The Relationship Between Multiple Sclerosis and Bipolar Disorder: A Comprehensive Review

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory demyelinating disease of the central nervous system, frequently accompanied by psychiatric comorbidities, including bipolar disorder (BD). Recent research highlights a higher prevalence of BD among MS patients compared to the general population, with studies reporting lifetime prevalence rates ranging from approximately 2% to over 8% in MS populations (Joseph et al., 2020; Mirmosayyeb et al., 2026; Jun-O'connell et al., 2016; Johansson et al., 2014; Fatheddine et al., 2024). Epidemiological evidence suggests that MS patients are at increased risk for BD, and vice versa, with hazard ratios indicating a significantly elevated risk (Mirmosayyeb et al., 2026; Johansson et al., 2014; Huang et al., 2021). The relationship appears multifactorial, involving neuroinflammatory processes, genetic susceptibility (notably HLA-DR2), neuroimaging findings of white matter lesions in frontal and temporal lobes, and possible medication effects (e.g., corticosteroids) (Mamtani et al., 2024; Rennert et al., 2024; Mirmosayyeb et al., 2026; Konradi et al., 2011; Bozikas et al., 2003; Lorefice et al., 2020). Clinical presentations are diverse: BD may precede, coincide with, or follow MS onset; mood symptoms can sometimes be the initial manifestation of MS or be exacerbated by MS treatments (Maamri et al., 2021; Xin et al., 2022; Hutchinson et al., 1993; Vohra & Leeming, 2010). The comorbidity negatively impacts quality of life and may accelerate disability progression in MS (Carta et al., 2014; Jun-O'connell et al., 2016; Mckay et al., 2018). Despite growing evidence for an association, diagnostic challenges remain due to symptom overlap and underdiagnosis. Further research is needed to clarify pathophysiological mechanisms and optimize management strategies (Vieito et al., 2025; Filser et al., 2022; Iacovides & Andreoulakis, 2011).

Is there an increased risk of bipolar disorder in patients with multiple sclerosis? N = 32

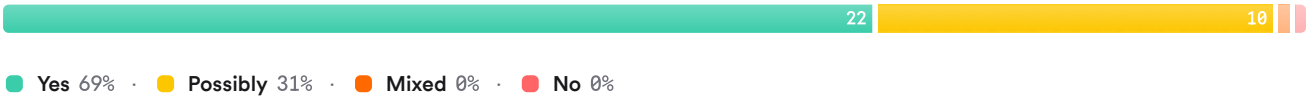

FIGURE 1 Consensus meter visualizing whether MS increases risk for bipolar disorder.

2. Methods

A comprehensive literature search was conducted across over 170 million research papers indexed in Consensus, including Semantic Scholar and PubMed. The search strategy targeted foundational concepts, mechanistic pathways, clinical presentations, critiques/contrasts, related disorders, and alternative terminology. In total, 422,818 papers were initially identified; after multi-phase filtering for relevance and quality—including citation graph traversal and machine-learned screening—50 papers were included in this review.

Search Strategy

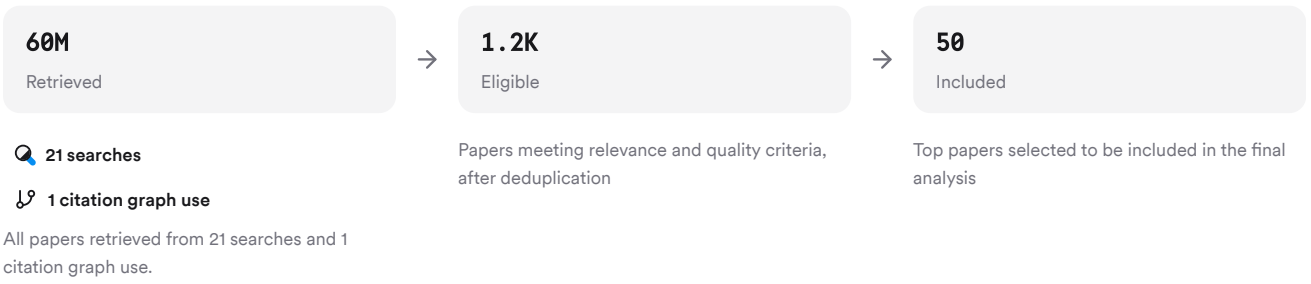

FIGURE 2 Flow diagram showing paper selection process for this review.

Six unique search strategies were used to capture epidemiology, mechanisms, clinical features, critiques/contrasts, related disorders, and terminology variants.

3. Results

3.1 Epidemiology & Prevalence

Systematic reviews and meta-analyses consistently report that BD is more prevalent among people with MS than in the general population. Pooled prevalence estimates range from about 2% to over 8%, with some studies suggesting up to a twofold increase in risk (Joseph et al., 2020; Mirmosayyeb et al., 2026; Jun-O'connell et al., 2016; Johansson et al., 2014; Huang et al., 2021; Fatheddine et al., 2024). Large cohort studies confirm this association across different populations (Meier et al., 2019; Johansson et al., 2014; Huang et al., 2021).

3.2 Clinical Presentation & Diagnostic Challenges

Case reports and series illustrate varied temporal relationships: BD may precede MS onset, occur concurrently with neurological symptoms, or develop after MS diagnosis (Mamtani et al., 2024; Maamri et al., 2021; Xin et al., 2022; Hutchinson et al., 1993). Mood episodes—including mania induced by corticosteroids—can complicate diagnosis. Neuroimaging often reveals demyelinating lesions in frontal/temporal lobes during mood episodes (Mamtani et al., 2024; Rennert et al., 2024). Diagnostic overshadowing can delay recognition of either condition when psychiatric symptoms dominate early presentations (Jun-O'connell et al., 2016).

3.3 Mechanistic Pathways & Genetic Susceptibility

Several studies implicate shared neuroinflammatory mechanisms (e.g., cytokine dysregulation), mitochondrial dysfunction, oligodendrocyte gene downregulation, and HLA-DR2 genetic associations as potential links between MS and BD (Mirmosayyeb et al., 2026; Konradi et al., 2011; Bozikas et al., 2003). Familial clustering supports a possible genetic predisposition but does not fully explain the comorbidity; environmental factors and brain lesions may also contribute (Kosmidis et al., 2012; Bozikas et al., 2003).

3.4 Impact on Quality of Life & Disability Progression

Comorbid BD in MS is associated with poorer quality of life than either condition alone; type II BD may have an even greater impact than major depressive disorder on functional outcomes (Carta et al., 2014). Psychiatric comorbidity—including BD—predicts greater disability progression in MS cohorts (Mckay et al., 2018), emphasizing the need for integrated care.

Results Timeline

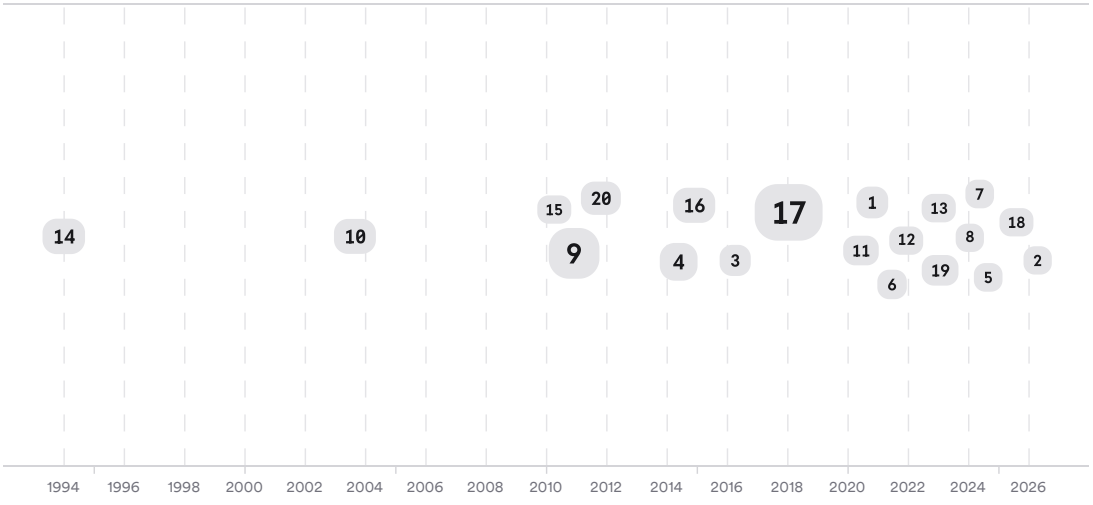

FIGURE 3 Timeline showing publication trends on MS–bipolar disorder comorbidity research. Larger markers indicate more citations.

Top Contributors

Type	Name	Papers
Author	M. Carta	(Johansson et al., 2014; Rennert et al., 2024; Iacovides & Andreoulakis, 2011)

Type	Name	Papers
Author	L. Lorefice	(Johansson et al., 2014; Rennert et al., 2024; Keskin et al., 2013)
Author	E. Cocco	(Johansson et al., 2014; Rennert et al., 2024)
Journal	*Journal of affective disorders*	(Johansson et al., 2014; Rennert et al., 2024)
Journal	*European Psychiatry*	(Mirmosayyeb et al., 2026; Jun-O'connell et al., 2016)
Journal	*Behavioural Neurology*	(Xin et al., 2022; Filser et al., 2022)

FIGURE 4 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The evidence robustly supports an increased prevalence of bipolar disorder among individuals with multiple sclerosis compared to the general population (Joseph et al., 2020; Mirmosayyeb et al., 2026; Jun-O'connell et al., 2016; Johansson et al., 2014). This association persists across diverse populations and study designs—including large-scale cohort studies and meta-analyses—though absolute prevalence estimates vary due to methodological differences (diagnostic criteria used; population characteristics) (Joseph et al., 2020; Mirmosayyeb et al., 2026). Mechanistically, both neuroinflammation (shared cytokine profiles) and genetic factors (notably HLA-DR2) are implicated as common substrates for both diseases; however, some genetic studies find no direct overlap between BD and MS susceptibility loci (Andreassen et al., 2014), suggesting complex or indirect relationships.

Clinical management is complicated by overlapping symptoms—mania or depression may be misattributed to either disease—and by treatment effects (e.g., corticosteroid-induced mania) (Mamtani et al., 2024; Xin et al., 2022). Neuroimaging findings support a role for demyelinating lesions in mood symptomatology but are not specific enough for differential diagnosis alone (Mamtani et al., 2024; Rennert et al., 2024).

Importantly, psychiatric comorbidity worsens quality of life and accelerates disability progression in MS patients; thus routine mental health screening is recommended for all individuals with MS (Carta et al., 2014; Jun-O'connell et al., 2016; Mckay et al., 2018). Despite these insights, underdiagnosis remains common due to lack of standardized assessment tools for subsyndromal affective symptoms in this population (Filser et al., 2022).

Claims and Evidence Table

Claim	Evidence Strength	Reasoning	Papers
Bipolar disorder is more prevalent among people with multiple sclerosis	Strong	Supported by multiple meta-analyses/cohort studies showing higher prevalence/risk ratios	(Joseph et al., 2020; Mirmosayyeb et al., 2026; Jun-O'connell et al., 2016; Johansson et al., 2014)
Shared neuroinflammatory mechanisms contribute to both conditions	Moderate	Cytokine dysregulation/immune activation found in both diseases; supported by mechanistic/pathology studies	(Mirmosayyeb et al., 2026; Konradi et al., 2011)
Genetic susceptibility (HLA-DR2) links some cases	Moderate	Familial clustering/HLA studies suggest partial overlap	(Kosmidis et al., 2012; Bozikas et al., 2003)

Claim	Evidence Strength	Reasoning	Papers
Comorbid BD worsens quality of life/disability progression	Moderate	Cross-sectional/cohort data show greater impairment when both conditions coexist	(Carta et al., 2014; Jun-O'connell et al., 2016; Mckay et al., 2018)
Symptom overlap complicates diagnosis	Moderate	Case reports/reviews highlight diagnostic overshadowing/misattribution	(Mamtani et al., 2024; Filser et al., 2022)
No direct genome-wide pleiotropy between BD and MS	Moderate	GWAS finds overlap between schizophrenia/MS but not BD/MS	(Andreassen et al., 2014)

FIGURE 5 Key claims and support evidence identified in these papers.

5. Conclusion

There is strong epidemiological evidence that bipolar disorder occurs more frequently among people with multiple sclerosis than expected by chance alone. This relationship likely reflects a combination of shared neurobiological mechanisms (neuroinflammation), partial genetic susceptibility (notably HLA-DR2), medication effects (corticosteroids), brain lesion localization (frontal/temporal white matter), as well as psychosocial stressors associated with chronic illness.

Research Gaps

Despite substantial progress in understanding the association between MS and BD, gaps remain regarding causality/mechanisms (especially at the molecular/genetic level), optimal diagnostic strategies for subsyndromal symptoms or early presentations, longitudinal course/prognosis of comorbid cases versus single-diagnosis cases across diverse populations.

Research Gaps Matrix

Topic/Outcome	Epidemiology Studies	Neuroimaging Findings	Genetic Studies	Treatment Outcomes
Prevalence/Incidence	12	GAP	GAP	GAP
Neurobiological Mechanisms	GAP	5	3	GAP
Clinical Course/Prognosis	6	GAP	GAP	GAP
Treatment Response	GAP	GAP	GAP	4

FIGURE Matrix highlighting where research on MS–bipolar disorder comorbidity is concentrated versus lacking.

Open Research Questions

Future research should focus on clarifying causal pathways using prospective designs; developing standardized diagnostic tools for affective symptoms in MS; exploring personalized treatment approaches; investigating long-term outcomes.

Question	Why
What are the precise neurobiological mechanisms linking multiple sclerosis to bipolar disorder?	Understanding shared pathways could inform targeted therapies/prevention strategies for at-risk individuals.
How does early identification/treatment of bipolar symptoms affect long-term outcomes in people with MS?	Early intervention may improve prognosis but requires robust longitudinal data to guide best practices.

FIGURE Open questions guiding future research directions on this topic.

In summary: Bipolar disorder is significantly more common among people with multiple sclerosis than the general population—a relationship likely driven by overlapping biological mechanisms—and addressing this comorbidity is essential for improving patient outcomes.

References

Andreassen, O., Harbo, H., Wang, Y., Thompson, W., Schork, A., Mattingsdal, M., , Z., Bettella, F., Ripke, S., Kelsoe, J., Kendler, K., O'Donovan, M., Sklar, P., McEvoy, L., Desikan, R., Lie, B., Djurovic, S., & Dale, A. (2014). Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. *Molecular Psychiatry, 20*, 207 - 214. https://doi.org/10.1038/mp.2013.195

Bozikas, V., Anagnostouli, M., Petrikis, P., Sitzoglou, C., Phokas, C., Tsakanikas, C., & Karavatos, A. (2003). Familial bipolar disorder and multiple sclerosis: a three-generation HLA family study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 27*, 835-839. https://doi.org/10.1016/s0278-5846(03)00116-7

Carta, M., Moro, M., Lorefice, L., Picardi, A., Trincas, G., Fenu, G., Cocco, E., Floris, F., Bessonov, D., Akiskal, H., & Marrosu, M. (2014). Multiple sclerosis and bipolar disorders: the burden of comorbidity and its consequences on quality of life.. *Journal of affective disorders, 167*, 192-7. https://doi.org/10.1016/j.jad.2014.05.024

Fatheddine, M., Elfahiri, F., Ennaciri, Z., Adali, I., & Manoudi, F. (2024). Psychiatric Comorbidities of Multiple Sclerosis: A Cross-Sectional Study. *SAS Journal of Medicine*. https://doi.org/10.36347/sasjm.2024.v10i06.003

Filser, M., Buchner, A., Fink, G., Gold, S., & Penner, I. (2022). The manifestation of affective symptoms in multiple sclerosis and discussion of the currently available diagnostic assessment tools. *Journal of Neurology, 270*, 171 - 207. https://doi.org/10.1007/s00415-022-11359-6

Huang, Y., Chien, W., Chung, C., Chang, H., Kao, Y., Wan, F., Huang, S., Chung, R., Wang, R., Wang, B., Tzeng, N., & Sun, C. (2021). Risk of Psychiatric Disorders in Multiple Sclerosis: A Nationwide Cohort Study in an Asian Population. *Neuropsychiatric Disease and Treatment, 17*, 587 - 604. https://doi.org/10.2147/ndt.s268360

Hutchinson, M., Stack, J., & Buckley, P. (1993). Bipolar affective disorder prior to the onset of multiple sclerosis. *Acta Neurologica Scandinavica, 88*. https://doi.org/10.1111/j.1600-0404.1993.tb05365.x

Iacovides, A., & Andreoulakis, E. (2011). Bipolar disorder and resembling special psychopathological manifestations in multiple sclerosis: a review. *Current Opinion in Psychiatry, 24*, 336–340. https://doi.org/10.1097/yco.0b013e328347341d

Johansson, V., Lundholm, C., Hillert, J., Masterman, T., Lichtenstein, P., Landén, M., & Hultman, C. (2014). Multiple sclerosis and psychiatric disorders: Comorbidity and sibling risk in a nationwide Swedish cohort. *Multiple Sclerosis Journal, 20*, 1881 - 1891. https://doi.org/10.1177/1352458514540970

Joseph, B., Nandakumar, A., Ahmed, A., Gopal, N., Murad, M., Frye, M., Tobin, W., & Singh, B. (2020). Prevalence of bipolar disorder in multiple sclerosis: a systematic review and meta-analysis. *Evidence-Based Mental Health, 24*, 88 - 94. https://doi.org/10.1136/ebmental-2020-300207

Jun-O'connell, A., Butala, A., Morales, I., Henninger, N., Deligiannidis, K., Byatt, N., & Ionete, C. (2016). The Prevalence of Bipolar Disorders and Association With Quality of Life in a Cohort of Patients With Multiple Sclerosis.. *The Journal of neuropsychiatry and clinical neurosciences, 29 1*, 45-51. https://doi.org/10.1176/appi.neuropsych.15120403

Keskin, N., Çakmak, S., Tamam, L., & Evlice, A. (2013). Comorbidity of Bipolar Disorder and Multiple Sclerosis: A Case Report. *Cukurova Medical Journal, 38*, 832-836.

Konradi, C., Sillivan, S., & Clay, H. (2011). Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis.. *Neurobiology of disease, 45 1*, 37-47. https://doi.org/10.1016/j.nbd.2011.01.025

Kosmidis, M., Bozikas, V., Giannouli, V., Karavatos, A., & Fokas, K. (2012). Familial Comorbidity of Bipolar Disorder and Multiple Sclerosis: Genetic Susceptibility, Coexistence or Causal Relationship?. *Behavioural Neurology, 25*, 341 - 349. https://doi.org/10.3233/ben-2012-110198

Lorefice, L., Fenu, G., Carta, E., Frau, J., Coghe, G., Contu, F., Barracciu, M., Carta, M., & Cocco, E. (2020). Bipolar disorders and deep grey matter in multiple sclerosis: A preliminary quantitative MRI study.. *Multiple sclerosis and related disorders, 46*, 102564. https://doi.org/10.1016/j.msard.2020.102564

Maamri, A., Ghabi, H., & Zalila, H. (2021). Bipolar disorder and multiple sclerosis. *European Psychiatry, 64*, S239 - S239. https://doi.org/10.1192/j.eurpsy.2021.640

Mamtani, H., Jain, K., Reddy, P., Arasappa, R., Ganjekar, S., Thippeswamy, H., Bhat, M., Netravathi, M., & Desai, G. (2024). The co-occurrence of multiple sclerosis and bipolar disorder: A case series on clinical and neuroimaging correlates.. *Asian journal of psychiatry, 96*, 104041. https://doi.org/10.1016/j.ajp.2024.104041

Mckay, K., Tremlett, H., Fisk, J., Zhang, T., Patten, S., Kastrukoff, L., Campbell, T., & Marrie, R. (2018). Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology, 90*, e1316 - e1323. https://doi.org/10.1212/wnl.0000000000005302

Meier, U., Ramagopalan, S., Goldacre, M., & Goldacre, R. (2019). Risk of Schizophrenia and Bipolar Disorder in Patients With Multiple Sclerosis: Record-Linkage Studies. *Frontiers in Psychiatry, 11*. https://doi.org/10.3389/fpsyt.2020.00662

Mirmosayyeb, O., Vaheb, S., Shaygannejad, A., Foroughi, E., Panah, M., & Shaygannejad, V. (2026). Bipolar disorder in people with multiple sclerosis: an updated systematic review and meta-analysis. *BMC Psychiatry, 26*. https://doi.org/10.1186/s12888-026-07839-y

Rennert, K., Verduijn, T., & Krol, D. (2024). [Multiple sclerosis and bipolar disorder: an overlap between soma and psyche].. *Tijdschrift voor psychiatrie, 66 3*, 165-167.

Vieito, P., Lagares, B., Iglesias, P., Cao, G., Pego, L., López, R., Ovies, F., Barcia, P., Magro, P., Pereira, G., Chaín, R., & Pérez, P. (2025). Neuropsychiatric Symptoms in Multiple Sclerosis: A Case Report. *European Psychiatry, 68*, S519 - S519. https://doi.org/10.1192/j.eurpsy.2025.1073

Vohra, A., & Leeming, C. (2010). Bipolar affective disorder as the initial manifestation of multiple sclerosis. *Irish Journal of Psychological Medicine, 27*, 97 - 98. https://doi.org/10.1017/s0790966700001142

Xin, G., Yee, K., & Kiat, A. (2022). A Case of Bipolar Disorder due to Multiple Sclerosis with Episodes of Mania. *Malaysian Journal Of Psychiatry*. https://doi.org/10.4103/mjp.mjp_19_22