.02–3.19
		22.0 (16.5–28.0	11.86		40.7	20.23	24.1%	
			(10.28–13.44)		(23.4–57.4)	(9.99–30.47)		

[a] Measure of effect modification on an additive scale (95% CI); attributable proportion (AP, %). HR adjusted by sex, gestational age, year of birth, maternal income, maternal age and maternal psychiatric history.

with previous findings, some stratified analyses should be interpreted carefully, because of the limited number of outcome events.[14]

Granting validity data for the PCRR are sparse, the positive predictive value is 75–80% in certain subgroups of child and adolescent PDs.[29] Diagnosing psychiatric conditions in children can be difficult, and most conditions are diagnosed after the child's reaches a certain age. Furthermore, *e.g.*, bipolar disorders might initially be present but initially diagnosed as depression, introducing misclassification of the outcome in this study.

The central analytic problem in the interpretation of the association between iGBS and PD is distinguishing the degree to which the association is driven by a causal effect of the infection or if it arises from a range of potential confounding variables that predict both infection risk in the mother and psychiatric risk in the child. Matching to a comparison population with no history of iGBS and adjusting for additional variables, several confounding factors were effectively controlled. However, our results might have been affected by unmeasured confounding since PDs in children and adolescents is a highly inhomogeneous outcome: some disorders have strong heritability; some are accounted for by environmental and/or socioeconomic exposures; and some are associated with general medical conditions (*e.g.*, immunological, cardiovascular, metabolic, and neurological disorders).[30] Racial differences in the carriage of invasive group B *Streptococcus* have been reported but could not be accounted for in this study. Therefore, possible residual confounding is difficult to rule out. However, based on the strength of the associations and prior research, we believe that these unmeasured factors are not likely to completely disregard the direction of the association found in our study.

Maternal educational level at the time of iGBS was used as a proxy for SEP, although it might have introduced misclassification, because educational level might change during life, after giving birth, and with age. In contrast, low maternal educational level might reflect a predisposition to mental health disorders in the child,[31] which would be comparable between the mothers in the exposed and comparison cohort in this study. We did not retrieve information regarding paternal SEP, which might have strengthened our analyses.

Gestational diabetes has been associated with elevated risk of iGBS and subsequent PD risk in offspring.[32] In our study, gestational diabetes appeared to be an attributable risk factor for PDs in children affected by iGBS, but the number of outcomes were low and therefore the estimates were imprecise. A low maternal educational level was found to interact with PD risk after neonatal iGBS, thereby increasing the risk of any PD. These subgroups may be important in future research, and further studies are needed to explain the associations.

Conclusion

Our findings suggest that iGBS prevention should be considered in future clinical practice for pregnant people. Successful prevention of iGBS would decrease not only the mortality attributable to iGBS but also the long-term risk of psychiatric disorders caused by the infection.

Ethical considerations

All data were analyzed on the servers of Statistics Denmark by using encrypted identification numbers; no contact was made with any individuals. By Danish law, analyses of registry-based data do not require ethical review board application or informed consent from participants. The study was approved by the Danish Data Protection Agency (record no. 2015–57-0002). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology for cohort studies and the Strengthening the

Reporting of Observational Studies in Epidemiology for Newborn Infections (STROBE and STROBE-NI) guidelines.

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Author contributions

Dr Horváth-Puhó and Prof Sørensen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* All authors. *Acquisition, analysis, or interpretation of data:* Lykke, Lawn, Horváth-Puhó. *Drafting of the manuscript:* Lykke, Horváth-Puhó. *Critical revision of the manuscript for important intellectual content:* Lykke, Sørensen, Lawn. *Statistical analysis:* Lykke, Horváth-Puhó. *Obtained funding:* Lykke. *Supervision:* Sørensen, Lawn, Horváth-Puhó.

Declaration of Competing Interest

All authors have no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106463.

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