INTRODUCTION

Neonatal jaundice is characterised by a rise in serum bilirubin during the first days of life. In Sweden, 4.2% of all neonates receive treatment for it. It can be of haemolytic or non-haemolytic aetiology. Non-haemolytic neonatal jaundice is very frequent, particularly among preterm infants. More than 40% of preterm born neonates will develop non-haemolytic jaundice, mostly associated with liver immaturity, but may also be related to dehydration sepsis, poor

Abstract

Aim: Neonatal jaundice is associated with higher risk of attention deficit hyperactivity disorder (ADHD), but it is unclear if the association is influenced by genetic and other familial factors. In this large population-based study, we investigated the association between neonatal jaundice and ADHD while adjusting for familial factors.

Methods: We linked several Swedish registers to identify all singleton births without congenital malformations between 1992 and 2000 (n = 814,420, including 384,290 full siblings) and followed them up until 2009. We calculated hazard ratios (HRs) for the association between neonatal jaundice and ADHD, adjusting for pregnancy, delivery and neonatal characteristics including prematurity, and parental age and education. We repeated the analyses among siblings to adjust for shared familial factors.

Results: At a population level, children treated for neonatal jaundice had an increased risk of ADHD (adjusted HR (aHR): 1.13, 95% CI: 1.05-1.22). In the sibling comparisons, there was no clear association between neonatal jaundice and ADHD (aHR: 1.03, 95% CI: 0.82-1.29).

Conclusion: We found no evidence of an independent association between neonatal jaundice and ADHD within siblings in this large population-based study, suggesting that the association is probably influenced by shared familial factors, such as parental genetic and/or lifestyle effects.

KEYWORDS
attention deficit hyperactivity disorder, neonatal jaundice, register study, siblings
feeding or genetic conditions. Haemolytic neonatal jaundice is mostly due to maternal immunisation against foetal red blood cells, and can be associated with a faster rise of bilirubin levels than non-haemolytic neonatal jaundice. Both forms of jaundice may lead to bilirubin levels needing treatment, but the thresholds for treatment take the aetiology into account because of the faster evolution of haemolytic neonatal jaundice.3

Modern treatment of neonatal jaundice is based on repeated assessment of total serum bilirubin (TSB), especially among at-risk neonates, and rapid initiation of phototherapy treatment when the levels are above age-specific thresholds. When the non-invasive phototherapy treatment does not lead to a correct decrease of the TSB, exchange transfusion is an option.2

Furthermore, neonatal jaundice is usually considered as a benign phenomenon, but can in rare cases lead to a dramatic and irreversible neurologic complication, kernicterus.4 Neonatal jaundice might also be associated with minor neurologic dysfunction of the regions afflicted by kernicterus, that is, oculomotor and cochlear nuclei, and basal ganglia.5 This is important, as the dysfunction of the basal ganglia is implicated in the setting up of several conditions, including attention deficit hyperactivity disorder (ADHD).6

With a prevalence of at least 5%, ADHD is a common neurodevelopmental disorder.7 It is associated with functional impairments such as school dysfunction, peer problems, family conflict, poor occupational performance, injuries, antisocial behaviour and traffic accidents.6 Since ADHD is a disorder with child onset, environmental risk exposures are presumed to be early, and neonatal jaundice might influence ADHD by causing impairments of the basal ganglia.

Previous studies on the association between neonatal jaundice and ADHD have shown slightly varying results. In a large study based on a patient register in North Carolina, Kuzniewicz et al8 found no association between neonatal jaundice and ADHD (RR 1.08, 95% CI 0.91-1.28). Jangaard et al9 used a population-wide maternity register in Nova Scotia and found an increased risk of ADHD for infants with severe hyperbilirubinemia (aRR 1.8, 95% CI 1.1-3.3), but not for mild hyperbilirubinemia (aRR 1.1 95% CI 0.9-1.4). Based on a Taiwanese matched cohort study, Wei et al found a hazard ratio of 2.64 (95% CI 2.13-3.28) for ADHD in the neonatal jaundice group. Moreover, based on a small Finnish cohort, Hokkanen et al10 found a persistent effect at age 30, with consequences not only on self-rated ADHD score, but also on academic achievement and employment.

However, none of these studies investigated the effect of haemolytic jaundice, resulting mostly from maternal alloimmunisation, and non-haemolytic jaundice separately, which is important as the kinetics of bilirubin change may be different. Moreover, brain and blood-brain barrier immaturity may induce a particular sensitivity to serum bilirubin in preterm infants, although previous studies did not find increased risk for ADHD.12 Lastly, none of these studies were able to adjust for unmeasured familial factors (including both genetic and environmental influences). This is important as studies have shown that associations between several other prenatal risk factors and neurodevelopmental traits were related to residual unmeasured confounding rather than reflecting a true causal association.13

Adjusting for measured confounders is not sufficient to control for genetic confounding, and combined with the high heritability of ADHD,14 this highlights the need for designs taking shared familial factors into account.

The aim of our study was to assess, in a large national cohort with family data and long-term follow-up, if haemolytic and non-haemolytic neonatal jaundice is associated with a higher risk of ADHD in childhood. Furthermore, we wanted to assess whether the association differs in preterm and full-term infants.

2 | MATERIALS AND METHODS

2.1 | Data sources and study population

This study is based on a linkage of national population-based registers in Sweden. We used the unique personal identification numbers assigned to each individual in Sweden15 to link data from several national population-based registers in Sweden: the Swedish Medical Birth Register (MBR)16 contains information on all children born in Sweden since 1973; the Multi-Generation Register17 was used to identify family members of index persons; the National Patient Register (NPR) covers all inpatient hospital admissions since 1969 and outpatient care since 200118; the Prescribed Drug Register (PDR) with information on all filled prescriptions in Sweden since July 1, 200519; the Migration Register provides information about migration in and out of Sweden20; the Cause of Death Register comprises all deaths among Swedish residents since 195221; and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) contains information on factors such as education, occupation and income for all individuals who are 16 years of age and older since 1990.22

Based on the MBR, we identified all 890 328 children born in Sweden between 1992 and 2000. We excluded children who had severe congenital malformation, twins, were stillborn, who died or migrated before age 3 years, lacked any parent’s identification number, or received an ADHD diagnosis before age 3 years. After exclusions, the sample consisted of 814 420 children (see Figure 1 for a derivation of the analytical sample). Furthermore, in order to account for

Key notes

- Neonatal jaundice is associated with higher risk of attention deficit hyperactivity disorder (ADHD), but it is unclear if the association is influenced by genetic and other familial factors.
- Using Swedish population registers, this study explores the association of neonatal jaundice and ADHD, taking into account familial factors shared between siblings.
- Our findings suggest that neonatal jaundice is not likely an independent cause of ADHD.
shared familial factors, we identified a subsample consisting of all full siblings (384,290 children from 181,354 families).

The study was approved by the Regional Ethical Review Board in Stockholm (DNR 2009/939-31/5).

2.2 | Measures

2.2.1 | Exposure classification

We used both the MBR and the NPR to retrieve information on neonatal jaundice, as the combined use of the registers has been suggested in order to decrease problems with missing data for infant diagnoses in a validation of the MBR.16 Neonatal jaundice was defined based on International Classification of Diseases (ICD) codes, which identify jaundice requiring treatment. As previously reported,4 we categorised neonatal jaundice as follows: ICD-9 (773A-C) and ICD-10 (P550, P551, P558, P559, P588, P589) for haemolytic jaundice due to isoimmunisation and ICD-9 (774B-D, 774G) and ICD-10 (P590, P593, P599) for other/non-haemolytic jaundice, as well as a combined measure of any neonatal jaundice.

2.2.2 | Outcome classification

Individuals with a diagnosis of hyperkinetic disorder (ICD-9: 314; ICD-10: F90) in the NPR, or ADHD (DSM-IV-TR: 314; ICD-10: F90) in the Pastill Register; or who had at least one filled prescription for ADHD medication in PDR [methylphenidate (N06BA04); amphetamine (N06BA01); dexamphetamine (N06BA02); or atomoxetine (N06BA09)] were identified as ADHD cases. This strategy to identify individuals with ADHD from the registers has previously been shown to have high specificity.23

2.2.3 | Covariates

Information on neonatal characteristics included: severe complications of jaundice (hydrops fetalis [ICD-9: 778A, 773D; ICD-10: P560, P569, P832] and kernicterus [ICD-9: 773E, 774H; ICD-10: P570, P578, P579]); child’s sex; birth weight (small, average or large for gestational age according to the Swedish reference growth curve24); mode of delivery (vaginal/Caesarean section); gestational age (categorised as full term [≥37 completed gestational weeks], moderate/late preterm [32-36 completed gestational weeks], and extremely/very preterm [<32 completed gestational weeks]); and any neonatal infection (ICD-9: 771; ICD-10: P36, P38, P39, R7881). Parental characteristics included: parity (categorised as 1, 2 or ≥3); maternal smoking during pregnancy (any/none); maternal region of birth (Sweden/other Nordic country/non-Nordic country); any diagnosis of maternal pre-eclampsia or hypertension during pregnancy (ICD-9: 642E-642H; ICD-10: O13-O15); maternal infections during pregnancy (ICD-9: 770; ICD-10: P239; or any record of urinary tract infection in MBR); Caesarean section (both planned and emergency); maternal and paternal age at child’s birth (categorised in 5-year categories: <20, 20-25, 25-30, 30-35, and >35 years); and highest achieved parental education (≤9 years/>9 years).

2.3 | Statistical analyses

Study participants were followed from age 3 until first diagnosis of ADHD, migration, death or end of follow-up (December 31, 2009), whichever came first. Only children with complete information on all variables (n = 739,750) were included in the analyses (see Figure 1 for information on missing values). The association between neonatal jaundice and ADHD was estimated as hazard ratios (HR) with corresponding 95% confidence intervals (CI), using Cox proportional hazards models with cluster robust standard errors and attained age as the underlying timescale. We also analysed the effect of haemolytic and non-haemolytic jaundice separately (179 children had a record of both haemolytic and non-haemolytic jaundice, and were therefore excluded from this analysis). Potential confounders were addressed in the fully adjusted models by controlling for neonatal sex, birth weight for gestational age, and infections, gestational age, parity, maternal smoking, region of birth, pre-eclampsia or hypertension, maternal infections, Caesarean section and parental age at child’s birth and education.

Since adjusting for measured confounders is not sufficient to control for genetic confounding, all analyses were repeated in the subsample of siblings. Comparing full siblings adjusts for confounding from environmental and genetic factors shared by siblings.13 Therefore, in order for neonatal jaundice to have a causal effect on ADHD, we would expect to see an association both at a population level and when comparing risks in full siblings. An association that is found at a population level only, and not among siblings, would instead indicate that the association is due to shared familial factors. In sibling comparison analyses, we adjusted for neonatal sex,
infections, birth weight, gestational age, year of birth, parity, maternal smoking, pre-eclampsia or hypertension, infections, Caesarean section and parental age at child’s birth. See Supplementary Materials for a more detailed description of these analyses.

We also analysed the association between neonatal jaundice and ADHD separately for children born full term (≥37 completed gestational weeks) and preterm (<37 completed gestational weeks), since their brain sensitivity to high circulating bilirubin levels may be different.

As a sensitivity analysis, we repeated the analyses excluding children with severe complications of jaundice (kernicterus or hydrops fetalis; n = 55). Furthermore, in an additional sensitivity analysis, we restricted the follow-up time for older siblings after the follow-up time available for the youngest sibling in the family.

SAS version 9.4 for Windows (SAS Institute Inc) was used for all analyses.

### RESULTS

Descriptive characteristics of the study population are shown in Table 1. Children diagnosed with neonatal jaundice (n = 28 674) were more likely to be boys, small for gestational age, born preterm, delivered by Caesarean section and to be prenatally exposed to maternal pre-eclampsia or gestational hypertension. Moreover, of children diagnosed with neonatal jaundice, 3484 were diagnosed with haemolytic jaundice and 28 050 with non-haemolytic jaundice. The mean follow-up time was 10.69 years (standard deviation: 2.75). In total, 18 820 children received a diagnosis of ADHD during the follow-up time. In the subsample of siblings, 13 596 children were diagnosed with neonatal jaundice (1836 with haemolytic and 11 661 with non-haemolytic jaundice) and 8546 received a diagnosis of ADHD during the follow-up time.

The association between neonatal jaundice and ADHD is shown in Table 2. Overall, children with any neonatal jaundice had an

### Table 1 (Continued)

| Characteristic | Individuals with neonatal jaundice (n = 28 674), n (%) | Individuals without neonatal jaundice (n = 711 076), n (%) |
|----------------|--------------------------------------------------------|-------------------------------------------------------------|
| Maternal education (≤9 y) | Low maternal education (≤9 y) | 1481 (9.21) | 64 837 (9.38) |
| Low paternal education (≤9 y) | 2290 (14.24) | 99 360 (14.38) |
| Attention deficit hyperactivity disorder | 979 (3.41) | 17 841 (2.51) |
| Follow-up time from age 3 onwards, years | Mean (standard deviation) | 10.61 (2.77) | 10.70 (2.75) |
| Minimum | 0.01 | 0.00 |
| Maximum | 15.00 | 15.69 |

(Continues)
increased risk of being diagnosed with ADHD, compared to children without jaundice (HR: 1.38, 95% CI: 1.30-1.48). Adjusting for potential confounders resulted in an attenuated estimate (aHR: 1.13, 95% CI: 1.05-1.22). Haemolytic jaundice was not associated with ADHD in the crude model (HR: 1.04, 95% CI: 0.84-1.28), and adjusting for confounders resulted in a similar estimate (aHR: 1.09, 95% CI: 0.88-1.34). Children with non-haemolytic jaundice had about 43% increased risk of developing ADHD, compared to children without jaundice (HR: 1.43, 95% CI: 1.34-1.53). The risk estimate was attenuated in the fully adjusted model (aHR: 1.14, 95% CI: 1.06-1.23).

Results from sibling comparison analyses are shown in Table 2. Children with neonatal jaundice had a similar risk of ADHD compared to their siblings without jaundice (HR: 1.10, 95% CI: 0.91-1.32). No difference was observed for haemolytic jaundice (HR: 0.80, 95% CI: 0.46-1.36) or for non-haemolytic jaundice (HR: 1.15, 95% CI: 0.95-1.39). Adjusting for potential confounders attenuated the estimates further, albeit with slightly wider confidence intervals (Table 2).

Analysing the association separately for children born full term and preterm resulted in a similar pattern. In full-term children, there was a 17% increased risk of ADHD among children exposed to neonatal jaundice at a population level (aHR: 1.17, 95% CI: 1.07-1.28), whereas the estimate was completely attenuated in sibling comparisons (aHR: 1.00, 95% CI: 0.75-1.35). Analysing preterm children resulted in a similar pattern (aHR: 1.11 95% CI: 0.99-1.24 at a population level, and aHR: 0.70, 95% CI: 0.24-2.07 in sibling comparisons).

Excluding children treated for severe complications of jaundice (kernicterus or hydrops fetalis) did not change the estimates (Supplementary Table S1). Furthermore, restricting the follow-up time for older siblings after the follow-up time available for the youngest sibling in the family resulted in similar estimates (Supplementary Table S2).

4 | DISCUSSION

In this population-based study with long follow-up time, we found a weak association between neonatal jaundice and later risk of ADHD at a population level. However, this association was absent in the sibling analysis, which suggests that the association was not explained by jaundice as such, but rather by familial factors shared by siblings, such as parental, genetic and/or lifestyle factors.

Most previous studies on the association between neonatal jaundice and ADHD report weak to moderate associations, with RR varying from 1.08 to 1.80 and overlapping confidence intervals, which is similar to our findings at a population level. Only one study, by Wei et al, reported a stronger association, where children with neonatal jaundice had an increased risk of ADHD, with a hazard ratio of 2.64 (95% CI: 2.13-3.28).

There are some differences between our study and the study by Wei et al that might explain these different results at a population level, including differences in exposure definition and mean follow-up time. In Sweden, only treated neonatal jaundice is recorded. This strengthens the accuracy of the diagnosis, as mild jaundice is very frequent and not well defined. However, as noted by Wei et al, the incidence of severe hyperbilirubinemia is higher in Asian populations. Therefore, the exposure definition in Asian-based studies may, to a higher degree, capture ‘severe hyperbilirubinemia’, while our exposure definition in the Swedish cohort may, to a higher degree, reflect ‘moderate hyperbilirubinemia’. Furthermore, the mean follow-up in the study from Taiwan was 6.6 years, which is short with regard to ADHD and probably explains the very low rate of ADHD in the Taiwanese cohort (3.98 per 1000 among the neonatal jaundice population and 1.53 per 1000 among the non-neonatal jaundice cohort) compared to the rate in our population (2.4%) and the known worldwide prevalence of childhood ADHD (about 5%).

Finally, differences in results across studies might be explained by differences in the confounder adjustment. None of the previous studies adjusted for familial socio-economic factors, and our study was the first to adjust for shared familial factors using a sibling comparison design. The association between neonatal jaundice and ADHD attenuated completely in the sibling comparisons, suggesting that the apparent association was likely influenced by familial factors shared by siblings. Since ADHD is highly heritable, maternal genetic effects likely influence both the mother’s and her children’s risk of developing ADHD. Furthermore, there is a genetic overlap between ADHD, risk-taking behaviour and lifestyle factors, such as body mass index and alcohol use during pregnancy, which are also

| TABLE 2 | Crude and adjusted hazard ratios and 95% confidence intervals for the association between neonatal jaundice and attention deficit hyperactivity disorder |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| Neonatal jaundice | Population | Sibling comparison | Population | Sibling comparison |
| | Number of exposed cases | Crude HR (95% CI) | Adjusted* HR (95% CI) | Number of exposed cases | Crude HR (95% CI) | Adjusted* HR (95% CI) |
| Any | 979 | 1.38 (1.30-1.48) | 1.13 (1.05-1.22) | 391 | 1.10 (0.91-1.32) | 1.03 (0.82-1.29) |
| Haemolytic | 95 | 1.04 (0.84-1.28) | 1.09 (0.88-1.34) | 41 | 0.80 (0.46-1.36) | 0.75 (0.42-1.34) |
| Non-haemolytic | 888 | 1.43 (1.34-1.53) | 1.14 (1.06-1.23) | 353 | 1.15 (0.95-1.39) | 1.09 (0.86-1.38) |

*Model adjusted for neonatal sex, infections, birth weight, gestational age, parity, maternal smoking, maternal region of birth, pre-eclampsia or hypertension, maternal infections, Caesarean section, and parental age and education.

*Model adjusted for neonatal sex, infections birth weight, preterm birth and year of birth, parity, maternal smoking, pre-eclampsia or hypertension, maternal infections, Caesarean section and parental age.
associated with neonatal jaundice in the offspring. Therefore, if unmeasured familial factors are not taken into account it will seem like neonatal jaundice is a cause of ADHD, whereas the association instead is most likely explained by familial factors such as parental genetic and/or lifestyle effects.

We analysed the effect of haemolytic and non-haemolytic jaundice separately because haemolytic jaundice results in a more rapid rising of serum bilirubin, which we expected might be associated with a higher risk of ADHD. Contrary to our hypothesis, there was no clear difference between the two forms of jaundice regarding the risk of ADHD, neither at a population level nor in the sibling comparison.

Neonatal jaundice is often associated to other comorbidities such as preterm birth or neonatal infections, and since preterm birth has been associated with ADHD independent of unmeasured confounding, we considered the possibility that neonatal jaundice might be a mediator on the pathway between prematurity and ADHD. We therefore adjusted for neonatal infections and stratified analysis on preterm vs full-term births. The associations between neonatal jaundice and ADHD were similar among the two groups. These results further strengthen the interpretation that neonatal jaundice is not likely a causal risk factor for ADHD, and the association between prematurity and ADHD is likely explained by other mechanisms.

Our study has some limitations. As it is based on national registers, the internal validity depends on the quality of the register data. We have no access to the actual bilirubinemia measures of infants, the internal validity depends on the quality of the register of healthy term and near-term infants with serum bilirubin levels of ≥ 325 μmol/L (≥ 19 mg/dL) who were born in Nova Scotia, Canada, between 1994 and 2000. Pediatrics. 2008;122(1):119-124.

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CONFLICTS OF INTEREST
H Larsson has served as a speaker for Evolan Pharma and Shire and has received research grants from Shire; all outside the submitted work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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