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Mental Health Disorders in Haemophilia: Systematic Literature Review and Meta-analysis

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Abstract

Aim: Despite significant advances in morbidity and mortality outcomes, quality of life for people with haemophilia (PWH) remains compromised. Underrecognized and undertreated mental health disorders decrease quality of life; however, reports are inconsistent regarding the true prevalence of mental health disorders in PWH.

Methods: We conducted a systematic literature search of Ovid MEDLINE, EMBASE, Psycinfo, and the Cochrane Library, and hand searched the journal *Haemophilia* to identify records and subsequently conducted a meta-analysis to determine the prevalence of depression, anxiety, and attention deficit hyperactivity disorder (ADHD) in patients with congenital haemophilia.

Results: Our search strategy identified 2315 records, and 28 studies met eligibility criteria. Meta-analysis demonstrated that PWH are at increased risk of depression (odds ratio (OR) 2.45; 95% Confidence Interval (CI) 1.64–3.68), anxiety (OR 1.74, 95% CI 1.01 – 3.00), anxiety / depression (OR 2.60, 95% CI 2.35 – 2.87), and ADHD (OR 3.48, 95% CI 1.74 – 6.96). We found considerable heterogeneity among the studies likely due to differences in assessment tools, populations studied, and year of publication. This suggests that standardized tools to diagnose mental health disorders in PWH are needed. Additionally, high-quality studies investigating mental health disorders in PWH are necessary to adequately document the prevalence of these disorders.

Conclusion: Overall, our meta-analysis suggests that the prevalence of depression, anxiety, and ADHD across decades is significantly increased in PWH compared to the general population.

Keywords

Haemophilia; Mental Health; Anxiety; Attention deficit disorder with hyperactivity; Depression; Prevalence

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Conflicts of interest

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INTRODUCTION

Haemophilia is the most severe bleeding disorder and is estimated to affect 400,000 individuals worldwide and 20,000 individuals in the United States. Therapeutic advancements for haemophilia from cryoprecipitate to gene therapy have dramatically altered the natural course of disease. Today, people with haemophilia (PWH) are expected to have a normal life expectancy. Despite this, quality of life for PWH remains compromised beyond the physical sequelae of their illness.

PWH face unique challenges from a young age, and these affect nearly every aspect of life including relationships with family and peers, emotional wellbeing, and behaviour. Studies have shown decreased quality of life measures in PWH compared to the general population. [1] A major determinant of decreased quality of life in PWH may be a high prevalence of mental health disorders (MHD). MHD may affect treatment adherence and academic achievement in PWH.[2] However, reports of the prevalence of MHD in PWH are variable; therefore, a true understanding of the impact of MHD on PWH and their caregivers is lacking.

Recent advances in haemophilia therapeutics have led to growing interest in measuring alternative and meaningful outcomes separately from joint health.[3] New therapies have comparable efficacy in reducing annualized bleeding rate (ABR), however, ABR is not a surrogate marker for the general wellbeing of PWH.[4] Previous studies of MHD in PWH provided inconsistent results and were potentially influenced by the human immunodeficiency virus (HIV) and hepatitis epidemics. Furthermore, drastic changes in haemophilia treatment paradigms over the years may have altered the prevalence of MHD in PWH. Therefore, we performed a systematic literature review to examine the evidence available and determine the prevalence of depression, anxiety, and ADHD in PWH.

MATERIALS and METHODS

We performed a systematic literature review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Inclusion and exclusion criteria were specified in advance. We use the abbreviation MHD to refer to a diagnosis of depression, anxiety, ADHD, and/or anxiety/depression.

Study selection and search strategy

A systematic literature search of Ovid MEDLINE, EMBASE, PsychInfo, and the Cochrane Library (including the Cochrane Database of Systematic Reviews and Cochrane Register of Controlled Trials) was conducted. The database search strategy was constructed and run by a specialized health sciences librarian trained in searching for systematic reviews. Results were filtered to English language only; no other filters or parameters were used. Hand-searching of the journal *Haemophilia* also was conducted for this search. References from included studies and narrative reviews were additionally examined. Relevant published studies up to January 2018 were identified. The full search strategy used for electronic databases is provided in Supplemental Data. Title and abstract screening for studies meeting inclusion criteria were independently carried out by 2 reviewers (A.A. and J.M.S.). Studies

were included if they reported outcomes in patients with congenital haemophilia. Single case reports, animal studies, duplicative studies, and review articles/meta-analysis without original data were excluded. Studies published only as abstracts were excluded since they have not undergone rigorous peer review. Studies with cohorts of less than 85% congenital haemophilia or more than 10% of subjects with history of intracranial haemorrhage were excluded.

Data extraction and synthesis

Two independent-blinded reviewers (A.A. and M.R.H.) extracted data from all eligible studies and data collected were entered into a RedCap database. Data extracted included study year of publication, study inclusion and exclusion criteria, study type, study country, number of participants, participant's demographics including control group if present, co-morbidities (HIV, Hepatitis B, Hepatitis C, and arthritis), MHD prevalence, MHD assessment tool, and authors' conflicts of interest. Subsequently, a third reviewer (J.M.S.) resolved discrepancies within the data collected between the initial reviewers.

For each MHD, odds ratio with 95% Confidence Interval (CI) and the pooled estimate were plotted in forest plots including the number of PWH and controls. A random-effects model was used to account for variability between studies, and the I^2 statistic were used to estimate total variability in outcome (statistical heterogeneity). An $I^2 > 40\%$ was considered to indicate statistical heterogeneity amongst studies.[5] Depending on the availability of control data in a given study, two types of control populations were used to calculate odds ratios (OR). If the study included a control population, then this was used to determine OR. However, if the study did not collect data on control subjects, then available data from the US (United States) general population, matched by study year, was used.[6–8] Studies investigating the prevalence of depression reported either symptoms or diagnosis; therefore, we matched the corresponding United States (US) general population data (symptoms or diagnosis). The largest portion (15/28, 54%) of studies included the US, and therefore US general population data were used as controls. Data analysis included Revman (Version 5.3, Copenhagen, Denmark) to generate forest plot, OR, and I^2 and MedCalc to calculate total prevalence of each MHD. All results were reviewed by a statistician.

Assessing quality

Two reviewers (A.A. and M.R.H.) assessed quality of studies using the National Institute of Health (NIH) NIH quality assessment tool for observational cohort and cross-sectional studies [9] which consists of 14 questions and a final overall rating. Subsequently, a third reviewer (J.M.S.) resolved discrepancies within the data collected. The questions evaluate research questions, selected population, participation rate, exposure, outcome, and confounding factors (Table 5).

RESULTS

Study selection and characteristics

Our search strategy identified 2315 studies, of which 28 studies met our eligibility criteria (Figure 1). Twenty-seven studies [10–36] had a cross-sectional design, and one study[37]

was a retrospective chart review (Table 1). None of the studies were prospective in nature. Most of the studies (15/28, 54%) included subjects from the US (Table 1). Thirteen studies were conducted in the US and 2 multinational studies included the US. The publications are spread evenly over the last 3 decades (~30% each) with only 2 studies [10, 11] published prior to 1990 (Table 1).

Population description:

The twenty-eight eligible studies included a total of 2926 PWH (Table 2). Surprisingly, haemophilia severity was reported in only 1719 PWH (59% of the total population). Of these, 1064 (82%) had severe haemophilia. Most treatment regimens (Table 2) were described as on-demand therapy (40%) while fewer reported prophylactic treatment (28%) or did not report treatment regimen (32%). Comorbidities were not consistently reported (Table 3). Of the comorbidities reported, HIV (543 PWH), hepatitis C (427 PWH), and arthritis (830 PWH) were the most frequently reported.

Most studies, (15/28, 54%), pooled results from subjects with haemophilia A and B. Therefore, our analysis combined haemophilia A and B results. Eight studies reported data on haemophilia A subjects alone and only one study reported data on haemophilia B subjects without combination with haemophilia A (Table 1). Therefore, subgroup analysis for individual MHD by haemophilia type was not performed.

Moreover, for each MHD, studies were distributed between paediatrics and adults, paediatrics, adults, or not reporting age. Half of the studies (14/28) included data from paediatric patients only and 8 reported on adult patients only (Table 1). The remaining studies included both adults and paediatric patients (3) or did not report age (3). Therefore, given that studies did not investigate an effect by age, our reported odds ratios and prevalence includes all ages. Of note, studies reporting on ADHD were all conducted in children, and therefore the prevalence of ADHD only reflects that in paediatric patients.

Meta-analysis

Depression, anxiety, and ADHD were each evaluated in a limited number of the 28 eligible studies. For example, 18 studies provided data for depression, but only 6 studies investigated the prevalence of ADHD. Further details regarding number of studies, total number of PWH, heterogeneity of studies and odds ratio for each MHD are provided in Table 4. A summary of studies is provided in Table 3.

Depression

Depression was the most studied MHD and was reported in two ways: a diagnosis of depression (formal diagnosis) or depressive symptoms (as reported by the patient). Depressive symptoms were reported in 10 of 28 studies and included 722 PWH [11–13, 15, 20, 24, 26, 28, 29, 33]. Studies were distributed somewhat equally between adults (4 studies) and paediatrics (5 studies) with 1 study not reporting the age of subjects. The prevalence of depressive symptoms was higher in PWH (41.7%, 95% CI: 25.4% - 56.8%) than in the general U.S. population (22.9%). Additionally, a formal diagnosis of depression was reported in 9 of 28 studies and included 1722 PWH which consisted of 4 adult studies,

3 paediatric studies, and 1 study having both adult and paediatric subjects[10, 14, 18, 22, 25, 33, 35–37]. The remaining study did not report age of subjects. The prevalence of depression diagnosis in PWH is 14.5% (95% CI: 6.8% - 15.6%) compared to 5.6% in the U.S. population. Overall, PWH were at increased risk of having either depressive symptoms (Figure 2A; OR 3.06, 95% CI: 1.48 – 6.28) or a diagnosis of depression (Figure 2B; OR 2.64, 95% CI: 1.83 – 3.79).

Although comorbidities were infrequently reported, four studies reported data on depression in HIV-positive and HIV-negative PWH[12, 14, 15, 18]. Our analysis revealed no difference in the prevalence of depression between these groups (Figure 2C; OR 1.62, 95% CI 0.77 – 3.41). These studies were statistically homogeneous (I^2 of 0%, $P = 0.62$).

Anxiety

Anxiety was reported in 13 of 28 studies including 1843 PWH.[10, 12–14, 16, 18, 22, 25, 30, 33–36] This comprised of 6 paediatric studies, 4 adult studies, two studies did not report the age, and 1 study combined results from paediatric and adult patients. Overall the prevalence of anxiety was 16.0% (95% CI: 10.8% - 22.0%). PWH had an increased risk of anxiety disorders with an OR of 1.74 (Figure 3A; 95% CI: 1.01 – 3.00).

Anxiety and Depression Combined

While most studies investigated depression alone, six studies reported anxiety and depression without separating those affected by depression, anxiety, or both.[19, 31–33, 35, 36] All six studies used the EuroQoL five dimension scale (EQ5D), and therefore this resulted in low statistical heterogeneity among studies ($I^2 = 0\%$, $P = 0.60$). These studies consisted mostly of adults (1465/1688 PWH) and were published within the last 5 years. The prevalence of anxiety/ depression in PWH was 39.7% (95% CI: 34.7% - 45%) with an OR of 2.60 (Figure 3B; 95% CI: 2.35 – 2.87) indicating increased risk of anxiety and depression in PWH.

Attention and Hyperactivity Disorder (ADHD)

A diagnosis of ADHD may affect quality of life, academic achievement, and increased risk-taking behaviour [38]. Only 6 studies (all paediatric) reported data on ADHD.[17, 18, 21–23, 27] The prevalence of ADHD in 371 paediatric PWH was 15.3% (95% CI: 6.3% - 27.3%). Pediatric PWH had an increased risk of ADHD with OR of 3.48 (Figure 3C; 95% CI: 1.74 – 6.96). The instruments used to report ADHD varied greatly among the studies, resulting in considerable statistical heterogeneity ($I^2 = 70\%$, $P = 0.005$).

Study Quality

All studies in our meta-analysis were deemed low to good quality based on the NIH quality assessment tool for observational cohort and cross-sectional studies (Table 5). Only six of the 28 studies met the criteria for good quality. Most of the studies were rated as fair (19/28) or low (3/28) quality. Reasons for low-quality ratings included lack of a clearly defined outcome measure, lack of a clear research question, variation across subject recruitment, and not examining different levels of exposure (factor level) as related to outcome (MHD). To investigate the effect of study quality on our results, we analysed the data excluding the 3

low quality studies which did not alter the conclusions of the results with similar odds ratios and prevalence of MHD. Complete details of the quality assessment for each study are listed in Table 5.

DISCUSSION

We examined the prevalence of MHD in people with haemophilia. Despite marked improvement in haemophilia treatment over the last three decades, MHD such as depression, anxiety, and ADHD remain prevalent in PWH. Our analysis revealed that at least 2 out of every 5 PWH suffer from depression and/or anxiety, and the prevalence of these disorders has not declined during the modern treatment era.

With an increased focus on preventing MHD in all patients over the last decade, we were surprised to find such a high percentage of PWH with depressive symptoms (41%) and diagnosis of depression (10.8%). Depression and depressive symptoms have substantial negative effects on PWH including poor treatment adherence and a cause of functional impairments.[39] This highlights that the high prevalence of depression and depressive symptoms in PWH is alarming. Further, the potential for an unrecognized diagnosis of depression may result in lack of appropriate mental health care for PWH. It remains possible that mental health concerns are overshadowed by other aspects of haemophilia care, hindering a focus on mental health and ultimately a diagnosis of mental health illness.

Anxiety, like depression, can be a barrier to treatment adherence. Additionally, anxiety is known to exacerbate pain perception in PWH.[40] A combination of poor treatment adherence and exacerbation of pain could lead to inappropriate management of bleeding events. Therefore, it is incredibly important given our meta-analysis indicating significantly high rates of anxiety that the haemophilia population is thoroughly screened and treated for anxiety.

Our analysis highlights that ADHD is also highly prevalent in PWH. While it is known that ADHD can greatly impact outcomes including poor academic achievement, treating ADHD may decrease high-risk behaviours such as substance abuse and frequent injuries. [38] For PWH, there is a discrepancy between intelligent quotient (IQ) and their academic achievement,[2] which may in part be due to increased rates of ADHD. However, limited studies are available to understand the impact of ADHD in PWH, and especially important is that no published literature on this topic exists since 2009. Studies to uncover the etiology of ADHD in PWH are imperative.

Many factors may contribute to MHD in PWH. Previous factors suggested to impact rates of MHD in PWH include overprotective parents, unemployment, fear about the future, treatment burden (multiple infusions, transportation of medication), and restricted daily activities. However, the direct impact on MHD in PWH is unknown. Significant improvements in haemophilia treatment during the last three decades have alleviated many of these cofounding factors (increasing rates of employment, hope for the future, improved factor products); therefore, we anticipated that the prevalence of MHD might have decreased over time. To the contrary, our meta-analysis reveals that high rates of depression and

anxiety in PWH are still present even in the modern treatment era. Moreover, MHD prevalence in the general population has been stable in the last 2 decades.[6–8] Thus the high prevalence of MHD in haemophilia cannot be explained by increased MHD in the general population.

We note that many studies allude to an effect of comorbidities, such as arthritis, HIV, or HCV, on MHD rates rather than focusing on haemophilia having a direct effect. Only HIV and its effect on depression is adequately studied in the haemophilia population. Furthermore, our meta-analysis suggests that HIV infection does not alter the prevalence of depression in PWH. Prospective studies comparing MHD in PWH and in patients with another chronic disease and similar comorbidities may help address this concern.

Across studies, differences exist in the assessment tools for MHD determination. For example, some studies report the MHD prevalence based on self-reporting while others performed patient interviews. Each of these methods carries a risk of bias. Limited studies reported depression, anxiety and/or ADHD based on strict Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. This was highlighted in our analysis of ADHD studies where some used strict ADHD diagnostic criteria, others reported ADHD symptoms, and still, others indicated ADHD by a ‘clinical’ diagnosis. This emphasizes the need to accurately screen patients for MHD symptoms and to prospectively investigate MHD prevalence in PWH.

A limitation of our study is that considerable differences exist in the assessment tools used across studies. Examples of anxiety assessment tools used in studies included generalized anxiety disorder 7 (GAD-7 which measures general anxiety) and a screen for child anxiety-related disorders (SCARED which measures general anxiety, separation anxiety, and phobias), but neither assess for all anxiety disorders such as panic disorder and post-traumatic stress disorder. In our analysis, the prevalence of anxiety in PWH (16.0%) was compared to the prevalence of all anxiety disorder in adult males in the US (14.3%).[7] We note, however, that generalized anxiety disorder only affects 1.9% of adult US males. [7] Therefore, future investigations of anxiety in PWH should incorporate assessments for all anxiety disorders and not simply generalized anxiety or a limited number of anxiety disorders. This also highlights that assessment tools used to determine rates of MHD should be standardized in order to compare rates across years and healthcare settings.

In addition to analysing the rates of MHD, we also investigated the study quality. We acknowledge that the studies analysed were mostly low to fair in quality. We note that study quality could affect the overall results. The World Federation of Hemophilia recognizes depression and anxiety as challenging comorbidities that can affect PWH. Therefore, we wanted to analyse the currently available data, and unfortunately, there is a paucity of high-quality evidence in regard to MHD in PWH. Additionally, our findings support recent efforts, such as CoreHem,[3] for mental health, quality of life, and overall function to be considered when measuring outcomes for new therapeutics including gene therapy. High-quality studies investigating MHD in PWH are necessary to adequately document their prevalence in the haemophilia population.

CONCLUSION

We found that MHD are overrepresented in PWH, carrying a significant impact on health and quality of life. There is a great need to use standardized assessment tools to report and diagnose MHD objectively in PWH. Clinicians should be aware of the increased prevalence of MHD in PWH, therefore incorporating screening for MHD in their routine clinical care. Further objective clinical research is needed to minimize confounding factors and assess the true burden of MHD in PWH in the current treatment era.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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J.M.S. designed the study; A.A. and J.M.S. screened studies for inclusion criteria; A.A. and M.R.H. extracted data from eligible studies; P.T.E. performed statistical analysis. All authors contributed to writing the manuscript and approved the final version.

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Figure 1.
Search results for mental health disorders in haemophilia

A

B

C

Figure 2. Pooled Odds Ratios of depression.

Comparison of depression between PWH and controls: (A) depressive symptoms, and (B) formal depression diagnosis. (C) Comparison of depression prevalence between HIV positive and HIV negative PWH. Boxes represent effect estimates from single studies, and box size is proportional to study weight. Diamonds represent pooled results, and the width of the diamond represents the confidence interval.

Figure 3. Pooled Odds Ratios.

Comparison of mental health disorder between PWH and controls: (A) anxiety, (B) anxiety/depressive combined, and (C) attention deficit hyperactivity disorder. Boxes represent effect estimates from single studies, and box size is proportional to study weight. Diamonds represent pooled results, and the width of the diamond represents the confidence interval.

Table 1.

Characteristics of included studies

Characteristics	Number of studies n= x/28, (%)
Study type	
Cross Sectional	27 (96%)
Retrospective Chart Review	1 (4%)
Country	
Multinational	3 (11%)
US [†]	13 (46%)
UK [‡]	3 (11%)
Turkey	2 (7%)
Italy	2 (7%)
Other [§]	5 (18%)
Year of publication	
<1990	2 (7%)
1990–1999	8 (29%)
2000–2009	8 (29%)
>2009	10 (36%)
Type of haemophilia	
Haemophilia A	8 (29%)
Haemophilia B	1 (4%)
Both	15 (54%)
Not Reported	4 (14%)
Population	
Pediatrics	14 (50%)
Adults	8 (29%)
Both	3 (11%)
Not Reported	3 (11%)
Median number participants/study (Q1, Q3)	61 (25,95)

[†]US- United States

[‡]UK- United Kingdom

[§]Each individually- Brazil, Egypt, Iran, China, Germany

Table 2.

Population demographics

Characteristics	Number of patients, n= x/2926, (%)
Severity of haemophilia	
Mild	236 (8%)
Moderate	327 (11%)
Severe	1064 (36%)
Inhibitor	92 (3%)
Not Reported	1207 (41%)
Treatment	
On Prophylaxis	810 (28%)
On-Demand	1184 (40%)
Not Reported	932 (32%)
Employment	
Employed	1071 (37%)
Not Employed	516 (18%)
Student	296 (10%)
Not Reported	1043 (36%)
Marital status	
Married/LTR [†]	879 (30%)
Not Married/LTR	592 (20%)
Not Reported	1455 (50%)
Arthritis	
Arthritis	830 (28%)
No Arthritis	738 (25%)
Not Reported	1358 (46%)
HIV[‡]	
HIV Positive	543 (19%)
HIV Negative	1489 (51%)
Not Reported	894 (31%)
Hepatitis C	
Hepatitis C Positive	427 (15%)
Hepatitis C Negative	772 (26%)
Not Reported	1727 (59%)

[†]LTR- Long-term relationship

[‡]HIV- Human immunodeficiency virus

Table 3.

Summary of studies.

Study/Year	Country [†]	HA/HB [‡]	Ped/ Adult [§]	MHD assessment tool [¶]	MHD prevalence n/total (%)	Comorbidities n/total (%) ^{††}
Spencer 1968	US	NR	P/A	Psychiatric evaluation	Depression 3/26 (12%) Anxiety 0/26 (0%)	NR
Klein 1982	US	NR	Ped	BDI	Depression 3/11 (27%)	NR
Dew 1990	US	NR	A	SCL90	Depression 32/75 (44%) Anxiety 25/75 (33%)	HIV 31/75 (41%)
Burton 1991	US	AB	Ped	CDI	Depression 12/22 (55%) Anxiety 9/22 (41%)	HIV 5/27 (19%)
Catalan 1992	UK	HA	NR	PSE / Catego	Depression 2/73 (3%) Anxiety 3/73 (4%)	HIV 37/73 (51%)
Riedel 1992	Germany	HA	NR	PDS	Depression 28/209 (13%)	HIV 181/209 (87%)
Bussing 1993	US	AB	Ped	K-SADS	Anxiety 9/23 (39%)	HIV 6/23 (26%)
Mayes 1996	US	AB	Ped	Psychiatric evaluation	ADHD 19/66 (29%)	HIV 18/66 (27%)
Thompson 1996	UK	AB	Ped	CAPA	Depression 1/64 (2%) Anxiety 1/64 (2%) ADHD 1/64 (2%)	HIV 31/64 (48%)
Miners 1999	UK	AB	A	EQ-5D	Anxiety/Depression 54/166 (33%)	HIV 31/168 (18%)
Celiker 2000	Turkey	AB	Ped	CDI	Depression 2/12 (17%)	Arthritis 12/12 (100%)
Shapiro 2001	US	HA	Ped	Self-report	ADHD 13/131 (10%)	NR
Sadowski 2003	Int.	HA	Ped	K-SADS	Depression 7/58 (12%) Anxiety 7/58 (12%) ADHD 3/58 (5%)	HIV 7/58 (12%) Arthritis 23/58 (40%)
Woodrich 2003	US	AB	Ped	ADHD-IV scale	ADHD 11/34 (32%)	NR
Bahls 2006	Brazil	NR	Ped	CDI	Depression 7/20 (35%)	NR
Ghanizadeh 2009	Iran	AB	Ped	K-SADS	Depression 5/83 (6%) Anxiety 4/83 (5%)	HCV 15/83 (18%) HBV 1/83 (1%)
Siboni 2009	Italy	AB	A	GDS-30	Depression 18/39 (46%)	HIV 5/39 (13%) HCV 36/38 (95%) HBV 4/38 (11%) Arthritis 37/39 (95%)
Spencer 2009	US	AB	Ped	ADHD-IV scale	ADHD 5/18 (28%)	NR
Hasan 2011	Egypt	HA	Ped	BDI	Depression 34/50 (68%)	NR
Khleif 2011	US	AB	A	Medical record review	Depression 5/63 (8%)	HIV 16/63 (25%) HCV 49/63 (78%) HBV 4/63 (6%) Arthritis 33/63 (52%)
Iannone 2012	US	AB	A	PHQ-9	Depression 15/41 (37%)	HIV 13/41 (32%) HCV 23/41 (56%) Arthritis 10/41 (24%)
Abali 2014	Turkey	HA	Ped	SCARED	Anxiety 16/42 (38%)	NR
Kodra 2014	Italy	AB	P/A	EQ-5D	Anxiety/Depression 28/73 (38%)	NR
Ozelo 2015	Int.	A	P/A	EQ-5D	Anxiety/Depression 46/150 (31%)	HIV 14/150 (9%)
Buckner 2016	US	HB	A	EQ-5D, PHQ-9, GAD-7 Self- report	Depression 66/299 (22%) Anxiety 70/299 (23%)	HIV 27/299 (9%) HCV 15/299 (5%) Arthritis 144/299 (48%)

Study/Year	Country [†]	HA/HB [‡]	Ped/ Adult [§]	MHD assessment tool [¶]	MHD prevalence n/total (%)	Comorbidities n/total (%) ^{††}
Hu 2017	China	HA	NR	CHO-KLAT	Anxiety/Depression 105/243 (43%) Anxiety 4/22 (18%)	NR
Sun 2017	Int.	AB	A	EQ-5D, self-report	Depression 88/675 (13%) Anxiety 97/675 (14%) Anxiety / Depression 313/675 (46%)	HIV 121/675 (18%) HCV 289/675 (43%) Arthritis 325/675 (48%)
Kempton 2018	US	AB	A	EQ-5D, self-report	Depression 73/381 (19%) Anxiety 53/381 (14%) Anxiety/Depression 165/381 (43%)	Arthritis 246/381 (65%)

[†]Int.- international, UK- United Kingdom, US- United States

[‡]HA- haemophilia A, HB- haemophilia B, AB - haemophilia A and B

[§]A- Adults, Ped- Pediatrics, P/A- Pediatrics and Adults

[¶]MHD- mental health disorder, BDI- Beck Depression Inventory, CAPA- Child and Adolescent Psychiatric Assessment, CDI- Children's Depression Inventory, CHO-KLAT- Canadian Hemophilia Outcomes- Kids' Life Assessment Tool, EQ-5D- EuroQoL five dimension scale, GAD-7- General Anxiety Disorder 7, GDS-30- Geriatric Depression Scale 30, K-SADS- Schedule for Affective Disorders and Schizophrenia for School-Aged Children, PDS- Paranoid-Depression Scale, PHQ 9- Patient Health Questionnaire 9, PSE- Present State Examination, SCARED- Screen for Child Anxiety Related Disorders, SCL90- Symptoms Checklist 90; ADHD- attention deficit hyperactivity disorder

^{††}HBV- hepatitis B virus, HCV- hepatitis C virus, HIV- human immunodeficiency virus, NR- not reported.

Table 4.

Pooled OR in haemophilia for each mental health disorder.

Outcome	Comparison	Number of Studies	Number of PWH	OR [‡] (95% CI)	Heterogeneity I ² (p-value)
Depressive symptoms	PWH [‡] vs Controls	10	722	3.05 (1.48 – 6.28)	92% (< .01)
Diagnosis of Depression	PWH vs Controls	9	1722	2.64 (1.83 – 3.79)	71% (< .01)
Depression & HIV status	PWH HIV [§] _{+ve} vs PWH HIV _{-ve}	4	421	1.62 (0.77 – 3.41)	0% (0.62)
Anxiety	PWH vs Controls	13	1843	1.74 (1.01 – 3.00)	95% (<.01)
Anxiety / Depression	PWH vs Controls	6	1688	2.60 (2.35 – 2.87)	0% (0.60)
ADHD [¶]	PWH vs Controls	6	371	3.48 (1.74 – 6.96)	70% (<.01)

[‡]PWH- people with haemophilia[‡]OR- odds ratio[§]HIV- human immunodeficiency virus[¶]ADHD- attention deficit hyperactivity disorder.

Table 5.

NIH Quality Assessment Tool for observational cohort and cross-sectional studies.

Reference	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
1. Clear research question or objective?	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
2. Clear study population?	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
3. Participation of eligible subjects over 50%	NR	Y	Y	NR	N	NR	NR	NR	NR	Y	NR	Y	Y	N	NR	NR	Y	Y	NR	Y	NR	NR	NR	NR	NR	NR	Y	Y
4. Similar subject recruitment	NR	NR	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
5. Sample size justification, power, or variance and effect estimates provided?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
6. Exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Sufficient time frame to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Examined different levels of the exposure as	Y	N	Y	N	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	N	Y	Y	N	N	N	N

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Reference	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
related to the outcome?	N	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
9. Exposure measures clearly defined, valid, reliable, and consistent across participants?	N	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
11. Outcome measures clearly defined, valid, reliable, and consistent across participants?	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
12. Outcome assessors blinded to the exposure status?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
13. Loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14. Measured and adjusted for potential confounding variables?	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Rating	L	F	G	F	F	F	F	F	F	G	F	F	G	F	F	F	G	F	G	F	F	L	F	G	L	F	F	F

Y- Yes, N- No, NA- not applicable, NR- not reported, L- Low, F- Fair, G- Good.