Received: 2 December 2021 | Revised: 7 October 2022 | Accepted: 22 October 2022

https://doi.org/10.1016/j.rpth.2022.100013

ORIGINAL ARTICLE

Autism spectrum disorders in boys at a major UK hemophilia center: prevalence and risk factors

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Funding information
Melanie Bladen and Nicola Thorpe received an educational grant from Pfizer to fund this research.

Handling Editor: M Sholzberg

Abstract

Background: Autism spectrum disorders (ASDs) are diagnosed by social communication difficulties strong, narrow interests, and repetitive stereotyped behavior. An apparently-elevated prevalence of ASD at a major UK hemophilia center warranted investigation.

Objectives: To screen boys with hemophilia for difficulties in social communication and executive function and identify the prevalence and risk factors for ASD.

Methods: Parents of boys with hemophilia aged 5 to 16 years completed the Social Communication Questionnaire, Children's Communication Checklist, and the Behavior Rating Inventory of executive function. Prevalence and potential risk factors for ASD were evaluated. Boys with an existing diagnosis of ASD did not complete questionnaires, but were included in the prevalence analysis.

Results: Negative scores on all 3 questionnaires were observed for 60 of 79 boys. Positive scores on 1, 2, and 3 questionnaires were seen in 12 of 79, 3 of 79, and 4 of 79 boys, respectively. In addition to the 11 of 214 boys with a prior ASD diagnosis, 3 further boys were diagnosed with ASD, yielding a prevalence of 14 (6.5%) of 214, greater than that of boys in the UK general population. Premature birth was linked to having ASD, but did not fully explain the increased prevalence with more boys born <37 weeks scoring positively on the Social Communications Questionnaire and Children's Communication Checklist compared with those born at term.

Conclusion: This study identified an increased prevalence of ASD at 1 UK hemophilia center. Prematurity was identified as a risk factor but did not fully explain the higher prevalence of ASD. Further investigation in the wider national/global hemophilia communities is warranted to determine whether this is an isolated finding.

KEYWORDS
autism spectrum disorder, child, communication, executive function, hemophilia A

Essentials

- Autism spectrum disorder (ASD) may occur in people with hemophilia.
- In this cohort, ASD occurred in 6.5% of boys with hemophilia.
- Hemophilia type, severity, or inhibitors were not associated with ASD, but prematurity was.
- Future research should evaluate reasons for increased prevalence of ASD in hemophilia.

1 | INTRODUCTION

Autism spectrum disorders (ASDs) are diagnosed by the presence of social communication difficulties, strong, narrow interests, and repetitive stereotyped behavior. Generally, ASDs persist across the life span and can be heritable [1–3]. The prevalence of ASD is variable internationally and very dependent on assessment and diagnostic criteria applied in different countries or regions [4]. In the UK, there are National Institute for Clinical Excellence guidelines for autism diagnostic assessments, which recommend detailed questions about parent's/carer's concerns, a developmental history, assessment of social skills, medical history, consideration of differential diagnosis, development of profile of young person's strengths and needs, and communication of assessment findings.

Diagnostic criteria in the UK are based on developmental and behavioral features consistent with ICD-11 (International Classification of Diseases, 11th Revision) or DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). Current National Health Service (NHS) practice varies and there is no evidence base or established clinical guidelines to aid more accurate assessment or diagnosis of ASD [1]. The most reliable and credible recent prevalence data come from a national survey published in 2017 by NHS Digital and the Office for National Statistics. These data put the prevalence of ASD in the UK at 1.2% in children between 5 and 19 years of age, with boys more commonly affected (1.9%) than girls (0.4%) [5]. These findings are also consistent with other published literature after 2010, which suggests overall ASD prevalence in children and young people in the UK rests between 1.0% and 1.7% [6–9].

Risk factors are thought to be multifactorial, with genetic and hormonal factors contributing to the bias toward boys [3]. Other factors associated with an increased prevalence include: a sibling with ASD; birth defects; trauma resulting in central nervous system dysfunction, eg, intracranial hemorrhage (ICH) and prematurity at <35 weeks [1]. Risk of ASD has been reported to increase with decreasing gestational age [10].

Hemophilia is an "X" chromosome-linked genetic disease, characterized by missing or low levels of blood clotting factor VIII or IX (hemophilia A or B, respectively). Bleeding can occur anywhere in the body, including joints, muscles, and the brain. Disease severity, classified as mild, moderate or severe, correlates with the percentage of normal levels of clotting factor present (mild, 5%-40%; moderate, 1%-5%; and severe, <1%). Factor replacement therapy is the gold standard treatment, given via regular injections to prevent bleeds (prophylaxis); and/or in response to an injury or suspected bleed (on demand), although extended half-life and nonfactor therapies [11] are now available requiring less frequent administration. Children with hemophilia can develop an "inhibitor," whereby they make antibodies, which reduce treatment efficacy. In recent years, treatment has significantly reduced annual bleed rates and improved quality of life for children and young people with hemophilia, bringing their functional ability more in-line with unaffected peers, although little is known about neuropsychological functioning [12].

A review paper on neuropsychological functioning in boys with hemophilia suggested a higher prevalence of attention-deficit/hyperactivity disorder (ADHD) and learning difficulties than in the general population [12]. Another study reported that boys with hemophilia aged 6 to 16 years and no history of ICH, brain injury or intellectual disability had impaired behavior regulation and executive function (EF) compared with controls, resulting in a lack of focus, inability to control emotions, follow instructions, and problem solve [13–15] (attributes common in ASD) [16]. Furthermore, boys with hemophilia and a history of ICH have also been identified as having impaired EF compared with controls [14,15]. No publications to date have reported any relationship between hemophilia and ASD. Clinical observation of an apparently-elevated prevalence of ASD at Great Ormond Street Hospital for Children NHS Foundation Trust UK (GOSH) warranted further investigation. The aims of this study were to evaluate performance of boys with hemophilia on 3 standardized questionnaires screening for difficulties in social communication and EF, and to investigate the prevalence of ASD in boys with hemophilia at GOSH and explore factors that might be associated with the diagnosis.

2 | METHODS

Ethical approval was granted by London Bloomsbury Research Ethics Committee (10MH17). Parents of boys aged 5 to 16 years with mild, moderate, and severe hemophilia A and B were invited to participate in this study by letter. Age-appropriate written information sheets were provided for all boys with hemophilia. Written consent from the parents and assent from the boys was obtained in all cases.

Data extracted from medical records included date of birth, birth history, gestation (prematurity classified as <37 weeks), mode of delivery (classified as vaginal delivery, vaginal instrumental, planned, or unplanned caesarean section), history of ICH, hemophilia diagnosis and severity, history of an inhibitor (HoI), coexisting medical history, ASD diagnosis, and age at diagnosis.

Recruited parents were asked to complete 3 questionnaires that screened for attributes prevalent in children with ASD. The questionnaires, which took about an hour to complete in total, addressed the

following: 1) difficulties in social interaction and behavior (Social Communications Questionnaire [SCQ]), 2) pragmatic difficulties, including initiating conversations, sequencing narratives in a coherent way and using conversational contexts (Children's Communication Checklist [CCC]), and 3) EF (the Behavior Rating Inventory of Executive Functioning [BRIEF]). EF is an umbrella term used to describe a collection of functions responsible for guiding, directing, and managing cognitive, emotional and behavioral functions particularly during active, and novel problem solving. If the threshold on all 3 questionnaires was met, boys, with consent of their parents, were offered a referral for neuropsychological assessment. Screening questionnaires are not diagnostic of ASD. Diagnosis of ASD requires in-depth information from multiple sources: parents and caregivers description of child development; school education assessment and observation and assessment by professionals. The screening questionnaires included were used as part of routine care in tertiary diagnostic clinics at GOSH.

Boys with a preexisting diagnosis of ASD (n = 11) were exempt from the questionnaire component of the study but were included in the prevalence analysis.

2.1 | SCQ

The SCQ is a 40-item yes/no parent-report questionnaire for evaluating children aged>4 years, whose mental age exceeds 2 years [17].

The items on the questionnaire were originally derived from the revised version of the Autism Diagnostic Interview [18]; that is used in clinical practice for diagnosis of ASD. The SCQ has high discriminant ability in differentiating ASD symptomatology from other associated behavioral and developmental difficulties [15]. A total score ≥15 is the threshold at which the likelihood of an individual having ASD means that further assessment is warranted. This threshold is based on a standardization sample in the development of the instrument [19]. In this sample, the SCQ with the cut-off at 15 showed a sensitivity of 0.85 and specificity of 0.75. The mean score for children with autism in the sample was 24.2, although a significant minority had scores approximately 15 and therefore a higher cut-off would have produced a high number of false negatives. The questionnaire has 2 versions; the Current version and Lifetime version. The Lifetime version was used in the study because this is typically used for diagnostic screening purposes, and concerns behaviors that have occurred at any point in the child's life [20].

2.2 | CCC

This 70-item questionnaire addressing language and communication can be completed by a parent or teacher in approximately 10 to 15 minutes [21]. The CCC provides subscale and pragmatic composite scores for each child. A composite score of <132 indicates a pragmatic language impairment. The checklist was developed to identify whether there is a subgroup of children with difficulties primarily affecting semantics and pragmatics within children with language impairments. (Semantic and pragmatic difficulties refers to difficulties with language content and use, eg, unusual word choices, overliteral response to questions, poor maintenance of the conversation topic, and answering beside the point of a question. Language impairment refers to difficulties with language form, including grammar and speech sounds, eg, immature sentence structure, unintelligible speech.) The checklist may indicate when a diagnosis of autistic disorder should be considered.

This checklist was developed from ratings for 76 children aged 7 to 9 years who had received special education for language impairment. The composite pragmatic impairment scale is formed from 5 subscales concerned with pragmatic aspects of communication (eg, inappropriate initiation, stereotyped conversation). The composite pragmatic impairment scale had interrater reliability (between 2 raters, usually teacher and a speech and language therapist) and internal consistency of approximately 0.80. This composite discriminated between children with a diagnosis of semantic-pragmatic disorder and those with other types of language impairment. *The majority of children with pragmatic language impairments in the test development did not have any evidence of restricted interests or significant difficulties with social relationships (although it should be noted children with a diagnosis of autism were excluded from the study).*

Bishop and Baird [22] studied whether the CCC provided valid and reliable information when completed by parents and a professional who knew the child well for 5 to 17-year-old referrals to a tertiary developmental pediatric center. Reliability, as measured by internal consistency, was ≥0.7 for most scales. Correlations between ratings for parents and professionals were in the range of 0.30 to 0.58 for individual pragmatic scales, with a correlation of 0.46 (n = 82) for the pragmatic composite. The typically developing comparison group with no developmental disorders (n = 31) scored close to the test ceiling on most scales. A pragmatic composite score of 140 was the lowest score obtained by a child in the normal comparison group [21–23].

(The second version—CCC 2—was published in 2003 and it screens for likelihood of a language disorder and/or ASD).

2.3 | BRIEF

The BRIEF questionnaire is widely used in schools and clinical settings; in typically developing children and those with medical or developmental disorders and is a valid and reliable tool for parents or teachers of children aged 5 to 18 years. It contains 86 items measuring different aspects of EF (inhibit, shift, emotional control, initiate, working memory, plan/organize, and organization of materials) [24,25], and are rated on a 3-point Likert scale, based on occurrence of the child's behavior: "never" (1 point), "sometimes" (2 points), or "often" (3 points). The Behavior Regulation Index and the Metacognitive Index combine to make the Global Executive Composite (GEC), an overall composite score of EF. A GEC threshold score ≥65 was considered positive. The BRIEF self-report and parent forms have demonstrated internal consistency reliability, convergent validity, and construct validity [25,26]. The findings suggest that children with ASD exhibit significantly greater EF challenges, as measured by the BRIEF-2, across scales and indices, relative to children without ASD [27].

2.4 | Statistical analysis

Data were summarized as mean and SD for normally distributed data, whereas median and interquartile ranges were used for skewed data and small subgroups. Comparisons between groups were made with 2 sample independent *t*-tests or Mann–Whitney U-tests, as appropriate. For each of the validated questionnaires, boys were dichotomized into those who did and did not reach the clinical screening threshold, as defined by the relevant questionnaire manuals. Categorical data were described as frequencies with percentages, and comparisons between groups made with Chi-squared tests; Fisher exact tests were used for small frequencies, where appropriate.

Prevalence of ASD in the study population was compared with recent and current UK data for ASD prevalence.

3 | RESULTS

There were 214 boys under care at GOSH with mild, moderate, or severe hemophilia, aged between 4.4 and 20.4 years (mean ± SD age, 12.4 ± 3.9 years): 175 (82%) with hemophilia A, 36 (17%) with hemophilia B, and 3 (1%) with hemophilia B Leyden. HoI was present in 13 (6%) of 214. Birth history was available in 93 of 214 boys, of whom 11 (12%) were born prematurely (<37 weeks). There were 17 (7.9%) of 214 boys with a history of ICH; 10 sustained during the neonatal period and 7 between the ages of 4 months to 5 years.

There were 11 of 214 boys with ASD, 3 of whom attended special schools, and all of whom were diagnosed via their local health care service. These boys were excused from completing the questionnaires, but were included in the prevalence analysis. A total of 82 of 214 families returned questionnaires for boys mean ± SD age 12.2 ± 3.6, range 5.7 to 12.4 years, a cohort that was representative of the larger population at GOSH (65 [79%] of 82 with hemophilia A, 15 [18%] of 82 with hemophilia B, and 2 [2%] with hemophilia B Leyden) (see Table 1). Of the 82 families who completed the questionnaires, there were 8 families in which >1 child completed the questionnaires: 5 families had 2 children complete questionnaires; 3 families had 3 children complete questionnaires. None of these families had a child identified as requiring further assessment following questionnaire analysis. There were 4 other families in which a sibling of a boy with hemophilia previously diagnosed with ASD completed the questionnaires. None of these siblings were identified as requiring further assessment.

Three questionnaires involving separate families were incomplete (1 CCC and 2 BRIEF). The screens on their completed questionnaires were negative. All questionnaires for the remaining 79 of 82 families were fully completed. Negative scores on all 3 questionnaires were observed for 60 (67%) of 79 of the boys. Twelve boys had a positive screen on 1 questionnaire only (SCQ, 1 [1%] of 79, CCC, 3 [4%] of 79, and BRIEF, 8 [10%] of 79). Three boys had a positive screen on 2 of the 3 questionnaires (SCQ and CCC, 1 [1%] of 79; CCC and BRIEF, 2 [3%] of 79). Four boys scored positively for all 3 questionnaires and, after being offered referral for neuropsychological assessment, 1 was diagnosed with ASD and 2 with ADHD. The family of the fourth boy declined further assessment. This boy has not been included in the ASD prevalence analysis. In addition, 2 other boys received an independent diagnosis of ASD during the study period. One was a study participant, but only scored positively on 1 questionnaire (CCC), so was not offered referral as part of this study. He received his diagnosis after a referral from local services to a community pediatrician. The other had declined participation in the study (Figure).

The 3 boys with a new ASD diagnosis, in addition to the 11 previously diagnosed suggested an ASD prevalence of 14 of 214 or 6.5% (95% CI, 3.6, 10.7). All 14 boys came from separate families. In comparison with UK National statistics data, this prevalence is considerably greater than the prevalence of ASD in boys within the same age bracket in the general population (1.9%) [4]. These National statistics data also estimate the prevalence of ASD in younger boys (5-10 years) to be 2.5%, a little higher (Table 2) [28]. In our study, 10 of 214 boys were diagnosed before the age of 8, suggesting a prevalence of 4.7% (95% CI, 2.2%, 8.4%) with risk ratio of 12.0 (95% CI, 5.7, 22.2). [21]. Again, prevalence in our population is higher than UK National statistics would suggest, and this is likely to be a conservative estimate, given that less than half of the boys in this hemophilia population were screened.

The mean age at ASD diagnosis of the 14 of 214 was 6 years (range, 3-12 years/median 5 years). There was no association between ASD diagnosis and hemophilia types A and B (P = .24); all severities (P = .43); severe (10 of 107 = 8.6%) vs not severe (4 of 93 = 4.1%) P = .19; HoI, (P = .33) or ICH (P = .91). Of 214 patients, prematurity status was available for 101 boys; for term boys 10 (11.2%) of 89 had ASD, for preterm boys 4 (33.3%) of 12 had ASD. Comparing ASD rates between term and preterm boys, P = .04. Comparing ASD rates between the 4 birth delivery groups there was no evidence of an association (P = .55) and no evidence of a difference (P = .75) when comparing unplanned caesarean section or instrumental vaginal delivery (3 of 18 = 16.7%) to uneventful vaginal delivery or planned caesarean section (11 of 80 = 13.8%), (Tables 3 and 4). Children born prematurely (<37 weeks) had significantly worse scores on average (higher SCQ scores and lower CCC scores) than those born at term (Table 5). Median GEC score was higher for premature children, but this was not statistically significant.

The 11 boys with prior ASD diagnosis did not complete the questionnaires, so there was no data on their performance in these measures. The median (IQR) SCQ score 21 (13-27) for the 4 boys with a new ADHD (n = 2) or ASD (n = 2) diagnosis, as well as median CCC score: 114 (104-123) and BRIEF (GEC) score: 77 (65-81), surpassed the threshold on all 3 questionnaires. By comparison, the median scores in the remaining 78 boys without a diagnosis of ASD or ADHD were within normal ranges (Table 6).

The mean ± SD age for the 76 boys without an ASD diagnosis who completed the BRIEF (excluding the 4 boys who were diagnosed with ADHD or ASD) was 12.3 ± 3.5 years and their mean ± SD GEC score was 49.5 (12.3). These were similar to scores from control data in other studies: Stabouli et al [29] (n = 51), where mean ± SD GEC score was 47.22 ± 8.02 in controls aged 11 ± 3.75 years [29], and

TABLE 1 Demographics.

Patient characteristics	Disease severity mild/moderate (*n* = 31)	Disease severity severe (*n* = 51) 7 with inhibitor	Total (*n* = 82)
Age in y mean (sd)	12.7 (3.7)	12.0 (3.5)	12.2 (3.6)
Median, y and range	13.3 (6.6, 18.4)	11.9 (5.7, 19.0)	12.4 (5.7, 19.0)
Diagnosis *n* (%)			
Hem A	22 (71.0)	43 (84.3)	65 (79.3)
Hem B	8 (25.8)	7 (13.7)	15 (18.3)
Hem B Leyden	1 (3.2)	1 (2.0)	2 (2.4)
Ethnicity			
White	25	35	60
Black	0	7	7
Asian	4	1	5
Mixed	3	3	6
Other		1	1
Other/mixed		1	1
Other/white		2	2
Previous/known			
ICH	0	6 (11.8)	6 (7.2)
Premature (missing for 1 severe case)	1 (3.2)	8 (16.0)	9 (11.1)
Mode of delivery	(2 missing)	(3 missing)	
Vaginal delivery	7 24.14	27 56.25	34 44.16
Vaginal instrumental	5 17.24	4 8.33	9 11.69
Planned caesarean	15 51.72	12 25	27 35.06
Unplanned caesarean	2 6.9	5 10.42	7 9.09
Mainstream school	All	All	All
Preexisting known intellectual disability or diagnosis of ASD	None	None	None
Number of families with a known sibling with ASD	2	2	4
Number of families in which >1 children completed the questionnaires			8 families >1 child completed 5 families had 2 children 3 families had 3 children

ASD, autism spectrum disorder.

Miles et al [15] (*n* = 16), where GEC scores were 48.6 ± 10.25 in controls aged 9.7 ± 4.5 years.

4 | DISCUSSION

This prospective study of patients from GOSH represents the largest populations of boys with hemophilia in the UK [30], which has allowed prevalence of boys with ASD to be quantified. Findings suggest a higher prevalence in boys with hemophilia compared with the UK National statistics for ASD prevalence in the general population of boys, and this is likely to be a conservative estimate, given that less than half of the boys in this hemophilia population were screened. We calculated prevalence very conservatively—ie, not 14 out of the 50% of boys tested (*n* = 82) but 14 out of 214 (the whole population of boys with hemophilia at our center), ie, we assumed the unscreened boys did not have ASD, hence our prevalence estimate is likely to be an underestimate and not an overestimate. Thus, the number of boys with ASD can only go up rather than down with further testing. There is clearly a need for further research in the wider national/global

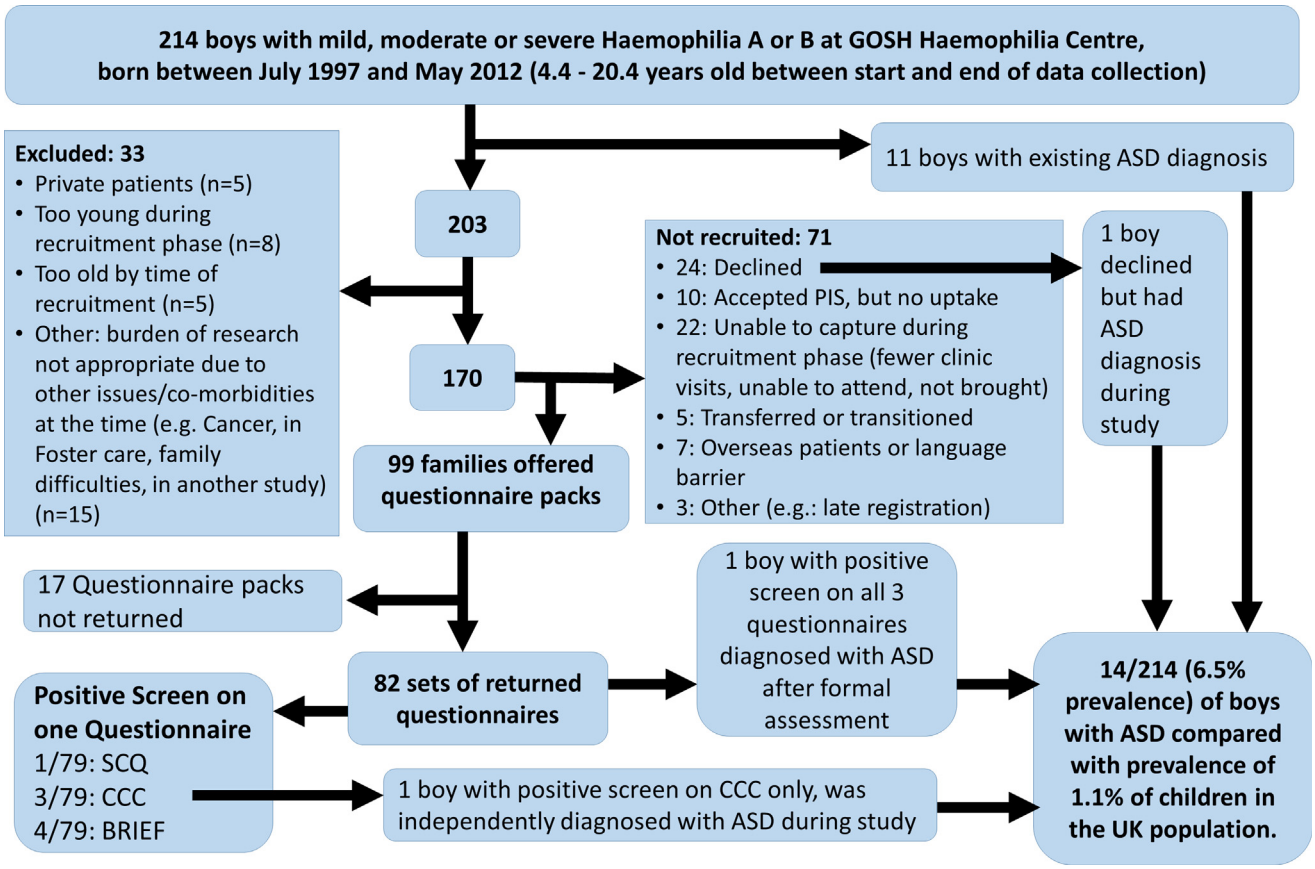

FIGURE Flow chart of study. ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; BRIEF, the Behavior Rating Inventory of Executive Functioning; CCC, Children's Communication Checklist; GOSH, Great Ormond Street Hospital; SCQ, Social Communications Questionnaire.

TABLE 2 Prevalence of ASD.

Study	Details age etc.	Time period	Size of cohort	No. of ASD cases	Prevalence rate per 100 (95% CI)
Our data	Boys with hemophilia (4.4-20.4 y)	2021	214	14 10	Boys (4-20 y): 6.5% (3.6, 10.7) Boys <8 y: 4.7% (2.3, 8.4)
NHS digital [5]	NHS Digital and Office for National Statistics UK National survey (5-19 y)	2017	18,029	Not reported 5:1, male:female ratio	Boys+Girls: 1.2% (1.0, 1.7) Boys (5-19 y): 1.9% Girls (5-19 y): 0.4% Boys (5-10 y): 2.5% Girls (5-10 y): 0.4%
Russell et al [8]	Millennium Cohort Study, UK parent reported (8-9 y)	2014	13,586 responses	Not reported 5:1 male:female ratio	Boys+Girls: 1.7% (1.4, 2.0) Boys: 2.5% Girls: 0.5%
Taylor et al [28]	Children aged 8 y UK wide	2010	132,143 124,135	515 101	Boys 8 y: 0.39% (0.36, 0.42) Girls 8 y: 0.08% (0.07, 0.1)
Baird et al [6]	Children aged 9-10 y in South Thames	2006	56,946	Not reported, 3.3:1 male:female ratio	Boys + Girls: 1.16% (0.90, 1.42) (9-10 y)
Baron Cohen et al [7]	Cambridge survey of SEN register and mainstream schools (5-9 y)	2009	11,700 questionnaires	Modeled on ratio of known:unknown cases of 3:2	Boys+Girls (5-9 y): 1.57% (1.0, 2.5) Boys: 1.53% (0.94, 2.17) Girls: 0.42% (0.09, 0.79)

ASD, autism spectrum disorder.

TABLE 3 Prevalence of autism spectrum disorder by diagnosis (n = 214).

	ASD diagnosis	
Diagnosis	**No**	**Yes**
Hemophilia A (n = 175)	166	9 (5.1%) (7 severe, 1 mod, 1 mild)
Hemophilia B (n = 36)	32	4 (11.1%) (3 severe, 1 mild)
Hemophilia B Leyden (n = 3)	2	1 (33.3%)
Total (n = 214)	200	14 (6.5%)

ASD, autism spectrum disorder.

TABLE 4 Characteristics of patients by autism spectrum disorder Status (n = 214).

	ASD diagnosis	
Patient characteristics	**No**	**Yes**
History of an inhibitor P = .99		
No (n = 201)	187 (93.0%)	14 (7.0%)
Yes (n = 13)	13 (100.0%)	0 (0%)
Intracranial hemorrhage P = .99		
No (n = 197)	184 (93.4%)	13 (6.6%)
Yes (n = 17)	16 (94.1%)	1 (5.9%)
Disease severity P = .53		
Mild (n = 70)	67 (95.7%)	3 (4.3%)
Moderate (n = 27)	26 (96.3%)	1 (3.7%)
Severe (n = 117)	107 (91.4%)	10 (8.6%)
Mode of delivery (n = 116 missing) P = .52		
Vaginal delivery(n = 46)	38 (82.6%)	8 (17.4%)
Vaginal instrumental (n = 10)	9 (90.0%)	1 (10.0%)
Planned caesarean section (n = 34)	31 (91.2%)	3 (8.8%)
Unplanned caesarean section (n = 8)	6 (75.0%)	2 (25.0%)
Prematurity (n = 113 missing) P = .04		
No (n = 89)	79 (88.8%)	10 (11.2%)
Yes (n = 12)	8 (66.7%)	4 (33.3%)

ASD, autism spectrum disorder.

hemophilia communities to understand whether this is an isolated finding, and to determine potential reasons and mitigating factors for this increased prevalence.

Prevalence rates for ASD vary globally with different diagnostic tools and assessment procedures being used. In general, UK surveys have consistently estimated overall ASD prevalence in children and young people at <2%. One UK publication relied on parent self-report to estimate ASD prevalence in the Millennium Cohort of children, which as authors acknowledge, may have resulted in overestimation of prevalence (1.7%) [8]. Another suggested modeling on the basis that for every child diagnosed with ASD, there are always other undiagnosed children in the population, again potentially overestimating the real prevalence (1.57%) [7]. Compared with these papers, the ASD prevalence from boys in this study exceeded the estimates published (6.5%).

Historically, reported ASD prevalence in the US has consistently been higher than in the UK. In 2020, the National Institute of Mental Health published data on the prevalence of ASDs in 8-year-old in the USA (1.9% overall, with 3% and 0.7% in boys and girls, respectively) [31]. Our data for boys with hemophilia exceed the elevated USA prevalence in boys aged 8 years by some margin (4.7% vs 3%). Notably, a more local recent publication on ASD prevalence in school-age children aged 4 to 15 years from the Department of Health in Northern Ireland identified a high prevalence (4.2% overall, with 6.4% and 2.0% in boys and girls, respectively), with similar prevalence in boys to our study (6.5% vs 6.4%) [32]. However, to provide context, they concede this is a considerable increase from their previous prevalence results, which they attribute to changes in routine monitoring, recording, and changes in the law (introduction of the Autism Act [Northern Ireland] 2011, with accompanying increase in awareness via campaigns and events). They warn that their figures from 2019/20 are not directly comparable with their much lower ASD prevalence in previous years. Given that these circumstances were not present in the population of boys with hemophilia in this study, the high prevalence observed here remains of significant concern.

There are several established risk factors for ASD in the general population. In this study, no association between ASD diagnosis and hemophilia types, severity, or presence of an inhibitor could be demonstrated. In addition, there was no association between ASD and mode of delivery, but there was a significant association between prematurity and ASD, with an increased prevalence in the premature group. Furthermore, children born prematurely had, on average, more positive scores on the SCQ and CCC questionnaires in comparison with those born at term.

The last 6 weeks of gestation are associated with a critical part of growth and development of the limbic system, cerebellum, and associated nuclei [10]. In the UK, the prematurity rate (babies born before 37 weeks) is approximately 1 (7.7%) of 13 [33]. A meta-analysis of the prevalence of ASD in children who were born preterm (<37 weeks) has been identified as 7% [34]. Our data, despite being in a small population, suggest a similar relationship between ASD diagnosis and boys with hemophilia born before 37 weeks. The prevalence of prematurity in our available cohort was 12% in comparison with 7.7% in the UK population. It would have been preferable to assess the rate of ASD adjusting for prematurity, but the substantial proportion of missing birth history data precluded this. Although prematurity is an established risk factor for ASD, it does not fully explain the substantially increased prevalence of ASD in boys with hemophilia at GOSH and these findings require further investigation.

Altered cytokine profiles and or inflammation have been identified as possible causes for low bone mineral density in people with

TABLE 5 Prematurity and questionnaire results.

Questionnaire threshold scores	Prematurity (*N* = 9)	Term (*N* = 72)	Comparison *P* values
Social Communication Questionnaire (Scores ≥15)			
Median SCQ score (IQR)	11 (6, 12)	5 (2, 8)	.01
Children's Communication Checklist (Scores <132)			
Median CCC score (IQR) 1 term missing	134 (134, 147)	152 (145, 157)	<.01
The Behavior Rating Inventory of Executive Function (Global Executive Composite Scores ≥65)			
Global Executive Composite Median score 2 term missing (IQR)	53 (49, 56)	48 (41, 56)	.10

CCC, Children's Communication Checklist; SCQ, Social Communications Questionnaire.

hemophilia [35], suggesting FVIII and IX may play a role outside of the coagulation system and indirectly modulate cytokines. There are several studies reporting on the role of cytokines in controlling brain development [36]. Factor VIII or FIX function in early brain development may warrant further investigation and support early prophylaxis.

ICH in premature children has also been associated with ASD in infants <34 weeks [1,37]. In addition, differences between children with cerebellar hemorrhagic injury vs controls who score positively on autism screeners (37% vs 0%) and internalizing behavioral problems (34% vs 9%) suggest a relationship between brain insults and ASD [37,38]. Boys with hemophilia are vulnerable to ICH in the perinatal period, during that time they are not usually covered by factor replacement therapy. It is not possible to rule out subclinical ICH in the perinatal period given the fragility of the brain during the ordeal of birth, and these may not have been investigated or reported in the absence of overt clinical findings. Although prior neurologic dysfunction is a known risk factor for ASD [1], no relationship between ASD and ICH was identified in this study. A large proportion of the known ICH events (7/17) in this cohort occurred between 4 and 60 months, but other unreported minor head injuries, conservative use of brain imaging, or periods of nonadherence to prophylaxis may have resulted in some ICH events in early childhood being missed.

The high screening threshold requirement in our study was purposeful. An ASD diagnosis is a significant event and we were reluctant to create unnecessary anxiety in families by recommending formal ASD assessment unless there was significant concern. The screening threshold in our study (positive screen on all 3 questionnaires) resulted in 4 boys being offered referral for neurodevelopmental assessment. Three of these boys met diagnostic criteria for ASD or ADHD, while the family of the 4th boy declined the assessment.

TABLE 6 Questionnaire results, excluding 4 boys diagnosed with ASD or ADHD during study.

Questionnaire threshold scores	Overall *N* = 78	Disease severity mild/moderate (*N* = 30)	Disease severity Severe (*N* = 48)	Comparison *P* values
Social Communication Questionnaire (Scores ≥15)				
Median lifetime total score (IQR)	5 (2, 8)	5 (1, 7)	5 (2, 10)	.37
Screened positive (%)	3 (3.9%)	1 (3.3%)	2 (4.2%)	.99
Children's Communication Checklist (Scores <132)				
Median CCC Score: (IQR) (*n* = 77, 1 severe missing)	151 (145, 156)	153 (147, 156)	150 (137, 157)	.51
Screened positive (%)	6 (7.8%)	2 (6.7%)	4 (8.5%)	.99
Behavior Rating Inventory of Executive Function (Global Executive Composite Scores ≥65)				
Global Executive. Composite median (IQR) *n* = 76 (2 severe missing)	48 (41, 55)	47 (39, 56)	49 (41, 54)	.72
Screened positive (%)	11 (14.5%)	4 (13.3%)	7 (15.2%)	.99

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CCC, Children's Communication Checklist.

However, another boy in the study reached the threshold on only one questionnaire (CCC) and therefore was not offered further assessment. His subsequent diagnosis of ASD (independent of this study), suggests that our threshold may have been too conservative.

A high screening threshold is supported by a review conducted by the National Institute for Clinical Excellence, which identified that none of the screening instruments designed to identify an increased likelihood of ASD met an acceptable level of diagnostic accuracy (defined as sensitivity and specificity of at least 80%). The instruments showed a variety of levels of sensitivity and specificity. The evidence was insufficient to identify if any particular instrument is effective in detecting children at risk of ASD. Negative scores do not rule out a diagnosis of ASD and positive scores may justify referral for assessment, but symptomology could be attributed to reasons other than ASD [1].

The 11 boys previously diagnosed with ASD in the center did not receive their diagnosis as a result of routine medical observation for their hemophilia care. None of the 11 were referred from, or diagnosed by, the GOSH hemophilia center. Questionnaire data were retrieved from 82 of 214 families, representing >40% of the boys with hemophilia in our center. Those families who consented to participate may have had private concerns about their child, thus potentially increasing the bias of the screened sample toward those with social or behavioral difficulties. However, many of the 132 of 214 boys with hemophilia were not approached or recruited for a variety of reasons, and screening all of them may have potentially identified additional children that warranted formal ASD assessment. As such the prevalence of ASD in boys with hemophilia may be >6.5% reported here.

The mean ± SD age for the 76 boys without an ASD diagnosis who completed the BRIEF (excluding the 4 boys who were diagnosed with ADHD or ASD) was 12.3 ± 3.5 years and their mean ± SD GEC score was 49.5 (12.3). These were similar to scores from control data in other studies [15,29].

The sociocultural determinants of health in any population are important. Race and ethnicity were not formally included in the analysis, but around 75% of the 82 enrolled in our study were white: 9% black, 6% Asian, and 9% mixed race, 1% other; with 12 (75%) of 14 with a diagnosis of ASD white. A recent study has identified increased prevalence rates of ASD in racial/ethnic minority groups in an English census of school children aged 5 to 19 years and that socioeconomic disadvantage may contribute to accessing services [39]. It is imperative therefore, that future studies explore to what degree social determinants of health, immigration, and race/ethnicity affect ASD.

Hemophilia is a coagulation disorder affecting the entire body and these findings suggest neurologic function may be impacted and surveillance is prudent. Difficulties associated with ASD can have a significant impact on the child, the family, and education, and therefore screening may be warranted in hemophilia centers. Surveillance could include screening for: developmental; behavioral or parental concerns; antenatal/prenatal/medical history; developmental milestones and factors associated with increased prevalence of ASD, especially when reviewing boys with hemophilia who are demonstrating attributes that are common in children with ASD. There is no consensus on the best screening questionnaires, but a standardized screening tool, for example, the SCQ, as well as liaison with the school to ascertain the child's functioning in another environment, all contribute to the picture of the child's functioning before potential referral for diagnostic assessment.

This study identified a higher prevalence of ASD in boys with hemophilia at 1 center. Further investigation in the wider national/global hemophilia communities is warranted to determine whether this is an isolated finding as diagnosis and prevalence rates vary. Substantiation of any association between hemophilia and ASD will ultimately facilitate appropriate improvements in the provision of care.

ACKNOWLEDGMENTS

The authors thank Anja Griffioen who designed the database and inputted the data, to Nicola Hubert who helped with data collection, and to Harriet Holmes who assisted in the literature search

FUNDING

Melanie Bladen and Nicola Thorpe received an educational grant from Pfizer UK to fund this research.

AUTHOR CONTRIBUTIONS

M.B. designed, performed the research, analyzed, wrote, and approved the final manuscript. N.T. analyzed and approved the final manuscript. D.R. analyzed, co-wrote, and approved the final manuscript. A.B. data collector, performed the research, and approved the final manuscript. E.M. analyzed, co-wrote, and approved the final manuscript. A.M. analyzed, co-wrote, and approved the final manuscript. L.W. performed the research and approved the final manuscript. E.M. substantially contributed to the analysis, writing, and approval of the final manuscript.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

INFORMED PATIENT CONSENT

Written consent from the parents and assent from the boys was obtained in all cases.

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