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DEPRESSION AND ANXIETY IN VON WILLEBRAND DISEASE: AN OVERLOOKED DIMENSION OF CARE

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ABSTRACT

Von Willebrand disease, the most common inherited bleeding disorder, is increasingly recognized to have significant psychological comorbidities, particularly depression and anxiety. This review synthesizes current evidence from observational, cohort, and qualitative studies to examine the relationship between von Willebrand disease and mental health outcomes. Across diverse methodologies, including validated symptom scales, diagnostic coding, and pharmacotherapy records, patients with VWD consistently exhibited higher rates of depression and anxiety compared with the general population. The association remained robust across age groups and von Willebrand disease subtypes, with adolescents and women demonstrating the greatest vulnerability. Factors such as chronic pain, joint complications, abnormal uterine bleeding, and diminished quality of life emerged as significant correlates of psychological distress. These findings highlight that psychiatric morbidity in von Willebrand disease is not merely secondary to bleeding symptoms but constitutes a central aspect of disease burden, contributing to increased healthcare utilization and reduced functional capacity. Integrating psychological screening and mental health support into routine hematologic care is therefore essential to optimize long-term outcomes. Recognition of the biopsychosocial dimensions of von Willebrand disease should inform clinical management strategies, ensuring that both physical and psychological components of the disorder are comprehensively addressed.

KEYWORDS

Von Willebrand Disease, Depression, Anxiety, Mental Health, Haemophilia

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Introduction**Von Willebrand's disease**

Von Willebrand disease (VWD) is the most common inherited bleeding disorder worldwide, with an estimated prevalence ranging from 0.1% to 1% of the general population, depending on diagnostic criteria. (Barlow et al., 2007; Bowman et al., 2010; Govorov et al., 2016; Roberts et al., 2023) It results from either a quantitative deficiency or a qualitative defect of von Willebrand factor (VWF), a multimeric glycoprotein synthesized by endothelial cells and megakaryocytes and stored in Weibel-Palade bodies and platelet α -granules, respectively. (Barlow et al., 2007; Eladly & Miesbach, 2022; Weyand & Flood, 2021)

Von Willebrand factor is synthesized in endothelial cells and megakaryocytes and is stored in Weibel-Palade bodies (in endothelium) and α -granules (in platelets) before release. It circulates as multimers of variable size and plays a pivotal role in both primary and secondary hemostasis: in primary hemostasis, it mediates platelet adhesion to subendothelial collagen through interactions with the glycoprotein Ib receptor, while in secondary hemostasis, it serves as a carrier and stabilizing molecule for coagulation factor VIII, preventing its premature clearance and degradation. (Eladly & Miesbach, 2022; Goudemand et al., 2025; Sabih & Babiker, 2025; Weyand & Flood, 2021) Defects in VWF concentration, structure, or function impair these mechanisms, leading to a bleeding phenotype characterized by mucocutaneous bleeding, easy bruising, gastrointestinal hemorrhage, and excessive bleeding following trauma or surgical procedures. (Barlow et al., 2007; Eladly & Miesbach, 2022; Goudemand et al., 2025) The VWF is primarily cleared by macrophages in the liver and spleen. (Weyand & Flood, 2021)

Although von Willebrand disease is inherited in an autosomal pattern and affects males and females equally, women are often more symptomatic due to menstruation and childbirth-related hemostatic challenges. (Barlow et al., 2007)

Von Willebrand disease is classified into three principal types based on quantitative or qualitative abnormalities of VWF, each with distinct clinical and genetic characteristics. (Eladly & Miesbach, 2022;

Goudemand et al., 2025) Type 1 VWD, accounting for approximately 60-80% of cases, results from a partial quantitative deficiency of and often follows an autosomal dominant inheritance pattern. Type 2 VWD, representing 15-30% of patients, arises from qualitative defects in VWF function and is subdivided into four variants (2A, 2B, 2M, and 2N) according to the specific functional abnormality. The subdivision of type 2 into the four variants is based on defined pathophysiologic mechanisms, for example type 2A involves loss of high molecular weight multimers, type 2B increased affinity for platelet GPIIb/IIIa, type 2M reduced platelet interaction without multimer loss, and type 2N reduced FVIII binding. (Sadler, 1994) Type 3 VWD, the rarest and most severe form (<1-5% of cases, approximately 1 per million population), results from near-complete absence of plasma VWF and is inherited in an autosomal recessive manner, often leading to a secondary factor VIII deficiency. (Fogarty et al., 2020; O'Sullivan et al., 2023; Tran et al., 2024; Weyand & Flood, 2021) The different sub-types have distinct genetic and inheritance patterns: most type 1 cases follow autosomal dominant inheritance with incomplete penetrance, whereas type 3 is typically autosomal recessive, and type 2N also shows recessive inheritance in many cases. (Johnsen, 1993) Accurate classification is clinically important, as VWD subtypes differ in inheritance patterns, laboratory features, and therapeutic approaches; these distinctions are emphasized in expert consensus documents such as the 2021 ASH guidelines. (Fogarty et al., 2020; Goudemand et al., 2025) Diagnosis of Type 1 VWD may be challenging when VWF levels or bleeding symptoms are mild, whereas Type 3 VWD is generally easier to identify due to severe bleeding and markedly reduced VWF and FVIII levels. (Tran et al., 2024)

The clinical phenotype varies with VWD subtype, VWF activity level, age, and sex. The symptoms of VWD include: mucocutaneous bleeding (common across all types), heavy menstrual bleeding (up to 75-100% of affected females), excessive bruising (62-81%), oropharyngeal bleeding (64%), epistaxis (56%), excessive bleeding from wounds (24-58%) and following dental procedures (26%) or surgery (24%). (Weyand & Flood, 2021) Joint bleeding, while seen in only 5-10% of patients with type 1 or type 2 VWD, in severe cases, particularly in Type 3, joint bleeding occurs in approximately 50% of patients, predisposing them to long-term arthropathy. (Fogarty et al., 2020; O'Sullivan et al., 2023; Van Galen et al., 2012, 2015) A critical aspect of the clinical history involves detailed menstrual evaluation, as women may not recognize bleeding as abnormal, particularly with a familial history of similar symptoms. (Weyand & Flood, 2021)

The diagnosis of von Willebrand disease is a complex process initiated only in patients with a suggestive personal or family history of bleeding. (Weyand & Flood, 2021) In the pediatric diagnostic system the latter stands as the major diagnostic circumstance reported in 60-80% of cases. (Goudemand et al., 2025) Initial assessment should employ a standardized bleeding assessment tool to objectively evaluate the phenotype, as many individuals, particularly women with heavy menstrual bleeding and a familial history of similar symptoms, may perceive their bleeding tendency as normal. (Fogarty et al., 2020; Roberts et al., 2023) Laboratory confirmation is challenging; no single assay is definitive, and screening tests like aPTT and prothrombin time are often normal. First-tier testing must include VWF antigen (VWF:Ag), a functional platelet-binding assay, and FVIII:C to avoid missing qualitative defects. However, diagnosis is complicated by significant assay variability (20-30%), the influence of VWF as an acute-phase reactant, and pre-analytical variables from off-site processing that can cause falsely low levels. Consequently, interpretation requires caution, and multiple evaluations are typically needed. (Weyand & Flood, 2021) Despite international consensus guidelines highlighting these challenges, awareness remains poor, leading to frequent diagnostic delays of up to 15 years, especially in women who are disproportionately diagnosed due to bleeding from menstruation and childbirth. (Eladly & Miesbach, 2022) This diagnostic gap is critical to address, as reduced VWF is a significant risk factor for excessive bleeding during trauma, surgery, or childbirth. (Roberts et al., 2023).

Depression and anxiety

Major Depressive Disorder (MDD) is a common and disabling psychiatric condition characterized by persistent low mood, diminished interest or pleasure in usual activities, alterations in appetite and sleep, psychomotor changes, fatigue, impaired concentration, excessive guilt or worthlessness, and recurrent thoughts of death or suicide. It represents one of the leading global contributors to disability and reduced quality of life. (Belzung et al., 2015; De Menezes Galvão et al., 2021a) Epidemiologic studies have reported lifetime prevalence estimates from around 10% up to over 16% in some populations. (Belzung et al., 2015; Breit et al., 2018) Risk factors for major depressive disorder include genetic vulnerability (heritability estimates often around 30-40%), early life stress, chronic medical illness, social isolation, and repeated psychosocial adversity. (Belzung et al., 2015)

The pathophysiology of major depressive disorder involves a complex interplay of biological systems, including disturbances in monoaminergic neurotransmission (serotonin, norepinephrine, and dopamine), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, inflammatory processes, reduced neurotrophic support, and abnormalities in neural circuitry and brain structure. For example, hyper-activity of the HPA axis (e.g., elevated cortisol, impaired feedback inhibition) is frequently documented in severe or melancholic depression. Elevated peripheral inflammatory markers, such as C-reactive protein or interleukin-6: and diminished brain-derived neurotrophic factor have also been linked with MDD, suggesting that impaired neuroplasticity and neurogenesis may contribute to illness onset and maintenance. (Breit et al., 2018; De Menezes Galvão et al., 2021b) Advanced neuroimaging modalities reveal widespread disruptions in both structure and connectivity across corticolimbic circuits, particularly involving the prefrontal cortex, hippocampus, amygdala, and anterior cingulate cortex, which underlie deficits in affective regulation and cognitive processing in depression. (Belzung et al., 2015; Breit et al., 2018)

Beyond mood symptoms, cognitive dysfunction is increasingly recognised as a core and often persisting component of MDD. Domains commonly affected include attention, processing speed, working memory, executive function and memory encoding/retrieval. (Carvalho et al., 2015; Knight & Baune, 2018; Pan et al., 2019) These deficits frequently persist even after mood remission and contribute substantially to poor psychosocial functioning, occupational impairment and relapse risk. (Bortolato et al., 2015; Carvalho et al., 2015).

Anxiety disorders are characterized by a state of persistent and excessive apprehension and fear, often in anticipation of a future threat. This manifests through a complex interplay of psychological and physiological symptoms, including hypervigilance, restlessness, and muscle tension. The core experience is one of a disproportionate and difficult-to-control worry that significantly interferes with daily functioning. (Craske & Stein, 2016) This heightened state of alertness mobilizes the organism's defensive systems in contexts where no genuine threat is present.

The neurobiology of anxiety involves dysregulation within key brain circuits. Neuroimaging studies consistently implicate the amygdala, a region critical for processing fear and emotional salience, as being hyperactive in individuals with anxiety disorders. This is often coupled with diminished top-down regulatory control from prefrontal cortical areas, such as the ventromedial prefrontal cortex, which normally helps to inhibit the amygdala's fear response. This imbalance creates a neural pathway where potential threats are overestimated, and fear responses are inadequately moderated. (Shin & Liberzon, 2010)

From a psychophysiological perspective, anxiety is strongly linked to a state of sustained hyperarousal of the autonomic nervous system. This manifests in symptoms such as increased heart rate, elevated blood pressure, and a heightened startle reflex. (Hamm, 2020) The underlying mechanism for this involves a chronic state of hyperarousal, driven by the sympathetic nervous system. The pervasive nature of these symptoms, which often include sleep disturbances, underscores that anxiety is not merely a psychological state but a whole-body condition with significant physiological correlates. (Craske & Stein, 2016)

Research consistently shows that anxiety disorders and long-term physical health conditions frequently occur together. This link works in both directions: receiving a diagnosis of a chronic disease can make an individual more vulnerable to anxiety, while pre-existing anxiety can lead to a more severe progression and worse overall prognosis for the physical illness. (Scott et al., 2016) The heightened state of physiological arousal and hypervigilance characteristic of anxiety can directly exacerbate the symptoms of many chronic conditions.

Both depression and anxiety are substantially more prevalent in people with chronic physical illnesses than in the general population, and this comorbidity contributes markedly to reduced quality of life and increased healthcare use. (Berk et al., 2023; Gold et al., 2020; Mariotti, 2015) The association between depression, anxiety and chronic illness is bidirectional: chronic medical conditions elevate the risk of developing depression and anxiety through psychosocial stress, functional decline, and the burden of ongoing disease management, whereas depression itself predisposes individuals to certain chronic diseases and exacerbates their progression through behavioural and biological mechanisms. (Mariotti, 2015; Renn et al., 2011; Van Der Kooy et al., 2007) Behavioural mechanisms include reduced physical activity, poorer diet, smoking, medication nonadherence and delayed care-seeking; these behaviours mediate part of the excess risk of complications and poor outcomes. (Puyat et al., 2017; Zheng et al., 2020) The constant need for self-management, fear of complications, experience of debilitating symptoms, and uncertainty about the future contribute directly to illness-related worry and generalized anxiety. (Roy-Byrne et al., 2008) Biological mechanisms plausibly linking depression and anxiety with worse outcomes in chronic disease include HPA axis dysregulation, autonomic imbalance (reduced heart-rate variability and sympathetic predominance), systemic inflammation, platelet activation and endothelial dysfunction.

The aim of the review

In this review we would like to analyze the comorbidity between von Willebrand's disease, depression and anxiety, as it is crucial to illuminate the complex biopsychosocial interplay between a chronic physical illness and mental health. Understanding this relationship can inform the development of targeted support interventions, reduce stigma, and highlight the need for multidisciplinary care teams that include both hematologists and mental health professionals. It would allow clinicians to screen for and address the significant psychological burden of a chronic illness, prevent the misattribution of fatigue and cognitive symptoms (common in anemia) solely to mental health disorders, and would ultimately lead to integrated treatment plans that address both the hematological and psychological dimensions of the patient's health.

Methodology

To investigate the comorbidity between von Willebrand's disease, depression, and anxiety, we conducted a systematic narrative review of the existing scientific literature. The primary database for this research was PubMed, which was comprehensively searched using a defined set of keywords and Medical Subject Headings terms related to von Willebrand disease, depressive disorders, and anxiety disorders. The retrieved articles were screened against pre-determined inclusion and exclusion criteria to identify the most relevant studies. Following the data collection phase, a thorough qualitative analysis was performed. This involved extracting and synthesizing key findings, methodological approaches, and patient demographics from the selected publications. The analysis focused on critically appraising the evidence for a comorbid relationship, exploring potential biopsychosocial mechanisms, such as the burden of a chronic illness, chronic pain and iron-deficiency anemia, as well as identifying significant gaps in the current understanding to guide future research directions.

Results

Analysed studies

Table 1. Analysis of Clinical Trials

Reference number	Title	Type of the study	Participants	Country of origin of the study
1	Depression and anxiety in persons with Von Willebrand's disease	observational study	77 representatives diagnosed with VWD	United States of America
2	Mental health in persons with von Willebrand's disease in the United States - a large national data based study	retrospective cohort study	records of over 184 million patients, including 66367 diagnosed with VWD	United States of America
3	Living with haemophilia and von Willebrand's: a descriptive qualitative study	qualitative descriptive study	9 members of The Haemophilia Society	United Kingdom
4	Heavy menstrual bleeding and health-associated quality of life in women with von Willebrand's disease	observational study	30 women from local register for patients with VWD at the Karolinska University Hospital	Sweden
5	Health-related quality of life in children with von Willebrand disease: results of the French real-life Willebrand Study Health-related Quality of Life study	prospective, observational study	117 children with VWD	France
6	Pharmacologically Treated Anxiety and Depression in People Diagnosed with von Willebrand disease: Matched Cohort Study	retrospective cohort study	1119 people diagnosed with VWD and 10423 controls	United Kingdom

The studies under analysis are presented in the same sequential order as outlined in the corresponding table (Table 1.):

I - Depression and anxiety in persons with Von Willebrand's disease (Roberts et al., 2023)

II - Mental health in persons with von Willebrand's disease in the United States - a large national data based study (Tran et al., 2024)

III - Living with haemophilia and von Willebrand's: a descriptive qualitative study (Barlow et al., 2007)

IV - Heavy menstrual bleeding and health-associated quality of life in women with von Willebrand's disease (Govorov et al., 2016)

V - Health-related quality of life in children with von Willebrand disease: results of the French real-life Willebrand Study Health-related Quality of Life study (Goudemand et al., 2025)

VI - Pharmacologically Treated Anxiety and Depression in People Diagnosed with von Willebrand disease: Matched Cohort Study (Hagberg et al., 2023)

A thorough analysis of the six studies detailed in the table above (Table 1.) provided the essential characteristics of the comorbidity between von Willebrand disease and depression and anxiety. In all the studies specific inclusion and exclusion criteria were applied.

The inclusion criteria involved: von Willebrand Disease diagnosis (common for all of the studies enlisted above, specific type of the disease for some of the studies), specific age group (≥ 12 years for the first study, 0–110 years for the second, 18–52 years for the fourth, < 18 years for the fifth), (Goudemand et al., 2025; Govorov et al., 2016; Roberts et al., 2023; Tran et al., 2024) female gender (the fourth study), (Govorov et al., 2016) ability to speak a certain language (English or Spanish for the first study), (Roberts et al., 2023) and provided written informed consent (for the first study). (Roberts et al., 2023)

The comorbidity between von Willebrand disease, depression and anxiety

The collective evidence from a diverse body of research (spanning large-scale epidemiological studies, detailed clinical cohorts, and intimate qualitative interviews) presents a consistent and concerning profile: von Willebrand Disease is significantly and intrinsically linked with a high burden of depression and anxiety. (Barlow et al., 2007; Goudemand et al., 2025; Govorov et al., 2016; Hagberg et al., 2023; Roberts et al., 2023; Tran et al., 2024) This comorbidity is mediated by a complex, synergistic biopsychosocial interplay of physiological, psychological, and social factors that permeate every stage of life, from childhood through adulthood. A principal conclusion is that psychiatric morbidity constitutes a fundamental, rather than ancillary, feature of VWD, compelling a transition in clinical practice from a purely biomedical to a biopsychosocial care model. The findings reveal that the burden of VWD extends far beyond the bleeding diathesis, embedding itself in the emotional and social fabric of patients' lives, and is influenced by a range of specific factors including pain, bleeding symptoms, social isolation, and demographic vulnerabilities.

The most immediate and striking conclusion from the analysis of these studies is the huge scale of the problem. The prevalence of depression and anxiety in people with VWD is substantially higher compared to the general population, which was demonstrated across different healthcare systems, research methodologies, and patient populations. The most compelling figures come from a detailed US multicentre observational study which actively screened patients using validated tools. (Roberts et al., 2023) This research found clinically significant symptoms of depression and anxiety in 63.6% and 58.3% of participants, respectively. These figures are profoundly high, indicating that most individuals in this dedicated clinical cohort were experiencing substantial psychological distress. The use of the PHQ-8 and GAD-7 scales suggests that these were not subclinical concerns but symptoms meeting the threshold for clinical significance, often in the moderate to severe range. This study establishes a high baseline for the psychological burden within a population engaged with specialist care.

This alarming prevalence is corroborated by a massive retrospective cohort study using the Epic Cosmos database, which encompassed over 184 million patients. (Tran et al., 2024) This study, while reporting lower absolute prevalences of 23.12% for depression and 32.90% for anxiety, confirmed a highly significant relative risk of 2.68 for both conditions compared to a carefully matched control group without VWD. The discrepancy in prevalence rates between the first study (Roberts et al., 2023) and the second one (Tran et al., 2024) is methodological and illuminating. The first one actively screened for symptoms in a research setting, likely capturing a broader spectrum of psychological distress, including those who may not have sought formal treatment. In contrast, the second study identified cases through ICD billing codes and presumably clinical diagnoses within electronic health records, capturing individuals whose symptoms were severe enough to come to the attention of a healthcare provider and be formally documented. Despite these different approaches, both

studies unequivocally demonstrate a severe mental health burden, with the first study revealing the depth of the symptom pool and the second one confirming its significant translation into clinical morbidity and a two-to-threefold increased risk.

Further supporting this conclusion is a UK retrospective cohort study using the Clinical Practice Research Datalink. (Hagberg et al., 2023) This study adopted a particularly rigorous definition of a mental health condition, requiring both a formal clinical diagnosis and a corresponding prescription within 90 days. This methodology ensures the identification of cases with clinically significant conditions warranting pharmacological intervention. The results demonstrated that people with VWD had a 37% higher risk of receiving treatment for anxiety (IRR=1.37) and a 35% higher risk for treated depression (IRR=1.35) compared to their matched controls. This finding is powerful because it moves beyond simple prevalence and demonstrates an increased incidence of treated disease, underscoring the severity and healthcare utilization associated with these comorbidities. Together, these three large studies (Hagberg et al., 2023; Roberts et al., 2023; Tran et al., 2024) form a triangulated and irrefutable argument: whether measured through active screening, diagnostic codes, or treatment records, patients diagnosed with VWD carry a profoundly heavier burden of depression and anxiety than the general population.

The high prevalence of mental health conditions in PwVWD is not random; the studies consistently point to a constellation of disease-specific and psychosocial factors that act as powerful drivers and predictors of psychological distress. These factors create a multifactorial model where the physical reality of the disease directly catalyzes psychological sequelae. The factors influencing symptoms in patients with bleeding disorders include: pain-related factors (pain intensity, pain persistence and pain sensitivity), joint health, viral co-infections (hepatitis or HIV infection), age (especially over 40 years old), (Schmidt et al., 2025) somatic burden, isolation, stigma, and social functioning. (Barlow et al., 2007)

Chronic pain and joint problems emerge from the data as one of the most potent and consistent predictors of psychological distress. The first study provided quantitative rigor to this link, identifying joint problems as a major independent predictor of depression, with an odds ratio (OR) of 6.3. (Roberts et al., 2023) This means that after controlling for other variables, individuals with VWD and joint problems were over six times more likely to be depressed than those without such issues. This is a staggering effect size that highlights the devastating psychological impact of chronic musculoskeletal pain and disability. Furthermore, this study found that both depression and anxiety scores were significantly correlated with higher levels of self-reported chronic pain, cementing the relationship between physical suffering and emotional distress.

The qualitative findings from the third study give another point of view to this statistical correlation. Participants in that study described facing significant physical challenges, including joint bleeds and comorbidities like arthritis, which impacted their education, work, and social lives. (Barlow et al., 2007) This narrative illustrates the pathway from a bleeding event to a psychological outcome: a joint bleed leads to pain and immobility, which disrupts education and employment, leading to financial strain and a loss of purpose, which in turn fosters feelings of anxiety about the future and depression rooted in loss and limitation. The pain is not merely a sensory experience; it is a constant, intrusive reminder of the disease, a barrier to participation in life, and a direct contributor to a cycle of debilitation and hopelessness. The finding from the fourth study that women with heavy menstrual bleeding reported a significantly impaired quality of life in the dimension of bodily pain further extends this concept beyond the joints to other forms of chronic pain associated with VWD. (Govorov et al., 2016)

The burden of VWD extends far beyond the joints and chronic pain into the realm of acute and often terrifying bleeding episodes. The second study provided critical evidence that the risk of depression and anxiety is significantly amplified by active bleeding symptoms. The study found that the highest rates of depression and anxiety were associated with symptoms like abnormal uterine bleeding, hematemesis, hemoptysis, hematuria, and melena. (Tran et al., 2024) These are not mere inconveniences; they represent episodes of acute crisis, a profound loss of bodily control, and often frightening clinical presentations that can evoke fear of severe illness or death. The unpredictable nature of these bleeds fosters a constant state of hypervigilance and anxiety, as articulated by participants in the third study, who experienced anxiety linked to the daily and unpredictable management of their condition. (Barlow et al., 2007)

The fourth study focused on women illuminates this dynamic with exceptional clarity, particularly concerning abnormal uterine bleeding. It reported that 90.9% of women with menstruation reported mood changes and 63.6% experienced anxiety due to their periods. This directly links a specific, recurring bleeding symptom to a profound psychological impact. The study further detailed how menstruation imposed substantial psychological and lifestyle limitations, causing reported limitations in family life (72.7%), vacations (68.2%),

leisure activities (63.6%), and sex life (63.6%). (Govorov et al., 2016) This data shows that heavy menstrual bleeding is not just a gynecological issue; it is a pervasive source of psychological trauma and social disruption. It robs women of their ability to engage in core life activities, leading to isolation, frustration, and a diminished sense of self, which are core components of depressive and anxiety disorders.

The psychological impact of VWD is deeply embedded in the social experience of the individual. The quantitative data from the first study identified single or unpartnered marital status as a powerful predictor for both depression (OR=7.0) and anxiety (OR=10.8). (Roberts et al., 2023) These are remarkably high odds ratios, suggesting that lacking a partner is one of the strongest risk factors for poor mental health in this population. This highlights the protective role of intimate social support and, conversely, the profound isolation and lack of a confidant that can accompany chronic illness.

The third study gives rich context to this statistic. Participants reported widespread experiences of stigmatisation and public misconception about their disorders. This stigma was not an abstract concept; it had real-world consequences, as many had experienced discrimination in educational and work settings. Being feared, misunderstood, or discriminated against because of one's condition fosters a deep-seated anxiety in social situations and can lead to a withdrawal from social life to avoid these negative experiences, a classic feature of both social anxiety and depression. The psychological burden was compounded by concerns about the future, including the ability to maintain employment, manage health costs, and form stable relationships, all of which contribute to chronic stress and depressive apprehension. (Barlow et al., 2007)

This social impairment begins early in life, as demonstrated by the fifth study. It found that adolescents with VWD reported their social lives as notably impaired, with relationships with friends being the most impacted dimension. The disease also limited physical activities, especially sports, creating a significant barrier to social integration and the normal adolescent experiences of team-building, physical play, and camaraderie. Furthermore, the study noted that adolescents' feelings of independence were affected. (Goudemand et al., 2025) This creates a difficult psychological conflict between the natural developmental drive for autonomy and the necessary reliance on family and healthcare systems for management of their disease, potentially fostering resentment, frustration, and a damaged self-esteem.

The burden of mental health comorbidities is not evenly distributed across the VWD population, the studies point to clear demographic subgroups that face a disproportionately high risk.

As one of the specific groups women and girls can be determined. A clear gender disparity exists. The second study explicitly stated that females with VWD had a higher prevalence of both depression and anxiety than males with the condition. (Tran et al., 2024) The sixth study refined this further, showing that the increased risk was driven primarily by females, specifying that females aged 20-39 were at greatest risk for treated anxiety, while girls aged 0-19 were at greatest risk for depression. (Hagberg et al., 2023) This data underscores the compounded burden faced by women and girls, who must navigate the dual challenges of a chronic bleeding disorder and gender-specific health issues like heavy menstrual bleeding, which the fourth study showed to be a major source of psychological distress. (Govorov et al., 2016) The hormonal fluctuations of the menstrual cycle and the social pressures surrounding femininity and motherhood likely intersect with the VWD diagnosis to create a unique and potent stressor.

Another group would be adolescents and young adults. The first study found that adolescent age was a strong predictor of anxiety (OR=6.7). (Roberts et al., 2023) This life stage, intensely focused on identity formation, social belonging, and increasing independence, is uniquely disrupted by VWD. The need to explain their condition to peers, the inability to participate in certain activities, and the looming transition from pediatric to adult care—a period often fraught with anxiety and potential for lapses in management—all contribute to this vulnerability. The fifth study finding that adolescents felt their independence was impacted directly speaks to this core developmental conflict. (Goudemand et al., 2025)

Individuals with milder forms of the disease are also a group worth analysing separately. A counterintuitive but critical finding from the first study was that individuals with low VWF (mild type 1 VWD) showed particularly elevated rates of depressive (86.7%) and anxiety (69.2%) symptoms. This is a profound insight that challenges assumptions about disease severity and psychological impact. This may be explained by the fact that these patients may not receive the same level of specialist support, patient education, and validation as those with severe, type 3 VWD. Their symptoms may be dismissed or overlooked by both them and healthcare providers, leading to a lack of official diagnosis, inadequate support, and a feeling of being unheard. (Roberts et al., 2023) This invalidation, coupled with very real symptoms that still impact their quality of life, can paradoxically increase psychological distress more than in patients with a clear, validated, and well-managed severe diagnosis.

The psychological burden of VWD creates a ripple effect that strains the entire family system. The fifth study documented a significant impact on family dynamics, including parental coping and financial strain. Parents reported high treatment dissatisfaction and burden, and the overall family impact was highest in children with type 3 VWD. This shows the constant vigilance, medical management, financial cost, and emotional worry required to care for a child with a chronic condition led to chronic stress and anxiety within the parents and the family unit as a whole. The disease, therefore, does not only affect the diagnosed individual but functions as a family diagnosis. (Goudemand et al., 2025)

This multifaceted psychological and physical burden culminates in a significantly reduced Health-Related Quality of Life (HRQoL). The first study confirmed this directly, finding that both depression and anxiety were significantly correlated with lower EQ-5D scores. (Roberts et al., 2023) Even when overall scores for an entire group were not significantly lower than population norms-as was the case for all women in the fourth study (Govorov et al., 2016)-specific, debilitating aspects like bodily pain were markedly impaired. This suggests that global HRQoL tools may sometimes mask the significant deficits in key domains that are most salient to patients' lived experiences.

Finally, the longitudinal aspect of the first study provides a crucial piece of information: the rates of depression and anxiety were similar before and during the COVID-19 pandemic. This temporal stability is highly significant. It indicates that the mental health burden in patients with VWD is not a transient phenomenon linked to a unique global stressor but is a stable and enduring feature of the condition itself. The baseline level of distress is so high that even a major societal disruption did not significantly alter its prevalence, underscoring that the source of this psychological morbidity is rooted in the chronic, lifelong nature of VWD itself. (Roberts et al., 2023)

Discussion

This review integrates findings from a broad spectrum of clinical and epidemiological studies to delineate the profound and consistent relationship between von Willebrand disease (VWD) and the comorbid conditions of depression and anxiety. The collective evidence indicates that psychological morbidity is not a secondary concern but a fundamental aspect of the VWD patient experience, necessitating a paradigm shift from a purely biomedical to an integrated biopsychosocial model of care.

The most immediate finding of this review is the significantly elevated burden of depression and anxiety in individuals with VWD. This is demonstrated across different healthcare systems and methodologies, creating an irrefutable argument. The high prevalence rates-ranging from active screening studies showing over 60% of patients with clinically significant symptoms (Roberts et al., 2023) to large database studies confirming a 2.5 to 3-fold increased risk (Tran et al., 2024)- indicate a public health concern within this patient population. The persistence of this association across diverse assessment modalities, including standardized symptom inventories, diagnostic classifications, and pharmacological treatment records, demonstrates that the comorbidity between VWD and depression and anxiety, confers significant clinical burden and contributes meaningfully to increased healthcare utilization.

These findings have urgent implications for clinical practice. Firstly, routine, standardized screening for depression and anxiety using validated tools must become a standard of care in hematology clinics. Relying on patient self-reporting is insufficient, as symptoms may be misattributed or normalized. Secondly, management must evolve into a multidisciplinary endeavor, integrating mental health professionals into the core care team for patients with VWD. This is crucial for addressing the full spectrum of patient suffering and improving adherence to often complex treatment regimens. Thirdly, clinicians must be attuned to the specific risk factors identified. A female patient with menorrhagia and joint pain, or an adolescent struggling with social integration, should be proactively assessed and supported. The management of heavy menstrual bleeding, in particular, should be recognized not only as a gynecological issue but as a primary intervention for improving mental health.

For research, this review highlights significant gaps. The biological mechanisms linking VWD to mood disorders remain speculative. Longitudinal studies are needed to track the onset and progression of mental health symptoms from childhood through adulthood. Finally, interventional research is critical to develop and test the efficacy of integrated care models and psychosocial support programs tailored to the unique needs of this population.

This review has several limitations. As a narrative synthesis, it is subject to the potential for author interpretation bias compared to a formal meta-analysis. The included studies themselves have limitations, including the cross-sectional design of several, which precludes causal inference, and the heterogeneity in how mental health outcomes were defined and measured. Furthermore, the patient populations were primarily from high-income countries, which may limit the generalizability of the findings to other healthcare settings.

Conclusions

The evidence from these six studies establishes a definitive and powerful link between VWD and the comorbidities of depression and anxiety. This relationship is not simple but is mediated through a network of interconnected pathways: physiological pathways driven by chronic pain and joint damage, (Roberts et al., 2023), the direct experience of debilitating and frightening bleeding episodes, (Govorov et al., 2016; Tran et al., 2024), psychological pathways fueled by the unpredictability of bleeds, (Barlow et al., 2007) fear of the future, (Barlow et al., 2007), a perceived lack of control over one's own body (Goudemand et al., 2025), social pathways carved by stigma and discrimination, (Barlow et al., 2007) social isolation indicated, (Roberts et al., 2023) and the impairment of key relationships and life activities, from friendships in adolescence (Goudemand et al., 2025) to marital partnerships in adulthood. (Roberts et al., 2023)

The picture that emerges is one of a whole-life condition. It begins in childhood, impairing social development and independence, (Goudemand et al., 2025) later intensifies in adolescence, particularly for girls, with the onset of menses creating a major new source of anxiety and disruption. (Govorov et al., 2016; Hagberg et al., 2023) It persists into adulthood, where chronic pain and joint disease become powerful drivers of depression, and social isolation compounds the distress. (Barlow et al., 2007; Roberts et al., 2023; Tran et al., 2024) The burden is shared by the family (Goudemand et al., 2025) and is reflected in a consistently diminished quality of life. (Roberts et al., 2023)

Therefore, the traditional model of care for VWD, which has focused predominantly on hematological parameters, factor levels, and acute bleeding control, is demonstrably insufficient. To address the full scope of the disease, a new, integrated standard of care is urgently needed. This model must be biopsychosocial in its approach, proactively addressing the factors identified here. This includes routine, standardized mental health screening during comprehensive care visits, the integration of psychological services directly into hemophilia treatment centers, proactive management of pain and gynecological issues not just as somatic problems but as core mental health strategies, and patient education that normalizes the discussion of mental health to destigmatize these conditions and encourage help-seeking behaviour. Ultimately, recognizing and addressing the profound psychological burden of VWD is essential to achieving the holistic well-being of those living with this complex condition. Treating the bleed is only half the battle; healing the mind is paramount to enabling a full, engaged, and healthy life.

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