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Review Article

Multiple Sclerosis and Suicide Attempts: A Review including a Meta-Analysis of Prevalence

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Background. Multiple sclerosis is an autoimmune inflammatory demyelinating disorder, and persons diagnosed with multiple sclerosis have a shorter life expectancy than the general population. Recent meta-analyses have examined the association between MS and suicide and between MS and suicidal ideation. The objective of the present review was to examine if MS is associated with a higher risk of suicide attempt. We hypothesised that MS patients were at increased risk of suicide attempts. *Methods*. Four databases (PubMed including MEDLINE, EMBASE, Web of Science, and PsycINFO) were searched systematically for studies assessing the risk of attempted suicide in people with MS. Eligibility criteria were studies designed as cohort, case-control, or cross-sectional studies with attempted suicide as the outcome and published in English. Lifetime prevalence of suicide attempt was calculated through a meta-analysis, and the results were presented as a forest plot. Sensitivity analyses were used to investigate the heterogeneity among studies. *Results*. 13 studies were identified from 533 records, providing a total population of 50,004 participants of whom 599 had attempted suicide. The weighted overall prevalence of suicide attempts among people with MS was 0.04 (95% CI 0.02-0.06) with a Cochran's Q value of 591.05, which rejected the null hypothesis of homogeneous studies. The performed sensitivity analysis resulted in an I^2 of 81% as the lowest possible value, which still indicated a high level of heterogeneity. *Conclusion*. To our knowledge, this is the first study to examine the association between MS and suicide attempts in a meta-analysis. The results suggest a significant association between MS and suicide attempts. However, the small number of the included studies and the heterogeneous nature of these studies indicate a need for more studies based on more homogeneous samples.

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disorder. The disease is characterised by white matter lesions in the central nervous system, which cause a variety of symptoms and affect mobility and cognition [1]. In 2020, the estimated number of people diagnosed with MS was 2.8 million worldwide [2]. The largest MS-diagnosed populations are found in Europe and North America. However, reliable data are scarce from large parts of Africa and Asia. Women are more often diagnosed with MS than men, and symptom onset frequently occurs around 30 years of age, but it is also met in juveniles, young adults, and elderly people [3].

Persons with MS (PwMS) have a shorter life expectancy than age- and sex-matched healthy individuals, although the discrepancy is decreasing [4]. The main causes of death in

PwMS include cardiovascular events, respiratory disease, suicide, and MS-related complications [5, 6]. PwMS also have a higher risk of being diagnosed with a mental disorder, specifically anxiety and depression, which might be related to lesions in the left temporal/parietal region [7–10]. An EU review by Wittchen et al. shows that the prevalence of mental disorder in neurological disorder is 38.2%, which is considered a lower bound estimate [11]. Persons with a neurological disorder have a significantly higher rate of suicide than other persons [12]. Also, PwMS have an adjusted incidence rate ratio (IRR) for suicide of 2.2 (95% CI 1.9-2.6); however, it is increased to 3.2 (95% CI 2.5-4.0) if the PwMS had four or more hospital contacts [12].

In the general population, mental disorder and serious and/or chronic illness are known to be a significant risk factor in suicidal behaviour [13]. However, several reviews emphasise the need for treatment of mental disorder among PwMS, e.g., psychological evaluation after diagnosis to spot early development of depression [9] and incorporate psychological intervention as a fundamental component of MS treatment [6, 14]. Mellentin et al. suggest that cognitive behavioural therapy and/or mindfulness-based therapy may benefit PwMS with a mental disorder as well as help them adjust to MS [8].

A recent meta-analysis of 8 studies found that the prevalence of suicidal ideation was estimated to be 13% (95% CI 0.09-0.17) in PwMS [15]. Reviews on suicide among PwMS found that the risk of suicide is considerably higher in PwMS than in the general population [16, 17]. Likewise, another meta-analysis of 16 studies found a significant association between MS and suicide with a pooled standardised rate ratio (SRR) of 1.72 (95% CI 1.48-1.99) [6]. The scoping review by Mellentin et al. was conducted to identify risk factors for suicidal behaviour in PwMS, and preventive measures were suggested [8]. Mellentin et al. recommended education of staff and monitoring of PwMS to enhance their quality of life, which might reduce the risk of psychosocial problems and suicidal behaviour.

These meta-analyses and reviews show that PwMS are at increased risk of suicidal ideation or death by suicide, but no review has included a meta-analysis focusing solely on the prevalence of suicide attempts in PwMS. Suicide attempt is known to be a significant risk factor for suicide, which might also be the case in PwMS [14, 18]. Knowledge of suicidal behaviour, including suicide attempts and self-harm, is relevant to prevent death by suicide in PwMS.

Our objective was to examine if MS is associated with a higher risk of suicide attempts. This was accomplished by reviewing the existing literature and subsequently estimating the prevalence of suicide attempts among PwMS. To our knowledge, this association had not been investigated previously, and we hypothesised that PwMS were at increased risk of suicide attempts.

2. Methods

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (2021) [19].

2.1. Search Strategy. On March 25, 2021, a systematic literature search was conducted in four databases: PubMed including MEDLINE, Web of Science, EMBASE, and PsycINFO (the two latter in Ovid). These databases were selected as a quick search revealed that they yielded the most results (see Table 1).

Search results were screened for potentially relevant studies based on title and abstract, which was followed by a full-text review and identification. An updated search was conducted in the same databases on November 9, 2022, that resulted in the inclusion of one additional study. A combined flowchart of study identification is presented in Figure 1.

2.2. Eligibility Criteria. Studies were included if they (1) were of a cohort, case-control, or cross-sectional design, (2) included PwMS and using suicide attempt as the outcome, and (3) were published in English. Studies were excluded if (1) they had no occurrence of suicide attempt, (2) the full text of the study was unavailable, or (3) if the report was a meeting abstract, case report, discussion, editorial, review, letter, or commentary. Records were screened for potentially relevant studies based on title and abstract. For retrieved reports, the assessment was performed by two investigators (TBdA and EC) independently. The results were then compared and discussed before a final joint decision was made.

2.3. Data Collection Process. Data were extracted from the included studies by two investigators (TBdA and EC). Data on the proportion of suicide attempts in PwMS were calculated from each study. The following items were also extracted from the studies: author, year of publication, country, design of study, sample size, number of suicide attempts, duration of follow-up, and time of inclusion.

2.4. Data Analysis. The data on prevalence was analysed with Meta XL, version 5.3 (2019) [21], and presented as a forest plot model, including overall estimates of prevalence and 95% confidence intervals (CIs). The overall estimate of prevalence was calculated as a weighted average of the estimates of prevalence from all the included studies. The specific meta-analysis model calculated the weights for each study. We estimated the lifetime prevalence of suicide attempts from a random effect model.

The heterogeneity between studies was measured by Cochran's Q test and I^2, the percentage of variation across studies that is due to heterogeneity rather than chance [22]. Heterogeneity reflects how much the population prevalence differs across the included studies. I^2 around 0 indicates that variation in prevalence is because of sampling error, where I^2 around 100 indicates that most of the variation is because of differences in population prevalence size. A sensitivity analysis was performed to identify potential causes of heterogeneity by excluding studies according to CI length, weight, population size, outliers, study design, follow-up, or clinical v. nonclinical from the meta-analysis, whereupon I^2 was recalculated. A funnel plot (double arcsin of prevalence by standard error of prevalence) was also performed to analyse heterogeneity among studies.

Table 1: Overview of the databases and search strategies for a systematic review on MS and suicide attempts.

Database	MeSH terms/keywords	In combination with	Filters/limits	Date for search
PubMed (including MEDLINE)	Suicide, Attempted Suicidal Ideation Suicide, Completed Suicidal Behavi* Self-injur* Self*harm*	Multiple sclerosis	Title MeSH major topic MeSH subheading MeSH terms English	25 March 2021
Web of Science	multiple sclerosis suicid* parasuicide self*harm* self-injur*	Title Topic Author keywords Keywords plus	English Document types: "article"	25 March 2021
EMBASE and PsycINFO	multiple sclerosis suicide attempt suicidal behaviour suicide suicid* suicidal ideation parasuicide self-injurious behaviour self*harm* self*damage self*mutilation		English language journal article	26 March 2021

MeSH = medical subject headings; * = truncation.

3. Results

3.1. Study Identification. A total of 533 potentially eligible records were identified in the four databases after the removal of duplicates. After eliminating an additional 475 records based on title and abstract, the remaining 58 reports were read in full, and 13 studies were ultimately included in the review (Figure 1).

3.2. Study Characteristics. The identified 13 studies included a total of 50,004 PwMS, of which 599 PwMS had suicide attempts. The smallest study by Sandyk and Awerbuch [23] included a population of 28 PwMS, and the largest study by Brenner et al. [24] had a population of 29,617 PwMS. Table 2 summarises the included studies.

3.3. Prevalence. Figure 2 shows that the overall prevalence was estimated to be 0.041, with a narrow CI length of 0.04. Six of the studies were clustered to the left of the overall prevalence. These studies had the largest populations and were weighted the highest with the exception of the study by Ouallet et al. [33] which had a small population of 70 and a small prevalence of 0.01, and the study by Eliasen et al. [31] which had a population of 362 and the second highest prevalence of 0.13. Four studies were weighted more than 9% and had a total weight of 37.91%. Eight studies had wide CI lengths ranging from 0.06 to 0.31. These studies were all based on small population samples of less than 300 and tended to show high prevalence ranging from 0.05 to 0.21, except for the study by Ouallet et al. [33]. The remaining five studies had larger population samples and narrow CI lengths and tended to show a lower prevalence of <0.02.

3.4. Heterogeneity. We estimated a high Cochran's Q value of 591.05 (p value < 0.0001), ascertaining that the null hypothesis of homogeneous samples was rejected. Heterogeneity was also assessed using the I^2 test and was calculated to be 98%, which proved that there was considerable heterogeneity in the sample of studies.

3.4.1. Sensitivity Analysis. A sensitivity analysis was performed because the I^2 test indicated substantial heterogeneity between studies.

As Table 3 shows, the lowest I^2 value (69%) was calculated by excluding studies of the lowest CI length; however, it seemed ill-considered to exclude the five studies with the lowest CI length and the highest weight. The meta-analysis after the exclusion of nonclinical studies resulted in an I^2 value of 81% with an overall prevalence of 0.06 (95% CI 0.04-0.10) indicating that a homogeneous sample would be difficult to achieve. The weight distribution ranged from 6.9% in the study by Sandyk and Awerbuch [23] to 16.5% in the study by Zhao et al. [34]. The study by Sandyk and Awerbuch [23] was the only study weighted below 10%. By excluding studies with a prevalence of more than 0.01 and less than 0.1, the recalculated meta-analysis resulted in an I^2 of 82% with an overall prevalence of 0.05 (95% CI 0.03-0.08). The weight distribution ranged from 9.5% in the study by de Cerqueira et al. [30] to 17.7% in the study by Zhao et al. [34].

The funnel plot (Figure 3) supported the hypothesis of the high level of heterogeneity among the identified studies. Still, as seen in the plot, studies with high level of prevalence were more likely to have large standard errors. Thus, a systematic correlation might exist between the sample size

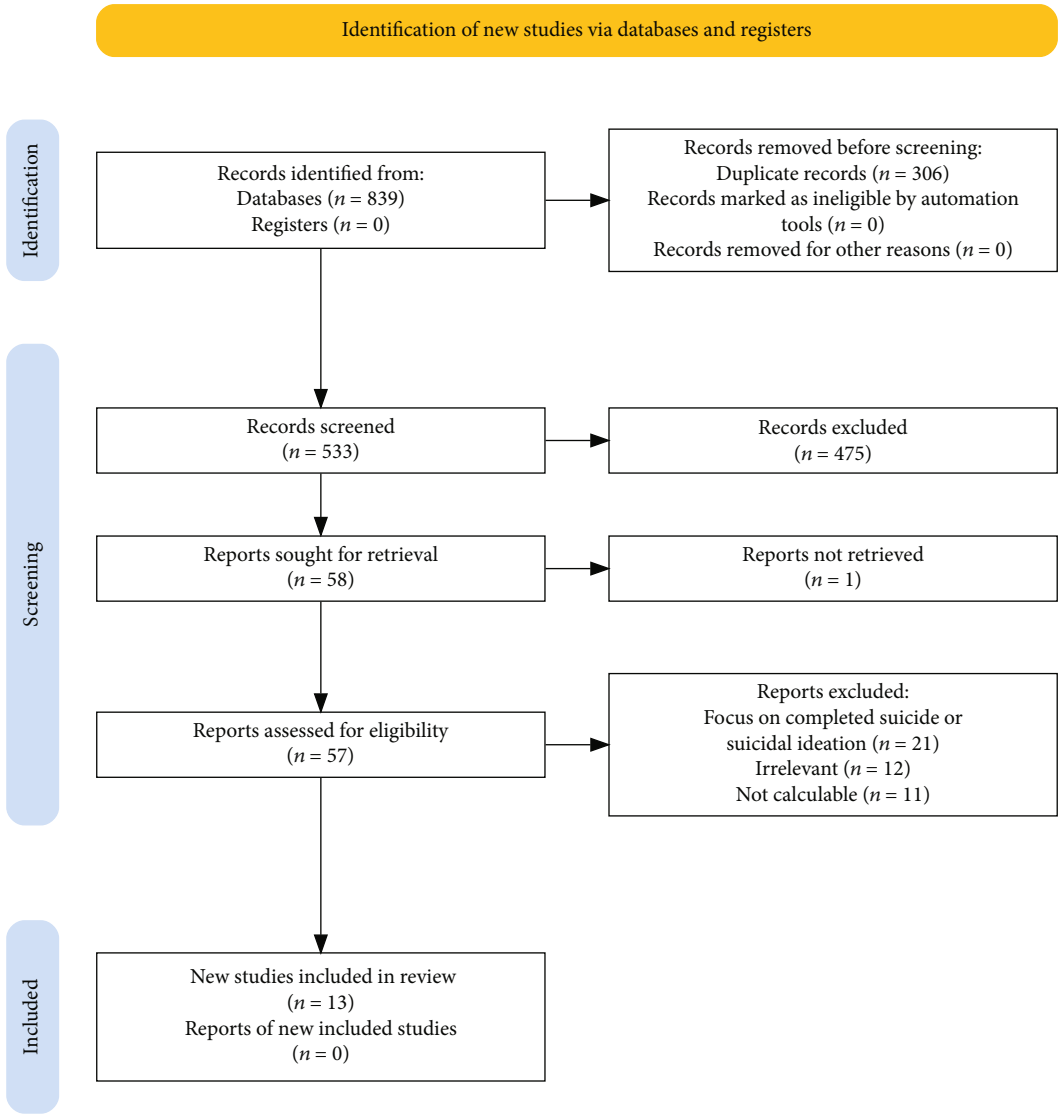

Figure 1: Flowchart of the screening process and study identification and selection for a systematic review on MS and suicide attempts generated by PRISMA flow diagram (2022) [20].

and the level of prevalence, where studies with low sample size (high standard error) is producing high estimates of prevalence (high double arcsin of prevalence) [36].

4. Discussion

4.1. General Interpretation. The aim of this study was to examine the association between MS and suicide attempts by estimating the prevalence of suicide attempts across identified studies on PwMS. To our knowledge, this is the first review and meta-analysis to focus exclusively on the association between suicide attempts in PwMS.

We identified 13 studies on MS and suicide attempts that varied in terms of population size, design, and country of origin. Our meta-analysis estimated the lifetime prevalence to be statistically significant at 4.1% (95% CI 0.025-0.06). In general, we found inconsistency in the estimated size of prevalence in the included studies. The high levels of heterogeneity among the studies could be explained by small-scale studies that were more likely to have a high level of prevalence.

It was evident that the high heterogeneity among the studies caused difficulties in estimating an unbiased pooled lifetime prevalence of suicide attempts among PwMS based on the meta-analysis. The studies were very different in relation to size, design, and quality. Three different designs were used, and the population size varied. Also, a wide range of prevalence was seen which indicated a high level of heterogeneity among studies. Although the sensitivity analysis showed that the studies included were highly heterogeneous, it remained unclear precisely what caused the heterogeneity. Excluding studies according to CI length, weight, population size, outliers, study design, follow-up, or clinical v. nonclinical did not provide an I^2 below 81%.

The meta-analysis suggested that the larger studies were the more reliable and were included in the pooled mean with higher weights. In general, the smallest studies all had a

Table 2: Summary of 13 included studies in a systematic review on MS and suicide attempts.

Author (year) [ref]	Country	Design	Population	Suicide attempts	Effect size proportion	Follow-up	Time of inclusion
Sandyk and Awerbuch 1993 [23]	USA	Cohort	28	6	$\widehat{p} = 0.214$	Retrospective lifetime	Treatment at clinic
Fisk et al. 1998 [25]	Canada	Case-control	2,542	17	$\widehat{p} = 0.007$	3-year prospective	Hospital separation
Feinstein 2002 [26]	Canada	Cross-sectional	140	9	$\widehat{p} = 0.064$	Retrospective lifetime	Treatment at clinic
Korostil and Feinstein 2007 [27]	Canada	Cross-sectional	140	7	$\widehat{p} = 0.05$	Retrospective lifetime	Treatment at clinic
Stenager et al. 2011 [28]	Denmark	Cohort	404	8	$\widehat{p} = 0.020$	Minimum 3-year prospective	Diagnosis
Capkun et al. 2015 [29]	USA	Cohort	15,684	15	$\widehat{p} = 0.00096$	Retrospective 4 years	Diagnosis
de Cerqueira et al. 2015 [30]	Brazil	Case-control	60	5	$\widehat{p} = 0.083$	Retrospective lifetime	Treatment at clinic
Brenner et al. 2016 [24]	Sweden	Case-control	29,164	423	$\widehat{p} = 0.015$	Retrospective 12.5 years	Diagnosis
Eliasen et al. 2018 [31]	Denmark	Case-control	362	48	$\widehat{p} = 0.133$	Retrospective 7 years	Diagnosis
Asgarian et al. 2020 [32]	Iran	Cross-sectional	276	21	$\widehat{p} = 0.076$	Retrospective lifetime	Diagnosis
Ouallet et al. 2020 [33]	France	Cohort	70	1	$\widehat{p} = 0.014$	24-month prospective	Treatment at clinic
Zhao et al. 2021 [34]	China	Cross-sectional	931	22	$\widehat{p} = 0.024$	Retrospective lifetime	Diagnosis
Sariaslani et al. 2021 [35]	Iran	Cross-sectional	203	17	$\widehat{p} = 0.083$	Unknown	Treatment at clinic

$\widehat{p}$ = proportion in the sample; separation = discharge from hospital.

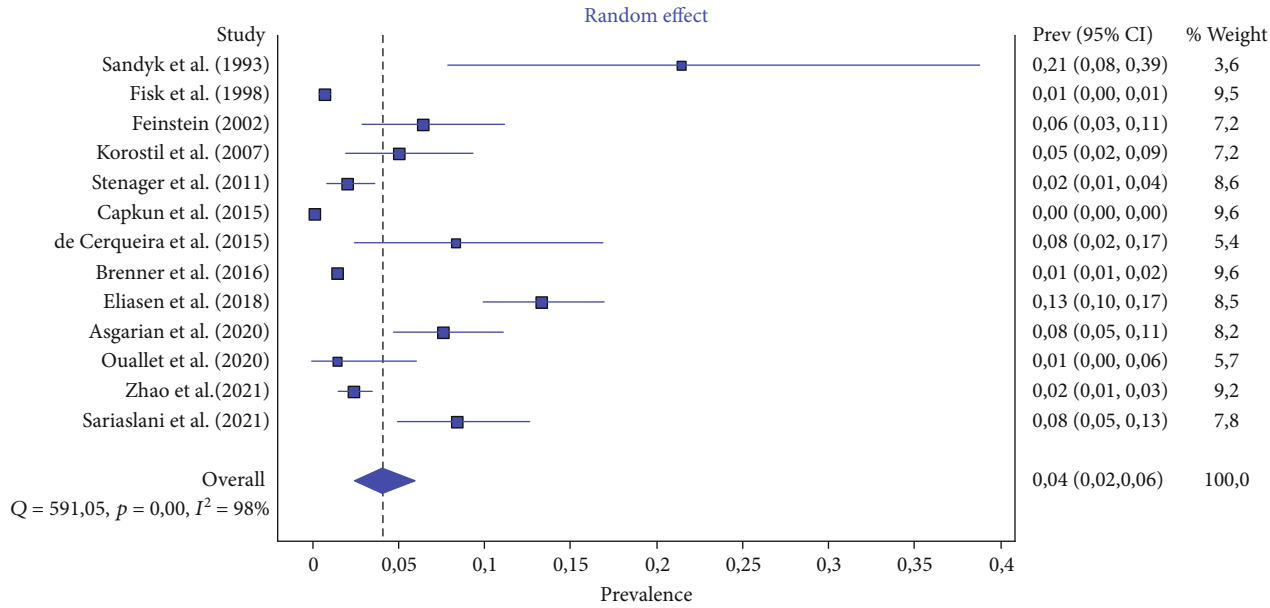

Figure 2: Forest plot of meta-analysis of prevalence by random effect model of the included studies in a systematic review on MS and suicide attempts. Q = Cochran's Q value. p = p value indicating level of statistical significance. I^2 = I-squared heterogeneity; Prev = prevalence; CI 95% = confidence interval.

higher prevalence, and these populations might be biased toward a higher baseline risk for suicide attempts or a better registration of suicide attempts, with the exceptions of the studies by Ouallet et al. [24] and Eliasen et al. [31]. Suicide attempts are widely underreported in registers, since not all suicide attempts require contact with the health services, and some might be incorrectly registered. Studies including direct interaction with their population are more likely to register all suicide attempt among their population. The funnel plot supports this association, as the studies with high prevalence have higher standard errors, which demonstrates less reliability of the estimated prevalence.

4.2. Comparison with the Previous Findings. Previous studies have shown that PwMS are more likely to develop mental disorder, suicidal ideation, or suicidal behaviour. A meta-analysis by Franklin et al. found a strong correlation between mental disorder, e.g., depression or anxiety, and suicidality, and mental disorder in combination with other factors was likely to constitute a more severe risk factor [13]. Reviews focusing solely on MS populations found a prevalence of anxiety of 35% in an MS population in a meta-analysis of nine studies. A meta-analysis by Rintala et al. found a 37% prevalence of major depressive disorder in early-phase MS (three studies), and an overall prevalence of 25% of any depression (nine studies) [9]. A review by Siegert and Abernethy found that the lifetime prevalence of depression was 50% in an MS population, and anxiety disorders also seem more prevalent [10]. A meta-analysis of suicidal ideation in PwMS (2020) reported a range from 2% in Brazil to 34% in the United States and a global prevalence of 13% [15].

The problem of heterogeneity in relevant studies was also evident in other meta-analyses. The meta-analysis of suicide by Shen et al. identified 16 studies of heterogeneous nature and excluded three very dominant studies in their sensitivity analysis, lowering their I^2 from 87.1% to 55% [6]. A meta-analysis on depression and anxiety by Rintala et al. found 41 studies on MS, and they noted that the clinical and statistical findings were heterogeneous and that the sensitivity and subgroup analyses might identify factors to explain this heterogeneity; however, only subgroup analyses of mild and moderate depression yielded an I^2 below 40%. Meta-analyses according to depression or anxiety scales consistently yielded high I^2 [9].

The risk factors for suicide attempts in a general population include prior nonsuicidal self-injury, prior suicide attempt, and psychiatric or personality disorders. Physical illness and/or neurobiological dysfunction also constitute a risk of suicide attempts [13, 37, 38]. A review by Castillejos et al. shows that a general adult European population has a lifetime prevalence for suicide attempt ranging from 0.55 to 5.04% with a pooled lifetime prevalence of 2.88% (95% CI 2.15-3.60) [39], while a general adult population in the US has a lifetime prevalence for suicide attempts in the range of 1.9-8.7% [40]. The same review (2008) shows a cross-national lifetime prevalence for suicide attempts in the range of 0.4-5.1% [40]. A review by Cao et al. shows that a general adult Chinese population has a lifetime prevalence for suicide attempts of 0.8% (95% CI 0.7-0.9) [41]. WHO states that more women are diagnosed with MS than men, which may partly explain the high prevalence found in our meta-study [3]. In the general population, suicide attempts peak in late adolescence [40]; however, the onset of MS symptoms most commonly appears around 30 years of age [3];

Table 3: Sensitivity analysis of studies in a systematic review on multiple sclerosis and suicide attempts.

Exclusion criteria	Included studies	I^2	Overall prev (95% CI)
CI length more than 0.1 Two studies excluded	Fisk et al., Feinstein, Korostil, et al., Stenager et al., Capkun et al., Brenner et al., Eliasen et al., Asgarian et al., Ouallet et al., Zhao et al., Sariaslani et al.	98%	0.03 (0.02-0.05)
CI length more than 0.06 Six studies excluded	Fisk et al., Stenager et al., Capkun et al., Brenner et al., Asgarian et al., Ouallet et al., Zhao et al.	98%	0.02 (0.01-0.03)
CI length more than 0.05 Eight studies excluded	Fisk et al., Stenager et al., Capkun et al., Brenner et al., Zhao et al.	99%	0.01 (0.00-0.02)
CI length less than 0.05 Five studies excluded	Sandyk et al., Feinstein, Korostil et al., de Cerqueira et al., Eliasen et al., Asgarian et al., Ouallet et al., Sariaslani et al.	69%	0.08 (0.05-0.11)
Weight less than 6% Three studies excluded	Fisk et al., Feinstein, Korostil et al., Stenager et al., Capkun et al., Brenner et al., Eliasen et al., Asgarian et al., Sariaslani et al., Zhao et al.	98%	0.03 (0.02-0.05)
Weight less than 8% Six studies excluded	Fisk et al., Stenager et al., Capkun et al., Brenner et al., Eliasen et al., Asgarian et al., Zhao et al.	99%	0.03 (0.01-0.04)
N less than 300 Six studies excluded Same studies as above	Fisk et al., Stenager et al., Capkun et al., Brenner et al., Eliasen, et al., Zhao et al., Asgarian et al.	99%	0.03 (0.01-0.04)
N more than 900 Four studies excluded	Sandyk et al., Feinstein, Korostil et al., Stenager et al., de Cerqueira et al., Eliasen et al., Asgarian et al., Ouallet et al., Sariaslani et al.	85%	0.07 (0.04-0.11)
Outliers excluded Three studies excluded	Fisk et al., Feinstein, Korostil et al., Stenager et al., de Cerqueira et al., Brenner et al., Asgarian et al., Ouallet et al., Sariaslani et al., Zhao et al.	91%	0.03 (0.02-0.05
Outliers excluded Six studies excluded	Feinstein, Korostil et al., Stenager et al., de Cerqueira, et al., Asgarian et al., Sariaslani et al., Zhao et al.	82%	0.05 (0.03-0.08)
Cross-sectional study design Five studies excluded	Sandyk et al., Fisk et al., Stenager et al., Capkun et al., de Cerqueira et al., Brenner et al., Eliasen et al., Ouallet et al.	99%	0.03 (0.01-0.05)
Cross-sectional or case-control study design Nine studies excluded	Sandyk et al., Stenager et al., Capkun et al., Ouallet et al.	94%	0.02 (0.00-0.07)
Cohort or case-control studies Eight studies excluded	Feinstein, Korostil et al., Asgarian et al., Sariaslani, et al., Zhao et al.	84%	0.06 (0.03-0.09)
Any follow-up but retrospective lifetime Seven studies excluded	Sandyk et al., Feinstein, Korostil et al., de Cerqueira et al., Asgarian, et al., Zhao et al.	83%	0.07 (0.03-0.11)
Any follow-up but retrospective of at least five years Five studies excluded	Sandyk et al., Feinstein, Korostil et al., de Cerqueira et al., Brenner et al., Eliasen et al., Asgarian et al., Zhao et al.	96%	0.07 (0.03-0.11)
Nonclinical studies Five studies excluded	Sandyk et al., Feinstein, Korostil et al., de Cerqueira et al., Asgarian et al., Ouallet et al., Sariaslani, et al., Zhao et al.	81%	0.06 (0.04-0.10)
Clinical studies Eight studies excluded	Fisk et al., Stenager et al., Capkun et al., Brenner et al., Eliasen et al.	99%	0.02 (0.01-0.04)
Antecedent studies, prior to 2000 Two studies excluded	Feinstein, Korostil et al., Stenager et al., Capkun et al., de Cerqueira et al., Brenner et al., Eliasen et al., Asgarian et al., Ouallet et al., Zhao et al., Sariaslani et al.	98%	0.04 (0.02-0.06)
Antecedent studies, prior to 2010 Four studies excluded	Stenager et al., Capkun et al., de Cerqueira et al., Brenner et al., Eliasen et al., Asgarian et al., Ouallet et al., Zhao et al., Sariaslani et al.	99%	0.04 (0.02-0.06)
Antecedent studies, prior to 2015 Five studies excluded	Capkun et al., de Cerqueira et al., Brenner et al., Eliasen et al., Asgarian et al., Ouallet et al., Zhao et al., Sariaslani et al.	99%	0.04 (0.02-0.07)

I^2 = I-squared heterogeneity; prev = prevalence; CI 95% = confidence interval; N = number of population.

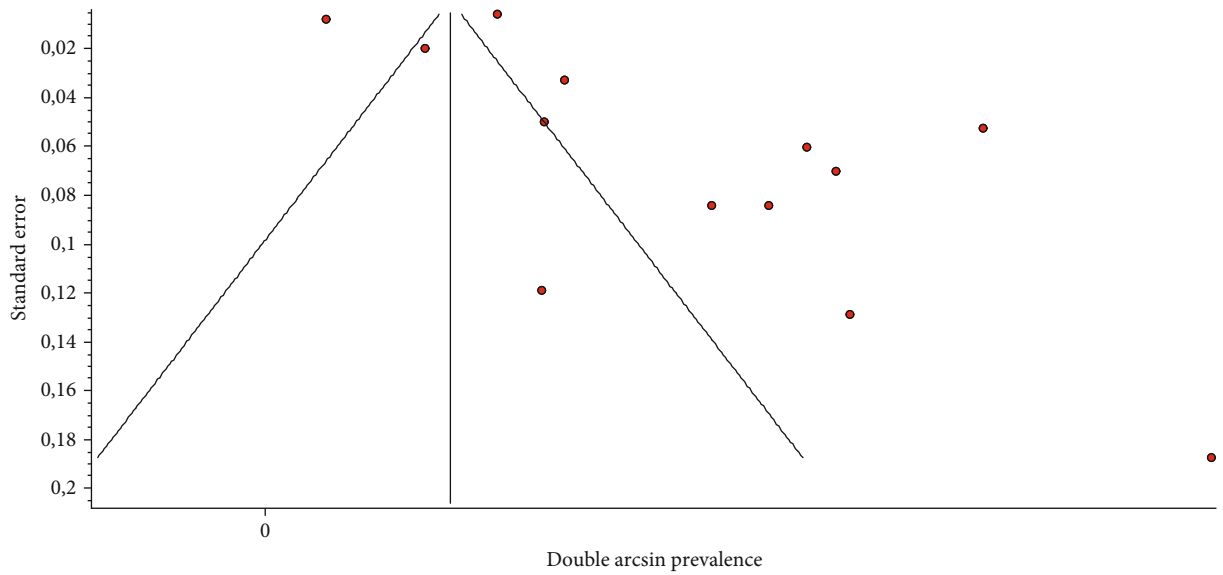

Figure 3: Meta-analysis funnel plot of the included studies in a review on MS and suicide attempts.

therefore, the suicide attempts in the MS population might happen among an older age group. Reviews on prevalence of suicide attempts in populations resembling an MS population included a meta-analysis of individuals with major depressive disorders, which found that the lifetime prevalence of suicide attempts was 31% [42]. As PwMS have a higher risk of being diagnosed with depression [7, 10], it is relevant to consider the possible effect treatment for depression may have. A review on suicide attempts in patients with Parkinson's disease (2019) found mixed results ranging from no risk to a lifetime rate of suicide attempts around 5% [43]. A review on patients with chronic epilepsy (2003) shows that the lifetime prevalence of suicide attempts in persons with epilepsy was 20.8% [44], while a review on persons living with HIV/AIDS (2021) found a lifetime prevalence of 158.3 per 1000 persons (95% CI 106.9-228.2) [45]. This review did not examine if neurological symptoms were more widespread in persons living with HIV/AIDS who attempted suicide [45]. A lifetime prevalence for suicide attempt in PwMS of 4.1%, although lower when compared to these populations, is significantly higher than the general population. However, it has proven difficult to compare suicide data across studies, countries, and/or over time as a recent review by Jakobsen et al. shows [46]. Inconsistencies in definitions, methods used for calculations, and reporting were addressed as early as 2001 by Welch [47].

4.3. Limitations. The decision to exclude literature not published in peer-reviewed journals might be considered a limitation; however, we deemed it necessary to only include peer-reviewed studies for a reliable meta-analysis. Solely including peer-reviewed studies might have resulted in publication bias. Furthermore, the inclusion of additional databases might have resulted in more studies.

Most of the studies included were conducted in Europe or North America, and we were able to identify only one study from each of South America and Asia and two from the Middle East. This geographical disparity might have influenced the results. Furthermore, the included studies had heterogeneous designs, which prevented deeper analyses than at the proportion level. The overall estimate might still be biased due to limited study populations and low numbers of high-quality studies included in this meta-analysis.

4.4. Implications. The high heterogeneity of the included studies disclosed a need for more studies with a homogeneous setup with comparable prevalence and follow-up. It would be advisable to use a well-defined MS diagnosis and well-defined registrations of suicide attempts with (if possible) uniform populations, i.e., a homogeneous population in terms of sex, age, and severity (progression) of illness.

It should be considered that a clinical population is further in the course of the illness than a register-based population and therefore is likely to experience more severe symptoms. Also, clinical studies are likely to uncover most suicide attempts, as the researchers have direct contact with the populations, whereas register-based studies are dependent on correct registrations of suicide attempts. Furthermore, as not all suicide attempts require contact with the health services, the registered numbers of suicide attempts are expected to be underestimated.

A lifetime prevalence of suicide attempts of 4.1% suggests that an MS population probably would benefit from preventive measure. Preventive measures could focus on the quality of life and depression rather than on the high risk for suicidal behaviour. To our knowledge, there is no existing screening tool solely developed for PwMS, neither would it be expedient to screen all PwMS continuously. Although there are several screening tools for detecting suicidal behaviour [48], screening as a standalone practice has proven ineffective in reliably predicting suicidal behaviour [49]. A valuable supplement to screening for suicidal ideation or suicidal behaviour could be gatekeeper training, i.e., the practice of being able to identify persons at risk of suicide by

recognising warning signs [50], though more evidence of the effectiveness of gatekeeping is in demand [51–54]. A review by Mann et al. found that gatekeeper training was most beneficial with a young target population [55]; however, it is difficult to evaluate the sole effect of gatekeeper training, when gatekeeping most often is implemented within broader programs for suicide prevention [52, 53].

We support the recommendations of Mellentin et al. that professionals (health, social, or administrative personnel) in contact with PwMS are attentive to signs of poor mental health and/or suicidal ideation. An effective means of preventing suicide attempts could be to encourage health professionals to ask the PwMS if they suffer from mental problems or suicidal ideation and to provide psychological intervention, which should be a fundamental component of the care provided for PwMS [8]. However, to ensure benefits from an outreach approach, the personnel must be updated on how to detect poor mental health and/or suicidal ideation. Furthermore, it is essential that they know where to refer these patients (e.g., general practitioner, psychiatrist, or centres for suicidal prevention). Neurological wards would likely benefit from the implementation of gatekeeper training.

5. Conclusion

The present review compared the results based on estimated proportions, and the findings from the meta-analysis suggest a significant association between suicide attempts and MS, substantiating our hypothesis that PwMS are at increased risk of suicide attempts. Therefore, we recommend that health personnel should be aware of the mental problems and/or suicidal ideation in PwMS in order to support them with the problems of mental health and social matters.

Data Availability

The data used to support the findings in this review consist of previously published studies. These prior studies are cited at relevant places within the text as references (#23-#35).

Conflicts of Interest

We know of no conflict of interest associated with this publication.

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