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ORIGINAL ARTICLE

The Association Between Neonatal Jaundice and Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder: Findings From the Millennium Cohort Study

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Abstract

Objective To examine the association between neonatal jaundice requiring hospital treatment and autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in offspring by age 14 years.

Methods We used data from the Millennium Cohort Study, a nationally representative longitudinal study of children born in the UK. Data on neonatal jaundice requiring hospital treatment and potential confounders were maternal-reported and collected at 9-months postpartum. Data on ASD and ADHD were based on maternal reported doctor diagnosis. A diagnosis of ASD or ADHD were assumed if parents reported ASD or ADHD diagnosis at age 5, 7, 11 or 14 years. We conducted crude and adjusted logistic regression analyses to examine the association between neonatal jaundice and ASD and ADHD, adjusting for a range of socioeconomic, maternal and lifestyle factors.

Results 18,294 singleton babies were included at baseline. Of these, 1,254 (6.9%) experienced neonatal jaundice that required hospital treatment, and there were 575 (3.7%) cases of ASD and 497 (3.2%) cases of ADHD by age 14 years. Findings were consistent across all crude and adjusted models, with the fully adjusted odds ratio for the association between neonatal jaundice and ASD being 1.43 [95% CI:1.09 to 1.89] and 1.26 [95% CI:0.92, 1.74] for ADHD.

Conclusion Neonatal jaundice was associated with an increased odds of developing ASD by age 14 years. While the link between neonatal jaundice and ADHD did not reach statistical significance, the possibility of an association cannot be ruled out. Future studies should investigate the biological mechanisms that may mediate this relationship.

Keywords Neonatal jaundice · Autism spectrum disorder · Attention-deficit/hyperactivity disorder · Millennium Cohort Study

Introduction

Neonatal jaundice is a common condition in newborns, characterised by elevated bilirubin levels that cause yellowing of the skin and eyes. Neonatal jaundice remains one of the leading causes of hospital readmissions in neonates (Bawazeer et al., 2021). While most cases are benign and resolve without complications, severe hyperbilirubinemia can result in neurotoxicity and long-term neurological damage, such as kernicterus and acute bilirubin encephalopathy (Bozkurt et al., 2020; Qattea et al., 2022).

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are among the most common neurodevelopmental conditions with a prevalence of approximately 1–2% and 5% respectively (Faraone et al.,

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2024; Sacco et al., 2024). ASD is a complex neurodevelopmental disorder characterised by sensory sensitivities, delayed or unusual language development, restrictive and/or repetitive behaviours or interests and persistent difficulties in social communication and interaction (Lord et al., 2018). Symptoms typically develop in early childhood, generally emerging in the first two years of life and has an estimated 4:1 male to female ratio (Barbaro & Dissanayake, 2009; Sacco et al., 2024). While genetics are the strongest contributor to ASD, with a 70–90% heritability estimate (Genovese & Butler, 2023), environmental factors are believed to play a role in the development of ASD (Duque-Cartagena et al., 2024; Kim et al., 2019; Maimburg et al., 2010).

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with symptoms typically occurring at an early age, usually before the age of 12, and these include lack of concentration, lack of attention, difficulty in completing tasks, forgetfulness and disorganisation (Magnus et al., 2023). In general, males are more likely to be diagnosed with ADHD compared to females, with the same 4:1 male to female preponderance as ASD in clinical studies and 2:1 in population studies (Faraone et al., 2024; Martin, 2024).

In recent years, there has been growing interest in the potential link between neonatal jaundice and neurodevelopmental disorders, particularly ASD and ADHD. A 2020 meta-analysis examining data from 21 observational studies suggested that children with a history of neonatal jaundice had an over 30% increase in the likelihood of being diagnosed with ASD compared to those who did not have neonatal jaundice (Jenabi et al., 2020). However, a subsequent meta-analysis suggests that these findings were due to methodological limitations of included studies such as high risk of selection bias, and unmeasured maternal and socioeconomic confounding (Kujabi et al., 2021).

Additionally, while fewer studies have examined the association between neonatal jaundice and ADHD, inconsistencies have also been observed potentially due to differences in the confounder adjustment, with some studies reporting an association, while others not (Kuzniewicz et al., 2009; Le Ray et al., 2021; Wei et al., 2015).

Therefore, the objective of this study was to analyse the association between neonatal jaundice requiring hospital treatment and ASD and ADHD by age 14 years (in males and females combined and stratified by sex) using a nationally representative sample of children, and adjusting for several socioeconomic, maternal and lifestyle factors.

Methods

Study Design

We used data from the Millennium Cohort Study (MCS), a nationally representative longitudinal study of children born in the United Kingdom (UK). There have been seven sweeps of data collection to date that are available for analysis: age 9 months, 3 years, 5 years, 7 years, 11 years, 14 years and 17 years (with data available on ASD and ADHD at ages 5, 7, 11 and 14 years). A total of 18,818 children were recruited at baseline. This reduced to 15,808 at age 3 years, 15,460 at age 5 years, 14,043 at age 7 years, 13,469 at age 11 years, 11,872 at age 14 years and 10,757 at age 17 years (Figure S1) (Centre for Longitudinal Studies, 2019; Connelly & Platt, 2014).

Study Population

Children born in the UK between September 2000 and January 2002, and living in 398 areas in England, Scotland, Wales and Northern Ireland were eligible for inclusion in the MCS. Participants were identified using government child benefit records, a benefit with almost universal coverage. Certain subgroups of the population, such as children living in disadvantaged areas, children of ethnic minority backgrounds and children growing up in the smaller nations of the UK were intentionally oversampled to ensure that typically hard to reach populations were adequately represented. Families who may have moved were also tracked via a range of services such as post office, phone records, and through stable contacts to minimise bias due to loss to follow-up. Children remained eligible for inclusion if they were living in the UK at age 9 months. (Connelly & Platt, 2014).

Exposure: Neonatal Jaundice Requiring Hospital Treatment

Neonatal jaundice requiring hospital treatment was measured via questionnaire during the first wave of data collection when the children were 9 months old. Mothers were asked "*whether there was anything wrong with their child at the time of birth or at any time during the first week".* They were then instructed to choose all that apply from a list of illnesses. This list included, "*Jaundice requiring hospital treatment".* If the answer box to this was ticked "yes", then neonatal jaundice was assumed.

Outcome: ASD and ADHD

At each stage of data collection at ages 5, 7, 11 and 14 years, parents were asked if a doctor or healthcare professional had ever told them that their child had ASD or ADHD. If they answered yes at any stage of the data collection, the child was considered to have ASD or ADHD.

Confounding Variables

We considered the following potential confounders, all of which were measured at baseline, when children were aged 9-months: maternal age, maternal education, household income, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy body mass index (BMI), history of maternal depression or anxiety, infant sex and parity. These confounders were decided a priori using previous literature (Buckley et al., 2024; Gao et al., 2023; Pagnin et al., 2019; Tusa et al., 2024). *Maternal age* referred to the age of the mother at the time of birth and was measured in years. *Maternal education* referred to the highest academic qualification achieved and ranged from Diploma or higher (including a higher degree, first degree, or diploma in higher education), A-levels (~13 years of schooling), O-level (~11 years of schooling) to less than O-level. *Household income* was categorised according to the Organisation for Economic Co-operation and Development (OECD) income-weighted quintiles. *Maternal smoking status* referred to the number of cigarettes they smoked per day before pregnancy and the number smoked per day if they changed the amount smoked during pregnancy. This was recategorised as non-smoker, quit during pregnancy and smoked during pregnancy. *Maternal alcohol consumption during pregnancy* was categorised as yes/no. *Pre-pregnancy BMI* was self-reported and based on measured maternal weight and height prior to pregnancy. This was recategorised as underweight (<18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25–29.9 kg/m2) or obese (≥30 kg/m2) based on standard BMI categories defined by the World Health Organization (WHO). *History of maternal depression or anxiety* was based on self-reported data where mothers were asked whether a doctor ever told them that they suffer from depression or anxiety. This was then recategorised as yes/no. *Infant sex* was categorised as male/female. *Parity* was derived from the number of siblings in the household and was recategorised as primiparous or multiparous.

Statistical Analysis

Primary Analyses

Data were analysed using Stata SE version 18.0. Crude and adjusted logistic regression analysis estimated odds ratios (OR) and 95% confidence intervals (95% CI) to examine the association between neonatal jaundice requiring hospital treatment (independent variable) and ASD and ADHD (dependent variables) in the offspring by age 14 years. For each outcome, four logistic regression models were carried out to assess potential confounding according to socioeconomic, maternal and lifestyle factors separately: Model 1 (null model) was the unadjusted model (i.e., crude analysis). Model 2 controlled for socioeconomic factors including maternal age, maternal education and household income. Model 3 controlled for maternal and lifestyle factors including maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI, history of maternal depression or anxiety, infant sex and parity. Model 4 consisted of the fully adjusted analysis; this adjusted for all the socioeconomic factors included in Model 2 and the maternal and lifestyle factors included in Model 3.

Subgroup Analyses

As a higher proportion of males were exposed to neonatal jaundice requiring hospital treatment (7.8%) compared to females (5.8%), we stratified the main analyses by sex (categorised by male or female) and repeated models 1–4.

Sensitivity Analyses

We examined the impact of neonatal jaundice requiring hospital treatment (independent variable) combined with preterm birth (interaction effect) and examined their associations with ASD and ADHD (dependent variables). Three exposures of interest were included in this analysis: 1) those exposed to neonatal jaundice requiring hospital treatment only (excluding those born preterm) 2) those exposed to PTB only (excluding those exposed to neonatal jaundice), and 3) those exposed to both neonatal jaundice requiring hospital treatment and born preterm. Preterm birth was determined based on maternal reporting of the child's gestational age in days. This was translated to weeks and reclassified as <37 weeks' gestation and ≥37 weeks' gestation.

To examine the impact of comorbid cases, we analysed the association between neonatal jaundice requiring hospital treatment and a diagnosis of both ASD and ADHD. We compared baseline characteristics of the cohort with the characteristics of those remaining in the study at age

Table 1 Maternal and child characteristics at baseline (9 months) among Millennium Cohort Study participants ($n = 18,294$)

Characteristics	No neonatal jaundice	Neonatal jaundice
Total population, n (%)	17,040 (93.2)	1254 (6.8)
Autism spectrum disorder (ASD), n (%)		
No	13,912 (96.4)	1008 (94.2)
Yes	513 (3.6)	62 (5.8)
Attention-Deficit/Hyperactivity Disorder (ADHD), n (%)		
No	13,971 (96.9)	1025 (95.8)
Yes	452 (3.1)	45 (4.2)
Infant sex, n (%)		
Male	8676 (50.9)	739 (58.9)
Female	8364 (49.1)	515 (41.1)
Parity, n (%)		
Primiparous	6972 (40.9)	721 (57.5)
Multiparous	10,068 (59.1)	533 (42.5)
Maternal age, years, n (%)		
14–19	1447 (8.5)	137 (10.9)
20–29	8007 (47.0)	557 (44.4)
30–39	7176 (42.1)	536 (42.7)
40–49	359 (2.1)	24 (1.9)
Unknown/Missing	51 (0.3)	0 (0.0)
Maternal education, completed, n (%)		
Less than O-level	3381 (19.8)	176 (14.0)
O-level	7462 (43.8)	598 (47.7)
A-level	1575 (9.2)	121 (9.7)
Diploma or higher	4051 (23.8)	334 (26.6)
Unknown/Missing	571 (3.4)	25 (2.0)
Maternal smoking status, n (%)		
Non-smoker	10,913 (64.0)	810 (64.6)
Quit during pregnancy	2149 (12.6)	170 (13.5)
Smoked during pregnancy	3952 (23.2)	273 (21.8)
Unknown/Missing	26 (0.2)	1 (0.1)
Maternal alcohol consumption during pregnancy, n (%)		
No	12,072 (70.9)	917 (73.1)
Yes	4912 (28.8)	337 (26.9)
Unknown/Missing	56 (0.3)	0 (0.0)
Maternal BMI, n (%)		
Underweight	938 (5.5)	70 (5.6)
Normal	10,072 (59.1)	747 (59.6)
Overweight	3123 (18.3)	222 (17.7)
Obese	1326 (7.8)	118 (9.4)
Unknown/Missing	1581 (9.3)	97 (7.7)
Household income, n (%)		
Lowest quintile	4294 (25.2)	286 (22.8)
2nd quintile	3848 (22.6)	254 (20.2)
3rd quintile	3222 (18.9)	228 (18.2)
4th quintile	2932 (17.2)	239 (19.1)
Highest quintile	2665 (15.6)	244 (19.5)
Unknown/Missing	79 (0.5)	3 (0.2)
Maternal depression or anxiety (ever diagnosed), n (%)		
No	12,894 (75.7)	885 (70.6)
Yes	4121 (24.2)	369 (29.4)
Unknown/Missing	25 (0.1)	0 (0.0)

14 years according to exposure to neonatal jaundice. Additionally, we conducted a complete-case analysis, repeating primary analyses (models 1–4) among participants with complete-case data on exposure, outcome and confounders to examine the impact of loss to follow-up. We conducted comparative statistics comparing logistic regression models 1–4 to the model without neonatal jaundice requiring hospital treatment (i.e., Model 0) (Methods S1).

Results

Characteristics of Study Participants

A total of 18,294 singleton mother–child pairs with data on neonatal jaundice requiring hospital treatment were included in wave one of the Millennium Cohort Study. Of these, 1,254 (6.9%) of the children experienced neonatal jaundice requiring hospital treatment. A total of 15,493 respondents answered the question on whether a doctor or healthcare professional had ever told them that their child had ASD or ADHD by age 14 years. Of these, 575 (3.7%) reported a diagnosis of ASD (of which 62 were exposed to neonatal jaundice requiring hospital treatment) and 497 (3.2%) reported a diagnosis of ADHD (of which 45 were exposed to neonatal jaundice requiring hospital treatment). A total of 191 (1.2%) reported a diagnosis of both ASD and ADHD (of which 19 were exposed to neonatal jaundice requiring hospital treatment). While characteristics of those exposed and unexposed to neonatal jaundice requiring hospital treatment were broadly similar, those in the exposed group were more likely to be primiparous, had higher levels of maternal educational attainment, higher levels of income and more likely to be ever diagnosed with maternal depression or anxiety (Table 1).

Association Between Neonatal Jaundice Requiring Hospital Treatment and ASD/ADHD

In the unadjusted analysis (Model 1), the OR for the association between neonatal jaundice and ASD in offspring by age 14 years was 1.66 [95% CI 1.27 to 2.18]. This association remained statistically significant across all models, with a fully adjusted OR of 1.43 [95% CI 1.09 to 1.89] (Table 2).

In the unadjusted analysis, (Model 1), the OR for the association between neonatal jaundice and ADHD in offspring by age 14 years was 1.36 [95% CI 0.99 to 1.86]. After fully adjusting for confounders in Model 4, the association attenuated slightly (aOR 1.26 [95% 0.92 to 1.74]) (Table 2).

Table 2 Logistic regression examining the association between neonatal jaundice requiring hospital treatment and ASD and ADHD by age 14 years among Millennium Cohort Study participants

ASD	No. of exposed cases (total no. of cases)	Model 1 OR [95% CI]	Model 2 OR [95% CI]	Model 3 OR [95% CI]	Model 4 OR [95% CI]
Neonatal jaundice	62 (575)	1.66 [1.27 to 2.18]	1.67 [1.27 to 2.19]	1.43 [1.08 to 1.88]	1.43 [1.09 to 1.89]
Subgroup by infant sex					
Neonatal jaundice (males)	51 (445)	1.54 [1.14 to 2.09]	1.54 [1.13 to 2.09]	1.43 [1.05 to 1.95]	1.43 [1.05 to 1.96]
Neonatal jaundice (females)	11 (130)	1.51 [0.81 to 2.82]	1.49 [0.80 to 2.79]	1.40 [0.74 to 2.63]	1.40 [0.74 to 2.62]
ADHD					
Neonatal jaundice	45 (497)	1.36 [0.99 to 1.86]	1.43 [1.05 to 1.96]	1.21 [0.88 to 1.66]	1.26 [0.92 to 1.74]
Subgroup by infant sex					
Neonatal jaundice (males)	38 (394)	1.25 [0.89 to 1.77]	1.31 [0.92 to 1.85]	1.19 [0.84 to 1.69]	1.23 [0.86 to 1.75]
Neonatal jaundice (females)	7 (103)	1.18 [0.55 to 2.57]	1.23 [0.57 to 2.68]	1.25 [0.57 to 2.73]	1.27 [0.58 to 2.79]

Model 1: Crude analysis

Model 2: Adjusted for maternal age, maternal education, household income

Model 3: Adjusted for maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI, history of maternal depression or anxiety, infant sex and parity

Model 4: adjusted for both Model 2 and Model 3 combined

ASD autism spectrum disorder, *ADHD* attention-deficit/hyperactivity disorder, *OR* odds ratio, *95% CI* 95% confidence interval [lower to upper]

Association Between Neonatal Jaundice Requiring Hospital Treatment and ASD/ADHD in Males and Females

In male offspring (n = 51 exposed cases), the aOR for the association between neonatal jaundice and ASD by age 14 years was 1.43 [95% CI 1.05 to 1.96]. Among female offspring (n = 11 exposed cases), the aOR was similar but the result was not statistically significant, possibly due to the smaller number of exposed cases in comparison to male offspring (aOR 1.40 [95% CI 0.74 to 2.62]) (Table 2).

Among male offspring (n = 38 exposed cases), the aOR for the association between neonatal jaundice and ADHD by age 14 years was 1.23 [98% CI 0.86 to 1.75]. Among female offspring (n = 7 exposed cases), the association did not change significantly (aOR 1.27 [95% CI 0.58 to 2.79]) (Table 2).

Sensitivity Analyses

When preterm birth was excluded, the aOR for the association between neonatal jaundice and ASD was 1.43 [95% CI 1.03 to 1.98]. This increased slightly to 1.52 in those exposed to both neonatal jaundice and born preterm compared to those not exposed to neonatal jaundice and not born preterm (aOR 1.52 [95% CI 0.94 to 2.46]) (p for interaction: 0.09) (Table 3).

When preterm birth was excluded, the aOR for the association between neonatal jaundice and ADHD was 1.37 [95% CI 0.95 to 1.99]. This reduced to 1.10 [95% CI 0.60 to 1.99] among those exposed to both neonatal jaundice and born preterm compared to those not exposed to neonatal jaundice and not born preterm (p for interaction: 0.76) (Table 3).

The aOR for the association between neonatal jaundice requiring hospital treatment and a diagnosis of both ASD and ADHD was not materially different to our main findings (aOR 1.31 [95% CI 0.80 to 2.13]) (Table S1). Supplementary Table S2 compares the baseline characteristics of the cohort to those remaining in the study at age 14 years based on exposure to neonatal jaundice with characteristics similar at both time points. Results of the complete-case analysis for ASD were similar to the main findings for ASD (aOR: 1.51 [95% CI: 1.14 to 2.03]) and for ADHD (aOR: 1.37 [95% CI: 0.99 to 1.91]) (Table S3). Results of the comparative statistics comparing logistic regression models 1–4 to the model without neonatal jaundice requiring hospital treatment (i.e., Model 0) are outlined in Results S1.

Discussion

This study analysed the association between neonatal jaundice requiring hospital treatment and diagnosis of ASD and ADHD in adolescent offspring by age 14 years (in males and females combined and stratified by sex), yielding three

Table 3 Sensitivity analyses examining the association between neonatal jaundice requiring hospital treatment combined with preterm birth and ASD and ADHD by age 14 years among Millennium Cohort Study participants

ASD	No. of exposed cases (total no. of cases)	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]	P for interaction
Neonatal jaundice and preterm birth[c]				
Neonatal jaundice only	43 (518)	1.70 (1.24 to 2.35)	1.43 (1.03 to 1.98)	
Preterm birth only	34 (509)	1.36 (0.95 to 1.94)	1.21 (0.84 to 1.74)	
Both	19 (53)	1.71 (1.07 to 2.74)	1.52 (0.94 to 2.46)	0.09
ADHD				
Neonatal jaundice and preterm birth[c]				
Neonatal jaundice only	33 (445)	1.49 (1.04 to 2.15)	1.37 (0.95 to 1.99)	
Preterm birth only	31 (443)	1.43 (0.98 to 2.07)	1.21 (0.83 to 1.77)	
Both	12 (43)	1.22 (0.68 to 2.20)	1.10 (0.60 to 1.99)	0.76

[a]Crude analysis

[b]Adjusted for maternal age, maternal education, household income, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI, history of maternal depression or anxiety, infant sex and parity

[c]Reference = not exposed to neonatal jaundice and not born preterm

OR odds ratio, *CI* confidence interval, *SGA* small for gestational age, *HDP* hypertensive disorders of pregnancy

principal findings. Firstly, neonatal jaundice was associated with a 43% increase in the odds of ASD in offspring by age 14 years after controlling for several maternal, lifestyle and socioeconomic factors. Secondly, neonatal jaundice was associated with a 26% increase in the odds of ADHD in offspring by age 14 years, albeit this result was not statistically significant after controlling for potential confounders. Thirdly, these results remained consistent when stratified by sex.

Our findings align with several prior studies reporting a positive association between neonatal jaundice and the likelihood of ASD. A previous study conducted in Taiwan using population-based data reported elevated ASD odds among children with a history of neonatal jaundice (hazard ratio (HR): 1.30, 95% CI: 1.01 to 1.69) (Chou et al., 2023), while a US case–control study suggested that neonatal jaundice was associated with ASD in those born preterm only (OR: 1.83, 95% CI: 1.05 to 3.19) (Cordero et al., 2020).

However, not all studies have supported this link. For example, a systematic review by Kujabi et al. (2021) concluded little evidence of an association between neonatal jaundice and ASD when they limited their meta-analysis to six low-risk of bias studies only (cohort studies risk ratio: 1.09, 95% CI: 0.99 to 1.20), (case–control studies OR: 1.29, 95% CI: 0.95 to 1.76). Additionally, Chen et al. (2023), using two-sample Mendelian randomisation, did not observe an association between neonatal jaundice (OR: 1.00, 95% CI: 0.97 to 1.02), direct bilirubin (OR: 0.97, 95% CI: 0.88 to 1.06) or indirect bilirubin (OR: 1.07, 95% CI: 0.88 to 1.30) and ASD. However, authors concluded that data from a larger sample may be needed as they did not reach their target statistical power of 80%. Our use of a large, contemporary UK cohort and adjustment for potential confounders provides further support for a potential link between jaundice and the odds of ASD. However, it is not possible to rule out the presence of unmeasured or residual confounding.

Regarding ADHD, our findings are somewhat consistent with previous studies. Two Taiwanese cohorts (Chou et al., 2023; Wei et al., 2015) reported an association between jaundice and ADHD (HR: 1.32, 95% CI: 1.18 to 1.48 and HR: 2.53, 95% CI: 2.23 to 2.88, respectively). Similarly, a Lebanese case–control study also reported a potential link, however the latter was limited by a small sample size (OR: 5.02, 95% CI: 1.43 to 17.53) (Assaf et al., 2024). In contrast, Kuzniewicz et al. (2009) found little evidence of an association between total serum bilirubin (TSB) levels and later ADHD (HR: 1.07, 95% CI: 0.90 to 1.27). Furthermore, using Swedish national registry data, Le Ray et al. (2021) found an increased likelihood of ADHD among children with history of neonatal jaundice (HR: 1.13, 95% CI: 1.05 to 1.22). However, this association attenuated in sibling-matched models, suggesting potential familial confounding may play a role in any neonatal jaundice and ADHD relationship (HR: 1.03, 95% CI: 0.82 to 1.29).

These finding raise questions of how and why neonatal jaundice may increase the likelihood of ASD or ADHD in the offspring. Around the time of birth, the human brain undergoes rapid synaptogenesis and experience-dependent synaptic pruning, resulting in an overabundance of neural connections that are selectively refined by environmental input. These processes are critical for laying the structural and functional foundations of lifelong cognitive, emotional, and sensory development (Gibb & Kovalchuk, 2018). However, unconjugated bilirubin has been shown to significantly disrupt several neurodevelopmental processes central to this period. Specifically, in vitro studies have demonstrated that unconjugated bilirubin reduces neurite length and synapse

density in neurons derived from forebrain neural progenitor cells (Zhang et al., 2024). Similarly, in a rat model of bilirubin encephalopathy, bilirubin exposure decreased apical dendritic length and arborization in newly generated hippocampal neurons (DCX+), potentially through down-regulation of brain-derived neurotrophic factor (BDNF) expression (Zhang et al., 2024). Further preclinical research has identified alterations in the expression of twelve genes implicated in key neurodevelopmental processes during early brain maturation (Llido et al., 2025). Among these is *Grm1*, which encodes metabotropic glutamate receptor 1 (mGluR1), a mediator of excitatory neurotransmission in the central nervous system. Notably, imbalances in excitatory and inhibitory synaptic transmission have been hypothesized to contribute to ASD symptoms (Ghatak et al., 2021; Horder et al., 2018). Importantly, studies also suggest that bilirubin concentration alone does not reliably predict the extent of these changes (Llido et al., 2025), indicating that other biological or environmental factors may modulate vulnerability to bilirubin-induced alterations. These findings support a model in which excess bilirubin exposure during a critical window of early brain development may subtly alter neurodevelopmental trajectories by disrupting key molecular and cellular processes. However, the vast majority of infants with neonatal jaundice experience typical neurodevelopment, suggesting that bilirubin alone is not sufficient to cause long-term impairment in most cases. This raises the possibility that exposure to excess bilirubin may act as an additive or interacting risk factor in individuals with predisposing genetic vulnerabilities, but this requires further investigation.

Study Strengths and Limitations

This study had several strengths. First, we used data from a large, nationally representative cohort of children born in the UK from 2000 to 2002. Secondly, this cohort contains information on socioeconomic and maternal factors which have not been consistently controlled for in previous studies (Kujabi et al., 2021). This allowed for the control of multiple potential confounders including maternal age and education, household income, maternal smoking status and alcohol consumption during pregnancy, pre-pregnancy BMI, history of maternal depression or anxiety, infant sex and parity.

There were also a number of limitations in this study that should be noted. First, data on potential confounders were self-reported by the mother at nine months postpartum and therefore subject to recall bias. However, studies have demonstrated considerable agreement between self-reported maternal and lifestyle factors and medical records between 6 months and 4–9 years post-delivery (Rice et al., 2007; Rolan et al., 2022). Second, the exposure of neonatal jaundice was potentially subject to recall bias as exposure data was collected at 9-months postpartum. However, when measuring neonatal jaundice, mothers were asked whether there was anything wrong with their child at the time of birth or at any time during the first week and were given a list of which included "*Jaundice requiring hospital treatment".* The requirement of hospital treatment may improve recall, and the event may be more memorable to the mother. Furthermore, the prevalence of neonatal jaundice in the current study (7%) is similar to that observed in a previous study by Le Ray et al. (4%) which used International Classification of Diseases (ICD) codes to identify jaundice requiring treatment (Le Ray et al., 2021). Third, as neonatal jaundice was categorised as jaundice requiring hospital treatment, those who had jaundice and did not attend a hospital may have been misclassified. Furthermore, the rate of exposure in the current study (7%) underrepresents infants with mild to moderate jaundice. However, if the observed association was causal, this would likely bias our results towards the null. Fourth, while multiple published studies include parent-reported neurodevelopmental disorders (Blumberg et al., 2013; Curran et al., 2018; Russell et al., 2014) reporting of ASD and ADHD may be limited by recall bias, potentially introducing misclassification of our outcomes. Fifth, the diagnostic assessments for both ASD and ADHD did not include confirmation from diagnostic tools such as the Autism Diagnostic Observation Schedule (ADOS) or the Autism Diagnostic Interview-Revised (ADI-R). However, the prevalence of parent-reported ASD within this cohort (3.7%) is comparable to English primary care data for 2020–2021 (O'Nions et al., 2023). While the prevalence of parent-reported ADHD in the current study (3.2%) falls within the range of UK-rates (3–5%) reported by the NHS (National Health Service, 2018), this is likely underestimated. Sixth, there is a lack of data on family history of ASD and ADHD, and genetic sequencing within the participants is not available and could not be controlled for in the current study. Furthermore, information on potentially important confounders including Apgar scores, folic acid supplementation during pregnancy, paracetamol or other medication use during pregnancy was not available. Therefore, the role that these data may play in any observed associations should be considered in future research. Seventh, loss to follow-up may have introduced attrition bias and limited generalizability of results. For example, the total population at age 9 months was 18,818 children. This was reduced to 11,872 at age 14 years. Participation in longitudinal research can be influenced by several factors, and children with behavioural disorders may be more likely to be lost to follow-up. Therefore, this may have biased our results towards the null (Bogdan et al., 2023; Wolke et al.,

2009). Finally, neonatal jaundice was not classified as haemolytic or non-haemolytic jaundice. Haemolytic and non-haemolytic jaundice differ from each other in aetiology and by distinguishing them from one another in future studies, more meaningful associations could be drawn.

Conclusion

Neonatal jaundice requiring treatment was associated with an increased odds of ASD in the offspring by age 14 years. Despite accounting for a wide range of potential confounding factors, it is not possible to rule out the presence of residual or unmeasured confounding. Further research should investigate the biological mechanisms implicated in this study. Adopting a multidisciplinary approach may strengthen the ability to identify causal links between neonatal jaundice and later neurodevelopmental outcomes, thereby supporting the development of more targeted early interventions to improve long-term outcomes.

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Declarations

Conflict of interest All authors declare that they have no affiliations/involvement with any financial or non-financial interest in the subject matter discussed in this manuscript.

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