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The association between white matter hyperintensities and suicide attempts in affective disorders: a systematic review and meta-analysis

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A growing body of literature examines the neurobiological bases of suicidal behaviors, including the potential relationship between white matter hyperintensities (WMHs) and a history of suicide attempts in patients with affective disorders. We aimed to synthesize these studies, evaluate their quality, and provide recommendations for future research. We conducted a comprehensive literature search using three approaches: (i) search across PubMed, PsycINFO, Scopus, and Web of Science until October 2024; (ii) screening of previous reviews and meta-analyses; and (iii) citation mining of the included studies. The PRISMA guidelines were followed, and a random-effects meta-analysis was performed to calculate pooled Odds Ratios (OR). Sixteen studies were included in the systematic review, involving 1393 participants. Of these, 8 were also included in the meta-analysis. The main analyses revealed an association between WMHs (either deep or periventricular hyperintensities), and a history of suicide attempts in individuals with major depressive disorder (OR = 2.15, 95% confidence interval (CI) 1.03 – 4.49) and bipolar disorders (OR = 2.15, 95% CI 0.89 – 5.20). The main limitations concern the small number of studies, the degree of heterogeneity among the lesion rating systems adopted, and the lack of data on the severity of WMHs. Also, only some of the studies controlled for key confounding variables that may influence results. Overall, we found that individuals with affective disorders who had WMHs, particularly periventricular rather than deep white matter hyperintensities, were more likely to have attempted suicide in their lifetime, suggesting a potential role as neurobiological markers for suicide attempts.

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INTRODUCTION

Suicide is a leading cause of death worldwide, especially among individuals with affective disorders [1–4]. Estimates suggest that 5 to 6% of patients with major depressive disorder (MDD) or bipolar disorders (BD) die by suicide, and many more attempt it, with somewhat higher rates in BD [5, 6]. Consequently, recent years have evidenced a growing emphasis in research on potential predictors and risk factors for suicide among high-risk populations [7–11]. Among these predictors, a history of suicide attempts represents one of the best-known risk factors for future death by suicide [12], entailing a personal as well as societal burden globally [13–15]. Given the clinical relevance of reliably identifying individuals at higher risk of suicide as well as the growing application of neuroimaging techniques for research purposes in psychiatry, studies have investigated brain alterations as potential predictive features of suicide attempts in patients with affective disorders.

While MDD and BD exhibit distinct clinical features, there is a symptomatic overlap during acute depressive phases, and neuroimaging studies have suggested a continuum of brain structural abnormalities [16]. Indeed, recent progress in the field of neuroscience have led to the development of advanced white matter analysis techniques. These methodological approaches include diffusional kurtosis imaging [17], white matter tract integrity [18], and neurite orientation dispersion and density imaging [19], which facilitate the specific evaluation of white matter microstructure and compartment-specific biomarkers of myelin integrity and axonal health. However, these advanced techniques are designed to capture sub-voxel microstructural features rather than macroscopic lesions that are more visible on conventional T2-weighted and FLAIR sequences. Indeed, many studies employing these traditional approaches revealed notable white matter abnormalities in both patients diagnosed with MDD [20–24] and BD [25–27]. For example, evidence has shown an association between affective disorders and white matter hyperintensities (WMHs) [28, 29], also called leukoaraiosis [30], which are brain lesions typical of aging that appear hyperintense on T2-weighted and FLAIR MRI signals, indicating ependymal loss, altered brain myelination, and small vessel disease [31–33]. The classification of WMHs is typically based on their anatomical location and characteristics. Indeed, these lesions are commonly divided into two categories based on their contiguity with

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ventricles: the deep white matter hyperintensities (DWMH), which are separated from the ventricles, and the periventricular hyperintensities (PVH), which are characterized by their contiguity with the margins of each lateral ventricle [34]. Previous studies [35–37] have underscored differences in terms of functional, histopathological, and etiological correlates between DWMH and PVH. Therefore, the former seem to be more implicated in axonal loss, vacuolation, and increased tissue loss in more severe lesions, suggesting infarction, in addition to demyelination and gliosis; while the latter are usually characterized by a more discontinuous ependyma and high extracellular fluid content, gliosis, loosening of the white matter fibers, and myelin loss. However, although several studies and lesion rating systems differentiate between DWMH and PVH, recent findings revealed that these lesions may be mostly part of a continuous pathology [38, 39], which underscore the limitations inherent to the WMHs approach. Since the risk of suffering from vascular diseases significantly increases with aging [40], studies on WMHs in depression, which have been mainly focused on older adults [41–44], should be interpreted with caution. However, some research suggested an association between WMHs and BD across a wider age range [45–48], although the increased prevalence of WMHs in adolescents and young adults with BD compared to controls is not yet supported by the evidence [49].

Neuroimaging methodological approaches have also been used to investigate structural brain correlates of suicidal behaviors [50–53]. Specifically, evidence showed that suicide attempters had white matter and gray matter alterations in several cortical and subcortical brain structures, especially within the prefrontal, limbic, parietal, and striatal areas [54–60]. However, while both MDD and BD are associated with high suicide rates, shared and distinct white matter correlates of suicide attempts in these disorders are not well understood. In this regard, a meta-analysis conducted by Grangeon et al. [61] found that among individuals with affective disorders, a significantly higher number of suicide attempters had DWMH and PVH than non-attempters, suggesting a relationship with both WMHs lesions. Nevertheless, these results must be interpreted cautiously since only four studies were included in the analyses.

To note, etiologies contributing to WMHs include cellular loss, ischemia, perivascular space dilatation, ependymal loss, and vascular-related demyelination, which increase with aging [32, 62, 63]. Interestingly, having a history of suicide attempts has been associated with accelerated epigenetic aging [64, 65], which has been linked with WMHs [66] and with childhood trauma in MDD [67], another well-known risk for suicide attempts [68]. These findings suggest that WMHs may serve as a significant biomarker for suicide attempts in individuals diagnosed with affective disorders. Nonetheless, further evidence is necessary to substantiate this relationship. Therefore, the present study aims to perform a systematic review highlighting common aspects and differences in terms of the methodological approaches and WMHs operationalization, and to update the first meta-analysis [61] on the association between WMHs and suicide attempts in patients with MDD and BD.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [69], and the 2020 checklist is presented in Supplementary Table 1. The protocol was preregistered on the Open Science Framework (OSF) website (https://doi.org/10.17605/OSF.IO/KHJ8Q).

Search strategy

As a preliminary step, we verified that no meta-analyses on this topic had been published since the previous meta-analysis by Grangeon et al. [61], nor pre-registered on PROSPERO or OSF. Subsequently, a systematic search of articles published until July 11, 2024, was run in four databases: PubMed, PsycINFO, Scopus, and Web of Science. The full search string is provided in the Supplementary Table 2. To ensure reliability, the searches were cross-checked by two reviewers (GT and GD). Duplicates were removed, and the same reviewers screened the titles and abstracts independently. The full texts of the potentially eligible records were then screened based on the predefined inclusion and exclusion criteria. Reasons for exclusions during the in-depth full-text assessment are provided in Supplementary Table 3. Additionally, as the included studies on neurobiological correlates of suicide attempts are expected to reference relevant articles for the current meta-analysis, forward citation mining was also conducted to identify these studies (Supplementary Table 4). Studies included in previous reviews investigating the neurobiological correlates of suicide attempts were also screened (Supplementary Table 5). Disagreements between reviewers were resolved through discussion among the research team members until a consensus was reached. A search update performed in October 2024 identified no additional studies.

Selection criteria

Studies were included if they: (i) employed a quantitative study design; (ii) included patients with MDD or BD types I or II; (iii) differentiated between patients with and without a history of suicide attempts, which refers to a self-inflicted potentially injurious behavior with the deliberate intention to procure one's death but with a non-fatal outcome; (iii) used a T2-weighted or FLAIR MRI scans to detect WMHs. No language restrictions were applied.

Studies were excluded if they: (i) did not include a comparison group composed of non-attempter patients with MDD or BD types I or II; (ii) did not differentiate between suicide attempts and other suicide-related outcomes (e.g. deliberate self-harm or non-suicidal self-injury); (iii) used other MRI sequences, such as Diffusion Tensor Imaging (DTI), fMRI, T1-weighted images; (iv) assessed changes in white matter volumes, water diffusion, amount of radial or axial diffusion, or any other parameters, but not WMHs.

In the event that articles were identified as potentially relevant but lacked either raw data of interest or effect sizes, the corresponding authors were contacted on at least three occasions to request data (Supplementary Table 6). If we could not include the article in the meta-analysis after contacting the corresponding authors, then we included those articles only in the systematic review. Finally, in contrast with the approach taken by the previous work by Grangeon et al. [61], our meta-analysis included both Pompili et al. [70] and Pompili et al. [71], despite the existence of a one-month overlap in their samples. Indeed, Pompili et al. [70] recruited participants from April 2005 to September 2006, while Pompili et al. [71] conducted their recruitment from September 2006 to June 2007.

Data extraction

We extracted the following information from the included studies: study identification (authors, publication year, country), study design, sample size, participant characteristics (mean age, standard deviation, and sex), type of diagnosis (MDD, BD type I, or BD type II), history of suicide attempts assessment, location of the WMHs, MRI magnetic field strength, T2 parameters, and lesion rating system (Table 1). We considered two distinct types of WMHs: (i) DWMH, which are lesions of the white matter primarily caused by cerebrovascular diseases; and (ii) PVH, which have a different etiology, including ependymal loss, varying degrees of myelination and cerebral ischemia [32, 33]. Importantly, to ensure a comparative analysis of results across studies employing different rating lesion systems, we considered the prevalence of WMHs defined as any presence or absence of structural lesions within the white matter, intended as the lowest lesion grade

Table 1. Features of the included studies.

Study (country)	Study design	Participants: N (age range; M; SD; females %)	Type of diagnosis (%)	History of suicide attempt assessment	WMHs locations	Magnet strength (T)	T2 parameters	Lesion rating system
Ahearn et al., [82] (United States)	Case-control	Attempters: 20 (NA; 66.0; 5.8; 85%) Non-attempters: 20 (NA; 66.4; 5.7; 85%)	Major depressive disorder (100%)	Patients with a history of suicide attempts were identified from the database of the NIMH-funded Mental Health Clinical Research Center	DWMH PVH	1.5 T	T2w images – axial series of fast spin-echo images (TR 4000 ms, TE 30 ms, 80 ms, 16 kHz imaging bandwidth, echo train length = 16; 256 × 256 matrix, 2-mm slice thickness, 1 excitation per phase encoding increment)	1) Coffey Lesion Classification System (Coffey et al., [93]) 2) Boyko Lesion Classification System (Boyko et al. [130])
Birner et al., [83] (Austria)	Cross-sectional	Euthymic patients with bipolar disorder: 52 (NA; 44.0; 14.0; 48%) Healthy controls: 54 (NA; 41.0; 16.0; 57.4%)	Bipolar disorder type I or II (100%)	1) Hamilton Rating Scale for Depression (Hamilton, [88]) 2) Beck Depression Inventory (Beck et al. [90])	WMHs	3 T	T2 FLAIR images – axial images (TR = 10000 ms; TE = 69 ms; inversiontime = 2500 ms; number of slices = 40; 3 mm slice thickness; in-plane resolution = 0.86×0.86 mm^2)	1) Computer custom written IDL program (Exelis Visual Information Solutions, USA) 2) DispImage analysis tool (Plummer, [96])
Ehrlich et al., [80][a] (United States)	Retrospective	Psychiatric inpatients: 153 (NA; 14.6; 3.4; 25.8%)	Major depressive disorder (52.1%)	Medical records	DWMH PVH	1.5 T	T2w images – parameters not specified (presumably the same of Ehrlich et al. [81])	Not specified (presumably the same of Ehrlich et al. [81])
Ehrlich et al., [81] (United States)	Retrospective	Patients with unipolar depression: 48 (6–21; 15.1; 2.8; 31.3%) Patients with bipolar disorder: 35 (6–21; 14.9; 3.5; 25.7%)	Major depressive disorder (31.4%) Bipolar disorder (22.9%)	Modified Pfeffer Rating Scale (Pfeffer et al. [131])	DWMH PVH	1.5 T	T2w images – axial and coronal planes (TR = 2000 ms; TE = 40/80 ms; 5-mm slice thickness with 2.5-mm skip; 256 × 192 matrix, 24 FOV, 1 average)	Coffey Lesion Classification System (Coffey et al. [93])
Ehrlich et al., [73] (United States)	Retrospective	Patients with major depressive disorder: 102 (18–35; 26.7; 5.5; 66.7%)	Major depressive disorder (100%)	1) Patients with a history of suicide attempts were identified from medical charts by trained raters 2) The lethality of suicide attempts was rated using the Lethality of Suicide Attempt Rating Scale (Smith et al. [132])	DWMH PVH	Not specified	1) T2w images – axial and coronal planes (TR = 2000 ms; TE = 80 ms; 5-mm slice thickness with 2.5-mm skip) 2) T2w images – axial and coronal planes (TR = 4150 ms; TE = 90/126 ms; 3/5-mm slice thickness with 2-mm skip) 3) T2w images – axial and coronal planes (TR = 2766/4150 ms; TE = 90 ms; 5-mm slice thickness with 2-mm skip)	Modified Fazekas Rating Scale (Greenwald et al. [92])

Table 1. continued

Study (country)	Study design	Participants: N (age range; M; SD; females %)	Type of diagnosis (%)	History of suicide attempt assessment	WMHs locations	Magnet strength (T)	T2 parameters	Lesion rating system
Furnica et al., [79] (Romania)	Cross-sectional	Attempters: 40 (18–51; 42.4; NA; 47.5%) Non-attempters: 45 (18–55; 39.5; NA; 46.7%)	Affective disorders (either major depressive disorder or bipolar disorders type I or II)[b] (100%)	General psychiatric evaluation	DWMH PVH	Not specified	Not specified	Fazekas Rating Scale – original version (Fazekas et al., [63])
Kieseppä et al. [84] (Finland)	Cohort	Bipolar disorder type I: 8 (NA; 46.2; 11.5; 38%) Bipolar disorder type II: 8 (NA; 45.5; 4.8; 50%) Major depressive disorder: 6 (NA; 50.9; 11.4; 83.3%) Healthy controls: 19 (NA; 49.6; 11.3; 57.9%)	Bipolar disorder type I (36.4%) Bipolar disorder type II (36.4%) Major depressive disorder (27.2%)	1) Clinician-rated Hamilton Rating Scale for Depression (Hamilton, [88]) 2) Beck Depression Inventory (Beck et al. [90])	DWMH PVH	Baseline: 1.5 T Follow-up: 3 T	Baseline: 1) T2w fast-spin echo images – axial plane (TR = 5300 ms; TE = 112 ms; 5-mm slice thickness; 256 × 256 matrix; 230 mm FOV) 2) T2 FLAIR images – axial plane (TR 10000 ms; TE 148; 5-mm slice thickness; matrix 256 × 256; 230 mm FOV) Follow up: 1) T2w fast-spin echo images – axial plane (TR = 4000 ms; TE = 80 ms; 5-mm slice thickness; 256 × 256 matrix; 240 mm FOV) 2) T2 FLAIR images – axial plane (TR 11000 ms; TE 120; 5-mm slice thickness; matrix 256 × 256; 240 mm FOV)	Modified Coffey Lesion Classification System (Lyoo et al. [133])
Komaki et al., [74] (Japan)	Cohort	Patients with major depressive disorder: 123 (17–83; 49.5; NA; 58.5%)	Major depressive disorder (100%)	Patients were excluded if they reported a high risk of suicide after clinical interview and the Hamilton Rating Scale for Depression score (Hamilton, [88]); however, three patients died by suicide after the recruitment	DWMH PVH	1.5 T	T2w and FLAIR images – axial, coronal, and sagittal planes (8 mm slice thickness; 2.5 mm gap)	Fazekas Rating Scale – original version (Fazekas et al., [63])
Lin et al., [76] (Taiwan)	Cross-sectional	Attempters: 34 (60 + ; 64.8; 5.3; 94.1%) Ideators: 35 (60 + ; 67.4; 5.7; 82.9%) Non-suicidal: 45 (60 + ; 67.8; 5.7; 73.3%) Healthy controls: 47 (60 + ; 68.7; 5.3; 63.8%)	Major depressive disorder – late-life (100%)	1) Hamilton Rating Scale for Depression (Hamilton, [88]) 2) Beck Scale for Suicide Ideation (Beck et al. [134]) 3) SAD PERSONS scale (Wu et al. [135])	DWMH PVH JVWMH JCWMH	3 T	T2 FLAIR images – axial plane (TR 9000 ms; TE 140 ms; TI 2250 ms; FOV = 220 × 220 mm^2; voxel size = 0.69 × 0.98 × 3.5 mm^3; 32 slices; 0.5 mm gap)	Lesion segmentation tool (Schmidt et al. [95])

Table 1. continued

Study (country)	Study design	Participants: N (age range; M; SD; females %)	Type of diagnosis (%)	History of suicide attempt assessment	WMHs locations	Magnet strength (T)	T2 parameters	Lesion rating system
Mehrhof et al. [49] (Canada)	Cross-sectional	Patients with bipolar disorder: 83 (13–21; 17.70; 1.61; 61.4%) Healthy controls: 64 (13–21; 17.36; 1.74; 57.8%)	Bipolar disorder type I or II (100%)	K-SADS Depression Rating Scale (Chambers et al. [136])	WMHs	3 T	T2 FLAIR images – axial plane (TR 9000 ms; TE 125 ms; TI 2800 ms; flipangle=90.1 × 1.1 × 3 $mm^{3;}$ FOV 24 cm; 50 slices; matrix 240 × 217; acquisition time = 5'30")	Written reports flagging and describing all brain abnormalities by visual examination
Pompili et al., [70] (Italy)	Cross-sectional	Attempters: 29 (NA; 42.17; 13.51; 82.8%) Non-attempters: 36 (NA; 44.61; 13.95; 47.2%)	Major depressive or bipolar disorders (100%)	1) Mini International Neuropsychiatric Interview (Sheehan et al., [89]) 2) Clinical interview 3) Medical records	WMHs	1.5 T	1) T2w images – axial and coronal planes (TR 647 ms; TE 17 ms; 5-mm slice thickness; matrix 231 × 192) 2) T2 FLAIR images – axial plane (TR 10000 ms; TE 125 ms; 5-mm slice thickness; matrix 144 × 256)	Modified Fazekas Rating Scale (Greenwald et al. [92])
Pompili et al., [71] (Italy)	Cross-sectional	Attempters: 44 (19–79; 45.6; 16.1; 49.1%) Non-attempters: 55 (19–79; 47.3; 14.5; 50.9%)	Major depressive disorder (38.4%) Bipolar disorder type I (40.4%) Bipolar disorder type II (21.2%)	Mini International Neuropsychiatric Interview (Sheehan et al. [89])	DWMH PVH	1.5 T	1) T2w images – axial and coronal planes (TR 2870 ms; TE 13/107 ms; 5-mm slice thickness; matrix 147 × 256) 2) T2 FLAIR images – axial plane (TR 10000 ms; TE 125; 5-mm slice thickness; matrix 144 × 256)	Modified Fazekas Rating Scale (Greenwald et al. [92])
Serafini et al., [77] (Italy)	Cross-sectional	Higher dysthymia, cyclothymia, irritability, and anxiety and lower hyperthymia: 140 (NA; 48.28; 15.05; 50%) Higher hyperthymia, and lower dysthymia, anxiety, and cyclothymia: 107 (NA; 48.09; 15.90; 55.1%)	Major depressive disorder (25.1%) Bipolar disorder type I (57.9%) Bipolar disorder type II (17%)	1) Medical records 2) Hamilton Rating Scale for Depression (Hamilton, [88]) 3) Mini International Neuropsychiatric Interview (Sheehan et al., [89]) 4) Beck Hopelessness Scale (Beck et al. [91])	DWMH PVH	1.5 T	1) T2w images – axial and coronal planes (TR 2870 ms; TE 13/107 ms; 5-mm thickness; matrix 147 × 256) 2) T2 FLAIR images – axial plane (TR 10000 ms; TE 125 ms; 5-mm slice thickness; matrix 144 × 256)	Modified Fazekas Rating Scale (Coffey et al. [137])

Table 1. continued

Study (country)	Study design	Participants: N (age range; M; SD; females %)	Type of diagnosis (%)	History of suicide attempt assessment	WMHs locations	Magnet strength (T)	T2 parameters	Lesion rating system
Serafini et al., [46][d] (Italy)	Cross-sectional	Patients with bipolar disorder admitted to the psychiatric inpatient units: 148 (19–83; 47.9; 16.1; 47.97%)	Bipolar disorder type I (100%)	Beck Hopelessness Scale (Beck et al. [91])	DWMH PVH	1.5 T	1) T2w images – axial and coronal planes (TR 2870 ms; TE 13/107 ms; 5-mm slice thickness; matrix 147 × 256) 2) T2 FLAIR images – axial plane (TR 10000 ms; TE 125 ms; 5-mm slice thickness; matrix 144 × 256)	Modified Fazekas Rating Scale (Greenwald et al. [92])
Takahashi et al. [78] (Japan)	Cross-sectional	Patients with major depressive or bipolar disorders: 52 (50 + ; 60.8; 7.0; 50%) Healthy controls: 14 (50 + ; 63.1; 9.4; 57.1%)	Major depressive disorder (80.8%) Bipolar disorder type I (11.5%) Bipolar disorder type II (7.7%)	General psychiatric evaluation	DWMH PVH	1.5 T	T2w images – axial plane (TR 3800 ms; TE 90 ms; 5-mm slice thickness; 2-mm interslice gap)	Fazekas Rating Scale – original version (Fazekas et al., [63])
Tamashiro et al. [75] (Brasil)	Cross-sectional	Patients with bipolar disorder[c]: 59 (60 + ; 68.76; 4.87; 66.1%)	Bipolar disorder (100%): Late-onset (16.95%) Early onset (83.05%)	Operational Criteria Checklist for Psychotic Illness (Azevedo et al. [138])	DWMH PVH	1.5 T	T2w fast spin-echo images – transaxial planes (TR 4000 ms; TE 98 ms; 6-mm slice thickness; matrix 256 × 256; flip angle 90°)	Visual scale of Scheltens et al. [94]

DWMH deep white matter hyperintensities, *JCWMH* juxtacortical hyperintensities, *JVWMH* juxtaventricular hyperintensities, *NA* not available, *PVH* periventricular hyperintensities, *WMHs* white matter hyperintensities.

[a]This record was excluded from the meta-analysis due to overlapping sample with Ehrlich et al. [81].

[b]Due to a typo reported in Table 3 (Furnica et al. [79]), it was not possible to discern the number of patients for each diagnosis.

[c]We only used data from 23 bipolar patients (13 attempters and 10 non-attempters) for the meta-analysis. The remaining participants did not answer the history of suicide attempts question.

[d]Some of the participants included in this record were also included in Serafini et al. [77].

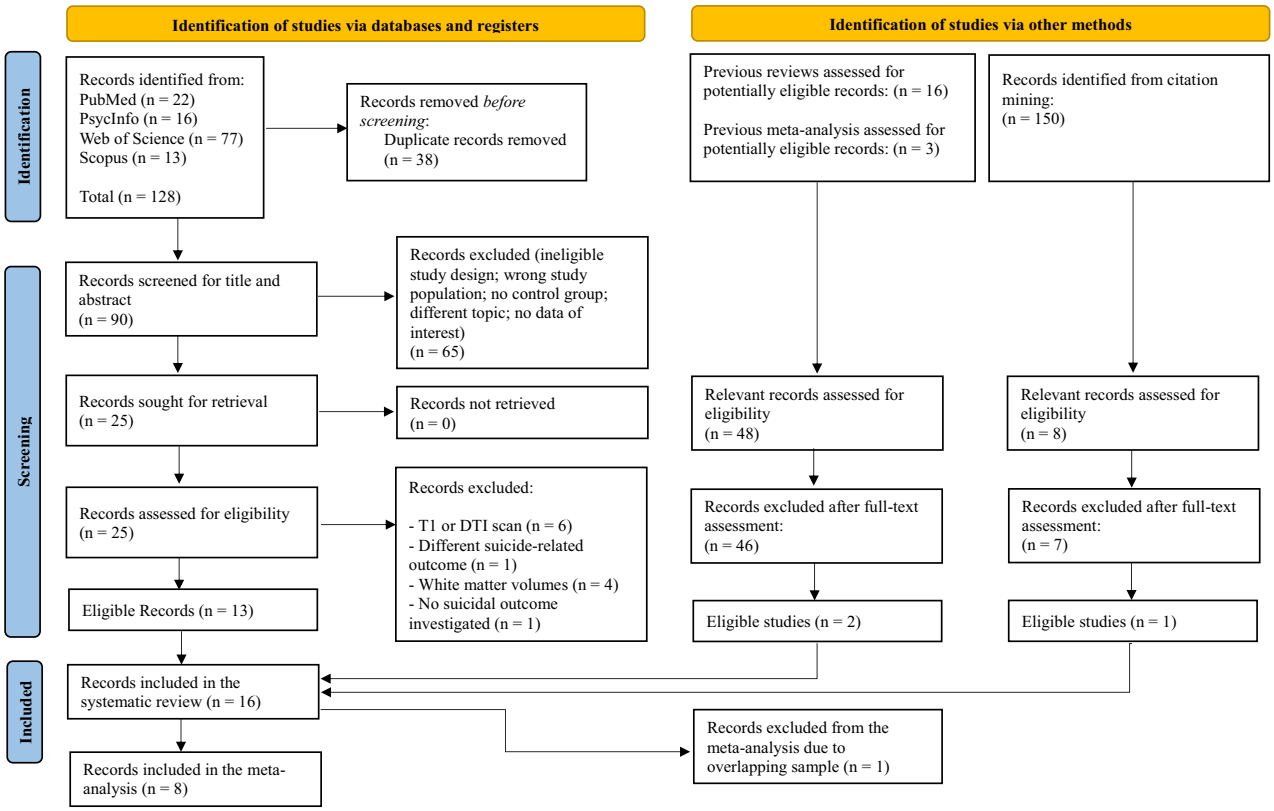

Fig. 1 Flow diagram of the different screening phases for the selection of the included studies according to the PRISMA 2020 statement.

according to the lesion rating system adopted by each study (e.g., for the Fazekas scale: 0 = absence of WMHs; 1/2/3 = presence of WMHs).

Quality assessment and publication bias

The risk of reporting bias was assessed by using the NIH Quality Assessment Tools [72]. Among the 16 included studies, ten [46, 49, 70, 71, 73–78] were rated as having "good" quality, while six [79–84] were rated as having "fair" quality. No studies were judged as having "poor" quality (Supplementary Tables 7 and 8).

Publication bias was evaluated using the funnel plot (Supplementary Figure 1). Visual examination of the funnel plot showed slight asymmetry, with more studies on the right side. Egger's regression test revealed an intercept value of 13.50 (95% confidence interval (CI): from −0.64 to 27.64) and a two-tailed p-value of 0.058, indicating that although some asymmetry in the funnel plot was detected, it was not statistically significant.

Statistical analysis

We conducted separate analyses combining four patients' conditions (i.e., MDD, BD, attempters, and non-attempters) and three outcomes (i.e., WMHs, DWMH, and PVH). Data were analyzed using the Comprehensive Meta-Analysis software version 3.7 [85]. A random-effects model was employed to calculate and pool together the odds ratios (ORs) derived from individual studies' raw data, with associated 95% CI for each study. The significance of the pooled effect sizes was determined using the Z test (p-value ≤ 0.05). Between-study heterogeneity was calculated using the I^2 statistic, with values of 0%, 25%, 50%, and 75% indicating no, low, moderate, and high heterogeneity [86]. Subgroup analyses including the two types of lesions, DWMH and PVH, and the different psychiatric diagnoses, MDD and BD, have been performed. Additionally, we conducted sensitivity analyses to explore methodological variations in study design and differences in terms of population age (children and adolescents: up to 21 years old; adults: up to 60 years old; older adults: over 60 years old) in order to explain potential sources of heterogeneity among the main analyses. However, due to the lack of studies that explicitly involved solely older adult participants, except for Tamashiro et al. [75], we considered a "mixed ages" group including studies with both adult and older adult participants. Furthermore, we adopted a statistical approach in order to reduce double-count statistical bias [87]. To exemplify, when calculating WMHs effect sizes, raw data from studies that investigated both DWMH and PVH in comparison to the same control group of patients were divided by the number of times the study was counted in the analysis.

RESULTS

Included studies

The PRISMA flow diagram of the study selection process is presented in Fig. 1. The database search yielded 128 results, of which 38 were duplicates. After the screening stages, 13 studies met the inclusion criteria [46, 49, 70, 71, 73–77, 79–82] and were included in the systematic review after the database search process. Additionally, two studies [78, 84] were included after assessing previous reviews for potentially eligible records, and another study [83] was included via citation mining. As a result, we were able to include 16 studies in the systematic reviews, of which eight were also included in the meta-analysis. Notably, one of the studies included in the systematic review [80] was excluded from the meta-analysis due to overlapping sample data with other included studies. Furthermore, of the eight studies in the meta-analysis, two studies were included after contacting the corresponding authors to request data of interests [49, 75].

Main characteristics

The main characteristics of the included studies are summarized in Table 1. In total, excluding the studies with an overlapping sample [77, 80] (Supplementary Table 9), the final sample consisted of

1,393 participants, of whom 533 (38.26%) had a diagnosis of MDD, 460 (33.02%) were diagnosed with BD (either type I or II), 202 (14.50%) with either MDD or BD type I or II, and 198 (14.22%) healthy controls. As shown in the Supplementary Figure 2, the publications trend exhibited non-linear tendencies over the period from 2000 to 2024, showing two peaks in 2008 and 2021. Overall, from 2000 to 2008, there was an apparent trend of increasing interest in this topic. However, during the subsequent six years, only a single study was published. Beginning in 2015, there was a sporadic publication of studies, with a peak in 2021 with three studies, after which the publication of new studies halted until 2024.

The majority of the studies (n = 10; 62.5%) adopted a cross-sectional study design [46, 49, 70, 71, 75–79, 83], followed by retrospective (n = 3; 18.75%) [73, 80, 81], cohort (n = 2; 12.5%) [74, 84], and case-control designs (n = 1; 6.25%) [82]. Moreover, seven studies (43.75%) were conducted in Europe [46, 70, 71, 77, 79, 83, 84], five (31.25%) in North America (including Canada) [49, 73, 80–82], three (18.75%) in Asia [74, 76, 78], and one (6.25%) in South America [75].

Three studies (18.75%) involved children and adolescents up to 21 years old [49, 80, 81], two studies (12.5%) only included adults (range: 18–51) [73, 79], one study (6.25%) included participants over 60 years old [76], while the remaining studies (n = 10; 62.5%) included both adults and older adults or did not specify the age range [46, 70, 71, 74, 75, 77, 78, 82–84].

Six studies (37.5%) employed more than one suicide-related outcomes assessment method [70, 73, 76, 77, 83, 84]; and the most used tools to discern a lifetime history of suicide attempts were the Hamilton Rating Scale for Depression [88] (n = 5; 31.25%) [74, 76, 77, 83, 84], registries or medical records consultation (n = 5; 31.25%) [70, 73, 77, 80, 82], Mini International Neuropsychiatric Interview [89] (n = 3; 18.75%) [70, 71, 77], general psychiatric evaluation or clinical interview (n = 3; 18.75%) [70, 78, 79], Beck Depression Inventory [90] (n = 2; 12.5%) [83, 84], and Beck Hopelessness scale [91] (n = 2; 12.5%) [46, 77].

Most studies (n = 13; 81.25%) [46, 71, 73–82, 84] distinguished between DWMH and PVH, of which one also identified juxtacortical and juxtaventricular hyperintensities [76]; whereas three studies (18.75%) did not differentiate the WMHs locations [49, 70, 83].

In terms of MRI parameters, ten studies (62.5%) utilized 1.5 T scans [46, 70, 71, 74, 75, 77, 78, 80–82], three studies (18.75%) utilized a 3 T scan [49, 76, 83], one study (6.25%) utilized a 1.5 T scan during the baseline assessment and a 3 T scan during the follow-up [84], while the remaining two studies (12.5%) did not specify the magnetic field strength [73, 79].

The Fazekas scale [63, 92] was used for rating lesions in eight studies (50%) [46, 70, 71, 73, 74, 77–79], The Coffey scale [93] was used in three studies (18.75%) [81, 82, 84], of which one also used the Boyko scale [82], while the Scheltens visual scale [94], the Lesion Segmentation tool [95], as well as the computer analysis tools [96] were used in one study (6.25%), respectively [75, 76, 83]. In addition, one study (6.25%) utilized written reports by neuroradiologists to assess WMHs [49], while another study (6.25%) did not specify which lesion rating system employed [80].

Meta-analyses

Main findings. Of the eight studies included in the meta-analysis, four [75, 79, 81, 82] showed a higher prevalence of DWMH in suicide attempters with affective disorders compared to non-attempters, while two reported no significant differences between groups [71, 73]. Additionally, five out of six studies that investigated PVH [71, 79–82] reported a higher prevalence in individuals with a history of suicide attempts compared to non-attempters, except for Tamashiro et al. [75]. Among the two studies that did not differentiate between DWMH and PVH, logistic regression models presented by Pompili et al. [70] identified WMHs as a significant predictor of a lifetime history of suicide attempts in patients with MDD and BD, while Mehrhof et al. [49] did not find any significant differences in terms of WMHs prevalence between attempters and non-attempters in patients with BD.

Among the four studies that included both MDD and BD [70, 71, 79, 81], two of them [70, 71] demonstrated that the type of affective disorder was not a statistically significant discriminator of the difference in the prevalence of WMHs between attempters and non-attempters. In contrast, two studies identified differences according to the type of affective disorder examined [79, 81]. In particular, Ehrlich et al. [81] found that the prevalence of WMHs in subjects with previous suicide attempts was statistically significant for patients with MDD but not for other psychiatric disorders, including BD. Conversely, Furnica et al. [79] observed a higher prevalence of both DWMH and PVH in individuals diagnosed with BD type I compared to those diagnosed with BD type II and MDD, with a similar prevalence observed in the latter two groups.

Association between suicide attempts and white matter hyperintensities in major depressive disorder. The results of the main analyses are reported in Table 2. Individuals with MDD who had attempted suicide were more likely to have WMHs (DWMH or PVH) compared to non-attempters with the same disorder (OR = 2.15, 95% CI: 1.03 – 4.49) (Supplementary Figure 3). When

Table 2. Odds ratio of studies comparing white matter hyperintensities rates in attempters and non-attempters patients with affective disorders.

Analysis	Records: K	Odds Ratio [95% confidence interval]	Overall effect: Z (P)	Heterogeneity: I^2 (P)
Major depressive disorder				
WMHs (DWMH + PVH)	7	2.15 [1.03–4.49]	2.03 (<0.05)	22.79% (0.255)
DWMH	3	1.02 [0.29–3.62]	0.03 (0.979)	67.21% (<0.05)
PVH	3	4.21 [1.86–9.52]	3.45 (0.001)	0% (0.710)
Bipolar disorders (type I or II)				
WMHs (DWMH + PVH)	5	2.15 [0.89–5.20]	1.71 (0.088)	0% (0.436)
DWMH	2	1.89 [0.77–4.63]	1.39 (0.164)	0% (0.496)
PVH	2	1.88 [0.21–17.06]	0.56 (0.574)	77.22% (<0.05)
Affective disorders (major depressive disorder and bipolar disorders)				
WMHs (DWMH + PVH)	14	2.41 [1.61–3.61]	4.26 (<0.001)	0% (0.731)
DWMH	6	1.33 [0.72–2.48]	0.91 (0.362)	38.42% (0.150)
PVH	6	2.73 [1.42–5.24]	3.01 (<0.05)	32.78% (0.190)

DWMH deep white matter hyperintensities, *PVH* periventricular white matter hyperintensities, *WMHs* white matter hyperintensities.

considering the two white matter lesions separately, the association with a history of suicide attempts was higher for PVH (OR = 4.21; 95% CI: 1.86 – 9.52) compared to DVMH (OR = 1.02; 95% CI: 0.29 – 3.62) (Supplementary Figures 4 and 5). Moderate heterogeneity was detected in DWMH ($I^2 = 67.21\%$), while no heterogeneity was detected in the WMHs ($I^2 = 22.79\%$) and PVH analyses ($I^2 = 0\%$).

Association between suicide attempts and white matter hyperintensities in bipolar disorders. Results indicated that attempters with BD (type I or II) were more likely to have WMHs (DWMH or PVH) than BD patients without a suicide attempt history (OR = 2.15, 95% CI: 0.89 – 5.20) (Supplementary Figure 6). Specifically, suicide attempters were more likely to have both DWMH (OR = 1.89, 95% CI: 0.77 – 4.63) and PVH (OR = 1.88, 95% CI: 0.21 – 17.06) than non-attempters (Supplementary Figures 7 and 8). High heterogeneity was detected for the PVH ($I^2 = 77.22\%$) analysis, while it was absent in the DWMH and WMHs analyses ($I^2 = 0\%$) (Table 2).

Association between suicide attempts and white matter hyperintensities in affective disorders. In analyses that included both MDD and BD, suicide attempters were more likely to have WMHs (DWMH or PVH) compared to non-attempters (OR = 2.41, 95% CI: 1.61 – 3.61) (Supplementary Figure 9). Similar results were observed when DWMH (OR = 1.33, 95% CI: 0.72 – 2.48) and PVH (OR = 2.73, 95% CI: 1.42 – 5.24) were analyzed separately (Supplementary Figures 10 and 11). Low heterogeneity was detected in the DWMH ($I^2 = 38.42\%$) and PVH ($I^2 = 32.78\%$) analyses, while no heterogeneity was found in the WMHs analysis ($I^2 = 0\%$) (Table 2).

Sensitivity analyses by population age. The sensitivity analyses revealed that attempters with MDD or BD (type I or II) were more likely to have WMHs compared to non-attempters in all the different group ages (Table 3). More specifically, children and adolescents with a history of a suicide attempt had a higher rate of WMHs than non-attempters (OR = 1.29, 95% CI: 0.07 – 22.57), with a moderate heterogeneity observed ($I^2 = 72.41\%$). Similar results also emerged for adults (OR = 1.53, 95% CI: 0.76 – 3.11) and mixed ages (adults and older adults) (OR = 3.01, 95% CI: 1.70 – 5.31), with no heterogeneity detected in both analyses ($I^2 = 0\%$) (Supplementary Figure 12). When DWMH and PVH were analyzed separately, adults with a history of a suicide attempt were less likely to have DWMH (OR = 0.74, 95% CI: 0.14 – 3.85) and more likely to have PVH (OR = 2.48, 95% CI: 0.91–6.73) compared to non-attempters. High and low heterogeneity was detected for the DWMH ($I^2 = 80.31\%$) and PVH ($I^2 = 39.97\%$) analyses, respectively. Furthermore, both DWMH (OR = 1.92, 95% CI: 1.01–3.65) and PVH (OR = 2.87, 95% CI: 1.06 – 7.79) were associated with a history of a suicide attempt in studies involving mixed ages (adults and older adults). The DWMH analysis reported no heterogeneity ($I^2 = 0\%$), while the PVH analysis showed low heterogeneity ($I^2 = 45.48\%$) (Supplementary Figures 13 and 14).

Sensitivity analyses by study design. Additional sensitivity analyses showed that the likelihood of having WMHs for those with a history of a suicide attempt, compared to non-attempters, was similar across case-control (OR = 2.43, 95% CI: 0.64 – 9.21), cross-sectional (OR = 2.29, 95% CI: 1.38 – 3.79), and retrospective (OR = 2.39, 95% CI: 0.77 – 7.43) study designs (Table 4) (Supplementary Figure 15). However, while heterogeneity was absent for both case-control and cross-sectional analyses ($I^2 = 0\%$), it was low for retrospective analysis ($I^2 = 46.46\%$). The studies with a case-control design reported a higher rate of both DWMH (OR = 2.25, 95% CI: 0.64 – 7.97) and PVH (OR = 2.67, 95% CI: 0.65 – 10.97) in attempters compared to non-attempters. Since both DWMH and PVH analyses included one study respectively, heterogeneity was not available. For the cross-sectional studies, results revealed that those with a lifetime history of a suicide attempt exhibited a higher rate of both DWMH (OR = 1.74, 95% CI: 0.99 – 3.07) and PVH (OR = 2.42, 95% CI: 0.92 – 6.38). No heterogeneity was detected for DWMH analysis ($I^2 = 0\%$), while PVH analysis showed moderate heterogeneity ($I^2 = 54.13\%$). Conversely, conflicting results emerged for the retrospective designs, where a lower DWMH prevalence was observed (OR = 0.30, 95% CI: 0.09 – 0.98), yet a higher PVH prevalence was noted (OR = 4.66, 95% CI: 1.27 – 17.13) among attempters in comparison to non-attempters. The heterogeneity was not available for DWMH and PVH analyses because both included only one study (Supplementary Figures 16 and 17).

DISCUSSION

This systematic review and meta-analysis provided an overview of the evidence on the association between white matter lesions, known as WMHs or leukoaraiosis, and a history of suicide attempts in affective disorders. Our findings revealed that individuals with MDD and BD (type I or II) who had DWMH or PVH were more likely to have attempted suicide in their lifetime, with PVH showing a stronger association than DWMH.

More specifically, we observed that for patients with MDD, detecting any presence of WMHs leads to a + 115% increased risk of having attempted suicide in their lifetime compared to those who had never attempted suicide. Interestingly, when considering specific WMHs for patients with MDD, suicide attempters were only 2% more likely to have DWMH compared to non-attempters,

Table 3. Odds ratio of studies comparing white matter hyperintensities rates in attempters and non-attempters patients with affective disorders divided by population age.

Analysis	Records: K	Odds Ratio [95% confidence interval]	Overall effect: Z (P)	Heterogeneity: I^2 (P)
Children and adolescents				
WMHs (DWMH + PVH)	2	1.29 [0.07–22.57]	0.17 (<0.863)	72.41% (0.057)
Adults				
WMHs (DWMH + PVH)	4	1.53 [0.76–3.11]	1.18 (0.236)	0% (0.531)
DWMH	2	0.74 [0.14–3.85]	−0.36 (0.718)	80.31% (0.024)
PVH	2	2.48 [0.91–6.73]	1.78 (0.075)	39.97% (0.197)
Mixed (adults and older adults)				
WMHs (DWMH + PVH)	8	3.01 [1.70–5.31]	3.79 (<0.001)	0% (0.986)
DWMH	4	1.92 [1.01–3.65]	1.99 (0.046)	0% (0.903)
PVH	4	2.87 [1.06–7.79]	2.07 (0.038)	45.58% (0.138)

DWMH deep white matter hyperintensities, *PVH* periventricular white matter hyperintensities, *WMHs* white matter hyperintensities.

Table 4. Odds ratio of studies comparing white matter hyperintensities rates in attempters and non-attempters patients with affective disorders divided by study design.

Analysis	Records: K	Odds Ratio [95% confidence interval]	Overall effect: Z (P)	Heterogeneity: I^2 (P)
Case-control				
WMHs (DWMH + PVH)	2	2.43 [0.64–9.21]	1.30 (0.193)	0% (0.901)
DWMH	1	2.25 [0.64–7.97]	1.26 (0.209)	NA
PVH	1	2.67 [0.65–10.97]	1.36 (0.174)	NA
Cross-sectional				
WMHs (DWMH + PVH)	9	2.29 [1.38–3.79]	3.22 (0.001)	0% (0.685)
DWMH	4	1.74 [0.99–3.07]	1.91 (0.056)	0% (0.915)
PVH	4	2.42 [0.92–6.38]	1.78 (0.075)	54.13% (0.088)
Retrospective				
WMHs (DWMH + PVH)	3	2.39 [0.77–7.43]	1.50 (0.134)	46.46% (0.154)
DWMH	1	0.30 [0.09–0.98]	−1.99 (0.046)	NA
PVH	1	4.66 [1.27–17.13]	2.32 (0.021)	NA

DWMH deep white matter hyperintensities, *NA* not applicable, *PVH* periventricular white matter hyperintensities; *WMHs* white matter hyperintensities.

while the odds of having PVH increased by 321%. Patients suffering from BD (type I or II) with any form of WMHs had the same increased risk of reporting a history of a suicide attempt as those with a MDD diagnosis (+115%), with an increased risk of 89% for DWMH, and 88% for PVH. Additionally, when we pooled both affective disorders together, the findings showed that patients with any WMHs were 141% more likely to have attempted suicide in their lifetime than those without WMHs. Separate analyses confirmed the association of previous suicide attempts with DWMH (+33%) and PVH (+173%) across diagnostic categories.

In comparison with the previous meta-analysis by Grangeon et al. [61], the present study included significantly more studies in the systematic review and meta-analysis, thereby providing results based on a substantially larger sample size. From a statistical perspective, additional analyses were conducted. Indeed, in addition to considering DWMH and PVH separately, global analyses that took into account any form of WMHs were performed, ultimately enabling us to obtain a global measure of the association between WMHs (DWMH or PVH) and a history of suicide attempts. Moreover, in order to identify potential sources of heterogeneity, sensitivity analyses focusing on age groups and study design were conducted. A comparison of the results obtained in this study with those reported by Grangeon et al. [61] reveals a degree of similarity, although there are discrepancies in the point values pertaining to the associations between DWMH and PVH with suicide attempts, which are weaker in the present study. The observed discrepancies are attributable, at least in part, to the considerably expanded sample size. These novel findings could also cast doubt on the potential role of WMHs, particularly DWMH, as biomarkers for suicide attempts.

Findings from sensitivity analyses by age group indicate that the association between WMHs and suicide attempts escalates with age, from +29% in children and adolescents to +53% in adults, up to +201% for mixed ages (adults and older adults). The association of PVH strengthens in comparison to that of DWMH across all age groups, although no data about the specific WMHs locations were available for children and adolescents. The observed findings are not unexpected in light of the well-documented rise in the prevalence of WMHs with brain aging [97]. The correlation between WMHs and a history of suicide attempts, however, needs further investigation, especially in young populations. Moreover, the substantial heterogeneity observed between the two studies that investigated this association in children and adolescents may underscore the critical importance of the lesion rating system employed. Indeed, conventional lesion rating systems were developed for elderly patients with vascular diseases and are not well-suited for assessing variability in lesions among younger populations. It is therefore noteworthy that Ehrlich et al. [81], who employed the Coffey scale [93] in children and adolescents, documented a remarkably high WMHs prevalence in their sample, while Mehrhof et al. [49], who utilized a straightforward visual examination by neuroradiologists in adolescents, recorded a complete absence of WMHs.

Sensitivity analyses on study design yielded analogous results regarding the association of WMHs with a lifetime history of suicide attempts among case-control (+143%), cross-sectional (+129%), and retrospective (+139%) studies. These findings suggest that this association remains consistent across different study designs, indicating that the type of design does not appear to influence this association or the heterogeneity of the main analyses. However, when WMHs subtypes were analyzed separately, retrospective studies, compared to the other designs, demonstrated a substantial discrepancy between DWMH (−70%) and PVH (+366%) regarding the prevalence of such lesions in attempters compared to non-attempters. It is noteworthy, however, that these findings are based on a single study, thereby precluding any inferences.

These results yield important considerations. Firstly, a history of suicide attempts is consistently linked to a higher prevalence of WMHs in both MDD and BD, suggesting that white matter lesions may serve as relevant markers of previous suicide attempts in patients with affective disorders. This extends the "vascular depression" hypothesis [98], which posits that depression may be caused by cerebrovascular diseases (in the form of WMHs) that affect subcortical areas implicated in mood regulation, highlighting that WMHs may also be a potential neurobiological component of suicide attempts and not only of depression. Additionally, our findings may be explained by the implication of accelerated epigenetic aging in the increased risk of WMHs pathophysiology [66] and in the occurrence of suicide attempts [64, 65]. Indeed, accelerated epigenetic aging in mood disorders may contribute to the gradual loss of vascular homeostasis that typically increases with age [99], and some vascular homeostasis-related markers (thrombospondin-1 and −2; and platelet-derived growth factor -AB and -BB) have been associated with suicide attempts [100]. Moreover, vascular implications may also be involved through pericyte dysfunction, associated with social stress and depression [101], ultimately impacting the disruption of the blood-brain barrier and the white matter [102].

The prevalence of WMHs may indicate a disruption of anterior fronto-limbic and fronto-striatal fiber tracts. Indeed, patients with MDD and a lifetime history of suicide attempts often report decreased integrity in the anterior thalamic radiation (via the anterior limb of the internal capsule) and in the cingulum bundle tracts, which carry medial prefrontal (cingulate) and thalamic inputs [103]. Similarly, PVH are adjacent to the genu/forceps minor of the corpus callosum (connecting prefrontal cortices), which has been found to be altered in those who attempted suicide in their lifetime [55]. Moreover, when considering the limbic system, the uncinate fasciculus (orbitofrontal-amygdala tract) was associated with lower fractional anisotropy in patients with MDD [104]. Lesion mapping of WMHs in patients with affective disorders similarly highlights the cingulate, uncinate, and related anterior tracts as correlates of mood disturbance [105]. Taken together, these fiber tract alterations suggest that WMHs may disrupt the fronto-cortical, cingulate-prefrontal, orbitofrontal-temporal networks, as well as the thalamo-cortical circuits, ultimately impacting emotion regulation and impulse control. Although the present study specifically focused on the prevalence of macrostructural white matter lesions visible on T2-weighted or FLAIR sequences, rather than on microscopic fiber abnormalities, high-resolution diffusion tractography may serve as an effective tool to bridge macro-structural and microstructural alterations in individuals at elevated risk for suicide attempts, beyond what is detectable through conventional T2 imaging, ultimately elucidating the neurobiological pathways through which WMHs may influence the risk of attempting suicide in patients with affective disorders [106, 107]. Future works on the topic can therefore use high-resolution diffusion MRI (e.g., DTI tractography) to analyze the microstructural integrity of white matter and thereby elucidate how WMH-related fiber damage may contribute to an increased risk of suicide attempts. Indeed, recent diffusion-based imaging studies highlight white matter abnormalities associated with suicidal thoughts and behaviors using advanced white matter analyses such as neurite orientation dispersion and density imaging [106] and free-water DTI [108]. These microstructural analyses may better explain why suicide attempters tend to have greater WMHs prevalence and disrupted tract integrity than non-attempters.

Furthermore, the strong association of PVH with suicide attempts across diagnostic categories suggests that PVH may be a more reliable marker for past suicide attempts than DWMH, emphasizing the necessity for detailed analyses of WMHs locations. Indeed, from a lesion model perspective, PVH result from chronic small vessel diseases around the lateral ventricles that are marked by ependymal loss, gliosis, demyelination, and axonal degeneration, leading to disruption of key fronto-limbic and executive networks [37, 109–111]. Concurrently, the presence of PVH significantly impacts cognitive impairment, executive functions, processing speed, and decision-making abilities [76], potentially exacerbating vulnerabilities to suicidal crises. Moreover, the disruption of emotional processing circuits by the PVH may potentially lead to an escalation of negative emotional bias, a reduction in stress resilience, and an intensification of affective dysregulation [71, 112], thereby impairing decision-making processes involved in suicidal behaviors [113].

It is noteworthy that, whereas in the MDD a significant discrepancy was observed between the WMHs types, with PVH being more strongly associated with suicide attempts than DWMH, the relationship between DWMH and PVH and the history of suicide attempts was found to be almost identical in the BD. This discrepancy can be attributed to the contrasting findings of the two studies that investigated PVH in BD, which indeed reported high heterogeneity. Therefore, while Pompili et al. [71] found that patients with a history of suicide attempts were 444% more likely than non-attempters to have PVH, the results of Tamashiro et al. [75] revealed that attempters were 43% less likely than non-attempters to have PVH. These conflicting results emphasize the need for further investigation of these associations. Moreover, it is important to note that WMHs alone cannot account for the complexity of the processes leading to suicide attempts and cannot be considered a standalone predictor. From a clinical perspective, ideally, suicide risk assessment should integrate clinical, socio-demographic, environmental, and neurobiological factors like WMHs, to achieve a comprehensive understanding of patients who may be at an elevated risk of suicide attempts [114]. Indeed, recent suicidal behavior models, including the Integrated Motivational Volitional model [115, 116] and the stress-diathesis model [117], underscore the significance of environmental, psychological, and cognitive factors in combination with a neurobiological predisposition for the enactment of a suicide attempt, irrespective of the presence or absence of a psychiatric disorder. All these elements, therefore, should be regarded not merely as inevitable precursors of a suicide attempt but rather as significant risk factors that may influence the suicidal process.

Finally, although the funnel plot did not show statistically significant publication bias, the limited number of publications on this topic in the last decade could indicate selective reporting, which could impact replication efforts [118, 119]. Indeed, while nine articles were published until 2010, obtaining promising results on the association between WMHs and a history of a suicide attempt, only seven articles were published from 2011 to 2024.

Limitations

While these findings are promising, caution is warranted due to several limitations inherent in the included studies, which constrain the generalizability of our results and point to areas for future research. Firstly, the included studies had moderate sample sizes and high heterogeneity, even though low prevalence rates and small samples are common issues in suicidology research [120]. Secondly, only some of the included studies controlled for confounding variables, such as the longitudinal trajectory of the disorder, possible psychiatric and non-psychiatric comorbidities, age, and sex. This aspect represents a significant limitation, since controlling for variables would be particularly important when studying WMHs, considering that the probability of being affected by WMHs rises with biopsychosocial features of aging [82, 121], such as elevated cardiovascular risk factors [122] and cerebral small vessel disease [123]. Also, Dotson et al. [124] observed a potential gender-based distinction in the presentation of WMHs, finding that the trajectory of affective disorders could be predicted over time in older men but not in women. Nonetheless, it should be noted that while not all studies controlled for confounding variables, especially non-psychiatric comorbidities, the majority of them excluded participants with major cardiovascular risk factors to mitigate this bias. Thirdly, all the studies included in the meta-analysis, except for Mehrhof et al. [49], employed 1.5 T MRI scans, which exhibit a markedly inferior spatial resolution compared to 3 T or 7 T images [125, 126], ultimately hindering a more precise detection of WMHs. Fourthly, except for Pompili et al. [71], most studies lacked detailed operational definitions of “suicide attempts”, though the greater attention paid to the nomenclature of suicidal thoughts and behaviors in recent years [127]. Precise definitions, such as those in the Columbia Suicide Severity Rating Scale [128], would enhance the accuracy of classifying different suicide-related outcomes. Additionally, although planned sensitivity analyses were intendedto compare the severity of the lesions, they were not performed due to a lack of data. Indeed, these data were derived from only two studies [75, 79], which employed different lesion rating systems with distinct parameters to assess lesion severity, ultimately limiting the possibility of a comparison.

CONCLUSIONS

Our systematic review and meta-analysis revealed an association between WMHs and a history of suicide attempts in affective disorders, particularly between PVH and suicide attempts in MDD. These findings suggest that WMHs, especially PVH, may potentially serve as a biomarker of suicide attempts. Nevertheless, it remains uncertain whether these lesions merely represent an epiphenomenon of affective disorders or can contribute causally to their etiology [129], thereby differentiating those at higher risk for attempting suicide. Consequently, future research is needed to confirm and eventually deepen our understanding of the nature of this association by leveraging high-resolution MRI and standardized suicide-related outcomes operationalization.

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GT: Writing – original draft, Formal analysis, Conceptualization; EM: Writing – review & editing; AL: Writing – review & editing; PB: Writing – review & editing; GD: Writing – review & editing, Supervision.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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