Journal of Psychiatric Research 151 (2022) 65–72

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Suicidal ideation in remitted major depressive disorder predicts recurrence

Caroline B.B.C.M. Heuschen [a,*], Roel J.T. Mocking [a], Jasper B. Zantvoord [a], Caroline A. Figueroa [b,g], Aart H. Schene [e,f,2], Damiaan A.J.P. Denys [a], Henricus G. Ruhé [e,f,1], Claudi L.H. Bockting [a,c,d,1], Anja Lok [a,c,d]

[a] Amsterdam UMC, University of Amsterdam, Department of psychiatry, Meibergdreef 5, 1105 AZ, Amsterdam, the Netherlands
[b] School of Social Welfare, University of California, Berkeley, United States
[c] Amsterdam Public Health Institute, Amsterdam UMC, Amsterdam, the Netherlands
[d] Centre for Urban Mental Health, University of Amsterdam, Amsterdam, the Netherlands
[e] Dept. of Psychiatry, Radboudumc, Nijmegen, the Netherlands
[f] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands
[g] University Medical Centre Utrecht, Heidelberglaan, 100 3584 CX, Utrecht

ARTICLE INFO

Keywords:
Suicidal ideation
Residual depressive symptoms
Major depressive disorder (MDD)
Remitted recurrent MDD

ABSTRACT

Introduction: Each year almost 800.000 people die from suicide, of which up to 87% are affected by major depressive disorder (MDD). Despite the strong association between suicidality and MDD, it remains unknown if suicidal symptoms during remission put remitted recurrent MDD patients (rrMDD) at risk for recurrence.

Methods: At baseline we compared sociodemographic characteristics and suicidal symptoms in un-medicated rrMDD participants to matched never-depressed controls. We used the $HDRS_{17}$ and $IDS\text{-}SR_{30}$ to assess suicidal symptoms and depressive symptomatology. Next, we studied the longitudinal association between baseline suicidal symptoms and time to recurrence(s) in rrMDD during a 2.5-year follow-up period using cox regression analyses. Further, we studied with longitudinal data whether suicidal symptoms and depressive symptomatology were cross-sectionally associated using mixed model analysis.

Results: At baseline, rrMDD participants ($N = 73$) had higher self-reported suicidal symptoms than matched never-depressed controls ($N = 45$) ($\chi^2 = 12.09$ $p < .002$). Self-reported suicidal symptoms were almost four times higher (27.9% versus 6.9%) compared to clinician-rated suicidal symptoms in rrMDD at baseline. Self-reported baseline suicidal symptoms, but not clinician-rated symptoms, predicted earlier MDD-recurrence during follow-up, independent of other residual depressive symptoms ($\chi^2 = 7.26$, $p < .026$). Higher suicidal symptoms were longitudinally related to higher depressive symptoms ($HDRS_{17}$; $F = 49.87$, $p < .001$), $IDS\text{-}SR_{30}$; ($F = 22.36$, $p < .001$).

Conclusion: This study showed that self-reported – but not clinician-rated - suicidal symptoms persist during remission in rrMDD and predict recurrence, independent from residual symptoms. We recommend to monitor both suicidal and depressive symptomatology during remission in rrMDD, preferably also including self-reported questionnaires apart from clinician-rated. It would be beneficial for future research to assess suicidality using questionnaires primarily designed for measuring suicidal ideation.

1. Introduction

Suicide is a major health challenge with 800.000 deaths worldwide annually (World Health Organisation, 2016). Even though more than 90% of people who died by suicide had one or more psychiatric disorders (Cavanagh et al., 2003; Dong et al., 2019), recent research challenges the view that suicidality is merely a symptom or manifestation of a given disorder (Aleman and Denys, 2014; Oquendo and Baca-Garcia, 2014; Pompili, 2019). Suicidal ideation and behavior has been shown to emerge from a combination of various factors, including mental illness, environmental, socio-demographics and cultural risk factors (Oquendo and Baca-Garcia, 2014).

* Corresponding author. Amsterdam UMC, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands.
E-mail address: c.b.heuschen@amsterdamumc.nl (C.B.B.C.M. Heuschen).
[1] shared second last authorship.
[2] deceased.

https://doi.org/10.1016/j.jpsychires.2022.04.005
Received 5 October 2021; Received in revised form 21 March 2022; Accepted 6 April 2022
Available online 11 April 2022

Still, psychiatry's current nosology only includes suicidal thoughts and behavior as a symptom of either major depressive disorder (MDD) or borderline personality disorder (BPD) (Oquendo and Baca-Garcia, 2014). MDD is commonly associated with suicidal ideation and behavior (Baldessarini and Tondo, 2020). Moreover, psychological autopsy studies have repeatedly reported depression as the most common mental disorder among suicide decedents (Cavanagh et al., 2003; Conwell et al., 1996; Ribeiro et al., 2018) with MDD accounting for 59–87% of all suicides (Cavanagh et al., 2003; Dong et al., 2019). However, these numbers should be interpreted with caution, since psychological autopsy studies might overestimate the prevalence of mental disorders and depression since these studies rely mostly on retrospective information provided by next of kin (Hjelmeland et al., 2012).

Despite the close association between MDD and suicidal ideation and behavior (Baldessarini and Tondo, 2020), less is known about the temporal association of the course of recurrent MDD and suicidality. Since MDD is a disease with a high recurrence rate, with 80% of MDD-patients experiencing an average of five lifetime recurrences (Bhagwagar and Cowen, 2008), studying the longitudinal association is important, as with every recurrence the risk for suicidal ideation increases (Courtet, 2010). Known predictors of time to recurrence are the number of previous episodes, the presence of residual symptoms, cognitive reactivity, daily hassles, coping related factors and marital status (Figueroa et al., 2015; Israel, 2010; Ten Doesschate et al., 2010). Of these factors, the presence of residual symptoms is the single most accurate marker for risk of relapse (Israel, 2010).

Interestingly, the majority of patients with MDD do not experience complete alleviation of depressive symptoms, even in remission (Israel, 2010; Judd et al., 1997, 1998; Mojtabai, 2001). Also, the current criteria for remission do not require that patients be completely asymptomatic (Israel, 2010; Keller, 2003). Consequently, there can be substantial variability and heterogeneity in presence of residual symptoms and ongoing levels of impairment of psychosocial and cognitive functioning in patients considered to be in remission (Israel, 2010; Zimmerman et al., 2007).

In MDD, suicidal ideation appears to resolve gradually after depressive symptoms have started to alleviate (Sokero et al., 2006). However, relatively few studies have considered recurrence of suicidal ideation in patients with MDD, despite the widespread assumption that suicidal ideation recurs consistently across depressive episodes (Williams et al., 2006). Consistently measuring suicidal ideation among individuals with MDD could prevent worsening of suicidal symptoms and recurrence of depression, even among those with minimal suicidal ideation at any presentation. Targeting suicidal beliefs and cognitions as a pre-emptive measure in individuals with MDD who report even minimal suicidal ideation at any presentation could aid to prevent more severe levels of suicidal ideation and MDD recurrence (Williams et al., 2006).

To date, to the best of our knowledge, there are no studies that reported on suicidal ideation in the remitted phase of MDD, as a predictor of MDD recurrence (Bockting et al., 2006; Conradi et al., 2008; Kessing et al., 1998, 2004; Mueller et al., 1999; Ten Doesschate et al., 2010). Moreover, it remains inconclusive whether suicidal ideation persists in the remitted phase of MDD and whether it should be seen independent or as part of residual symptoms (Madsen et al., 2019). This emphasizes the need for longitudinal studies which specifically investigate the association between suicidality and recurrent MDD both in the remitted phase and over time.

Therefore, we investigated suicidal symptoms in remitted participants suffering from recurrent depression and examined how suicidal symptoms longitudinally relate to MDD recurrence as well as to residual symptoms. We followed-up a patient cohort for 2.5 years and hypothesized that (I) the presence of baseline suicidal symptoms in rrMDD participants would predict future recurrence and that (II) suicidal and depressive symptoms would be associated over time.

2. Methods

2.1. Design

This study is a secondary analysis of the DELTA-imaging study. At baseline we compared remitted un-medicated recurrent MDD-patients with matched never-depressed controls and assessed sociodemographic and clinical characteristics among which are suicidal symptoms. Next, we used a prospective cohort-design to monitor recurrences in the MDD-participants during a 2.5-year follow-up period. We measured suicidal and depressive symptoms every 3–4 months and tested the longitudinal association between suicidal symptoms, depressive symptomatology and MDD recurrence in rrMDD. More study details are described in a dedicated methodological paper (Mocking et al., 2016).

2.2. Participants

Inclusion criteria for the rrMDD group were: ≥2 previous MDD-episodes according to the structured clinical interview for DSM-IV Disorders (SCID) (Harrington et al., 2012) being in stable remission [≥8 weeks with a 17-item Hamilton Depression Rating Scale (HDRS) ≤7] (Mocking et al., 2016). We included participants aged 35–65 years, to achieve a more homogeneous age group (Mocking et al., 2016). Next, we included never depressed controls without personal (SCID) or first-degree familial psychiatric history, matched for strata of age, sex, educational level, working class and ethnicity (Mocking et al., 2016).

In order to obtain a homogeneous sample, we excluded participants with current diagnoses of alcohol/drug dependence, psychotic or bipolar disorder, predominant anxiety or severe personality disorder (all SCID); electroconvulsive therapy within 2 months before study entry; history of severe head trauma or neurological disease; severe general physical illness; no Dutch/English proficiency (Mocking et al., 2016). All participants had to be without psychoactive drugs/medication for >4 weeks before baseline assessments. Incidental benzodiazepine use was allowed, but this had to be stopped ≥2 days before assessments (Mocking et al., 2016).

2.3. Recruitment

To minimise selection biases, both groups were recruited through identical advertisements in freely available online and house-to-house papers, posters in public spaces and from previous studies in our and affiliated research centres (Mocking et al., 2016). One previous study from which participants were recruited is the Depression Evaluation Longitudinal Therapy Assessment (DELTA)-study (Bockting et al., 2005).

2.4. Measurements

2.4.1. Assessment of depressive symptoms

We used the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) and Inventory of Depressive Symptomatology Self-Reported ($IDS\text{-}SR_{30}$) to assess depressive symptomatology every four months for 2.5 years (Rush et al., 2000). Previous research has shown that patient and clinician rated measurements are complementary in the assessment of MDD (Tada et al., 2014; Uher et al., 2012). The $HDRS_{17}$ is a clinician-rated major depressive disorder (MDD)-symptom scale to assess the severity of depression (Hamilton, 1967; HAMILTON, 1960). The $IDS\text{-}SR_{30}$ is a self-reported MDD-symptom scale to assess severity of depressive symptoms (Rush et al., 2000) and has excellent psychometric properties (Rush et al., 1996). The recall period for both questionnaires was the past 7 days.

2.4.2. Assessment of suicidality

We assessed suicidality every four months for 2.5 years, in two ways: clinician-rated using the $HDRS_{17}$ item 3 (range: 0. absent; 1. feels life is

not worth living; 2. wishes he/she were dead or any thoughts of possible death to self; 3. ideas or gestures of suicide; 4. attempts of suicide), and self-reported using the IDS-SR_{30} item 18 (range: 0. I do not think of suicide or death; 1. I feel that life is empty or wonder if it is worth living; 2. I think of suicide or death several times a week for several minutes; 3. I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life). The recall period for both questionnaires was the past 7 days.

2.4.3. Assessment of recurrence

We assessed recurrence using the SCID (Harrington et al., 2012). To this end, trained interviewers called patients every four months for 2.5 years.

2.5. Covariates

The following variables were measured and considered as potential confounders: age, gender, smoking, alcohol use, ethnicity, number of depressive episodes during the last ten years (SCID), psychiatric comorbidity, family history, current treatment, current occupation and residual depressive symptoms.

2.6. Statistical analysis

2.6.1. Data preparation

Suicidality by $HDRS_{17}$ at follow-up and by IDS-SR_{30} at baseline and follow-up was analyzed as an ordinal measurement, to include the ranking of items. However, this was not possible for $HDRS_{17}$ at baseline, because the distribution resulted in insufficient power. Therefore, suicidality by $HDRS_{17}$ at baseline was recoded as a dichotomous variable. To this end we created two categories: no suicidal symptoms (score of 0) vs. presence of suicidal symptoms (scores $\geq$1). This cutoff value has been commonly used in previous studies (Dold et al., 2018a; Park et al., 2014; Pu et al., 2017).

For both questionnaires we excluded the suicide related items ($HDRS_{17}$ item 3, IDS-SR_{30} item 18) from the total score, in order to test suicidal ideation independently from total scores.

2.6.2. Descriptive statistics

We compared the demographic characteristics of rrMDD and controls using t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally continuous variables and χ^2 tests for categorical variables. We used χ^2 statistics to examine whether rrMDD had more suicidal symptoms at baseline, compared to matched never-depressed controls. If confounders were identified, we corrected for these using ordinal logistic regression.

2.6.3. Covariates

In order to derive the most parsimonious models, we considered variables relevant covariates if they were related to both the dependent and independent variable with a lenient threshold of $p < .1$, using dedicated statistical tests including independent t-tests, chi-square tests, one-way analyses of variance, cox-regression (statistics for all covariates available upon request) (Mocking et al., 2016).

2.6.4. Analysis

2.6.4.1. Primary analysis: baseline suicidal symptoms are predictive for recurrence in rrMDD. We assessed whether suicidal symptoms were predictive for future recurrences in rrMDD using Cox regression analysis. Time to recurrence, within the 2.5 years follow-up, was the dependent variable and presence of suicidal symptoms at baseline the independent variable. Subjects who did not experience recurrence or were missing to follow up were right censored. To estimate time to recurrence we used the Kaplan Meier analyses.

2.6.4.2. Secondary analysis: the association between suicidal symptoms and depressive symptom severity over time. We studied with longitudinal data how suicidal and depressive symptoms were cross-sectionally associated during follow-up in the rrMDD group using mixed model analysis. We created sum scores (suicide items excluded) for $HDRS_{17}$ and IDS-SR_{30} separately, for both the study-entry and the follow up measurements. The sum scores acted as dependent variable in the mixed model analysis. The severity level of suicidal symptoms was used as a time varying covariate and acted as independent variable. We created a time variable with eight measurements: intake plus seven follow-up measurements (T1-8). The most parsimonious model was analyzed; unstructured. For the analysis of $HDRS_{17}$, time and suicidal symptoms were included as fixed effects. For analysis of IDS-SR_{30}, suicidal symptoms were included as a fixed effect. Time was added as a repeated measure within-subject factor.

2.6.4.3. Sensitivity analysis. We conducted sensitivity analysis excluding participants who started to use antidepressants during naturalistic follow up.

Throughout the study we performed identical analyses both for clinician-rated $HDRS_{17}$ and self-reported IDS-SR_{30}. We performed all statistical analysis using SPSS version 24 and regarded two tailed *p*-values <.05 as statistically significant.

3. Results

3.1. Demographic and clinical characteristics (Table 1)

Forty-five controls and 73 rrMDD participants were initially eligible (Fig. 1). For the $HDRS_{17}$, of the 73 MDD-patients, 61 (83.6%) had at least one follow-up measurement and 49 (67.1%) completed follow-up for 2.5 years. For the IDS-SR_{30}, of the 73 MDD-patients, 42 (57.5%) had at least one follow-up measurement and 38 (52.1%) completed follow-up for 2.5 years.

We observed significant differences between rrMDD and never-depressed controls for the following baseline characteristics: the number of alcoholic drinks during the week, residual depressive symptoms and self-reported suicidal symptoms (Table 1).

Although average residual symptoms were low, rrMDD showed significantly higher levels of residual depressive symptoms than controls (Table 1; $HDRS_{17}$, IDS-SR_{30} scores; $p < .001$). Also, self-reported suicidal symptoms were significantly higher in rrMDD; 28% (19/68) in rrMDD versus 2.3% (1/43) in never-depressed controls (IDS-SR_{30} scores; $\chi^2 = 12.09$ (df = 2) p = .002). There was no significant difference in clinician-rated suicidal symptoms; 6.9% (5/72) in rrMDD versus 2.2% (1/45) in never-depressed controls ($HDRS_{17}$ scores; $\chi^2 = 1.97$ (df = 2); p = .37). Moreover, clinician-rated suicidal symptoms (6.9%) differed from self-reported suicidal symptoms (27.9%) in rrMDD at baseline.

3.2. Primary analysis: baseline suicidal symptoms are predictive for recurrence in rrMDD

During the 2.5 years follow up, 48% of rrMDD-participants experienced at least one recurrence. Self-reported suicidal symptoms were statistically significant associated with time until recurrence (IDS scores; $\chi^2 = 7.26$ (df = 2); p = .026; Fig. 2). No confounders (age, gender, smoking, alcohol consumption, nationality, number of previous depressive episodes, psychiatric comorbidity, psychiatric family history, current treatment and occupation) were identified.

Post-hoc analysis showed that a score of one (I feel life is empty or wonder if it is worth living) on the IDS-SR_{30} suicide item was significantly associated with time until recurrence (Wald test 6.578 (df = 1) p = .010). A score of two (I think of suicide or death several times a week for several minutes) on the IDS-SR_{30} suicide item was not (Wald test 1.957 (df = 1) p = .162). Correction for residual depressive symptoms

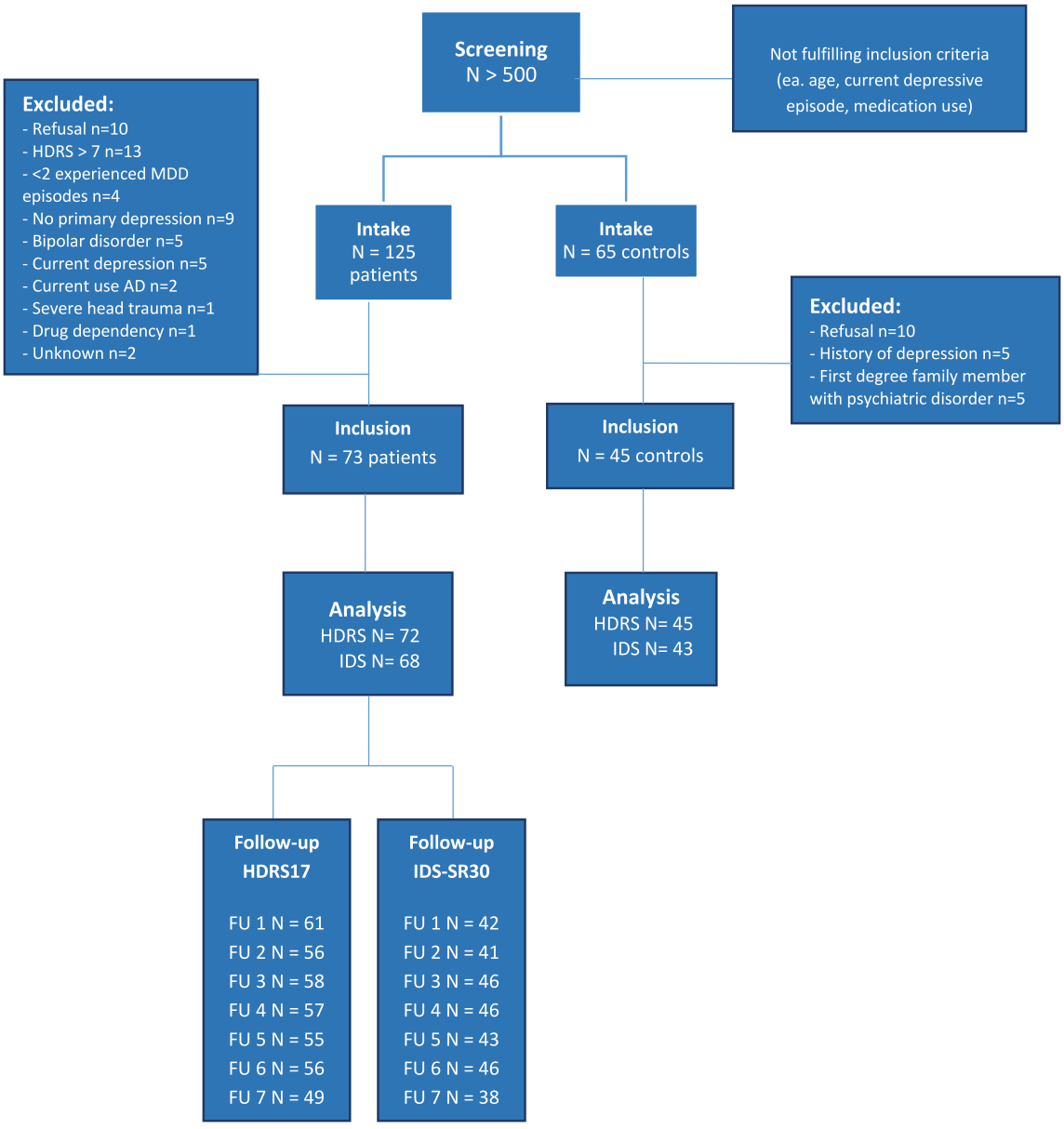

Fig. 1. Flowchart.

did not change this finding; a score of one on the IDS-SR_{30} suicide item was still significantly associated with time until recurrence (Wald test 4.641 (df = 1) p = .031). A score of two on the IDS-SR_{30} suicide item was not (Wald test 2.088 (df = 1) p = .148).

Clinician-rated suicidal symptoms (dichotomous) were not associated with time to recurrence (HDRS scores; χ^2 = 0.03 (2) p = .99; Baseline $HDRS_{17}$ scores in rrMDD: score 0, n = 67 vs. score ≥1, n = 5). We corrected for gender in the analysis of the $HDRS_{17}$, no other confounders were identified (see above).

3.3. Secondary analysis: the association between suicidal symptoms and depressive symptom severity over time in rrMDD

Mixed model analysis with longitudinal data showed that higher suicidal symptoms were cross-sectionally associated with higher depressive symptoms during 2.5 years in this recurrent sample ($HDRS_{17}$; F = 49.23, (df = 2), p < .001), IDS-SR_{30}; F = 21.65, (df = 2), p < .001) (Figs. 3 and 4). In the analysis of $HDRS_{17}$ gender was included as covariate. For analysis of IDS-SR_{30} no covariates were identified.

3.4. Sensitivity analysis

Although no participants used antidepressants during baseline (exclusion criterion) and the majority of the rrMDD participants did not use antidepressants during the follow up period, three participants used antidepressants when experiencing a recurrence during follow-up and two participants started to use antidepressants while in remission. Sensitivity analyses excluding these patients showed no differences in results (details available upon request). add percentages.

4. Discussion

In this study we found, in line with our first hypothesis, that self-reported suicidal symptoms after remission predicted an unfavorable longitudinal course of MDD, independent of other residual depressive symptoms. Moreover, we found discrepancies in clinician versus self-rating assessments. Regarding our second hypothesis, we indeed found that higher suicidal symptoms were longitudinally related to higher depressive symptoms. As indicated below, we think that these findings

Table 1
Sample characteristics at baseline.

		rrMDD	HC		Between-group statistics	df	p
		(n = 73)	(n = 45)	χ^2	T		
Female	N (%)	48 (66%)	31 (69%)	0.12		1	0.73
Age	Years; mean (SD)	53.23 (7.83)	51.47 (8.11)		−1.17	116	0.24
Netherlands	N (%)	50 (73%)	36 (80%)	0.84		1	0.36
West European	N (%)	61 (84%)	37 (82%)	0.04		1	0.85
Employment status[a]	Levels (n)	28/29/16	21/19/5	1.88		1	0.17
Smoking[b]	Levels (n)	24/33/15	18/19/8	0.56		2	0.76
Alcohol (week)[c]	Levels (n)	17/7/9/7/8/6/7	21/4/3/1/5/3/6	1.04		1	0.31
No. of alcoholic drinks (week)[d]	Levels (n)	11/6/12/9/2/3/1	6/3/13/1/0/0/0	6.53		1	0.01
Alcohol (weekend)[e]	Levels (n)	15/5/12/5/15/10	7/6/8/4/7/9	0.12		1	0.73
No. of alcoholic drinks (weekend)[d]	Levels (n)	0/7/4/10/3/9/7/6/1/1/1	2/4/5/11/2/6/1/2/0/0/1	1.03		1	0.31
Age of onset	Years; mean (SD)	26.68 (10.75)					
Episodes (last ten years)	Median (IQR)	2.00 (1)					
Episodes (lifetime)	Median (IQR)	4.00 (5)					
HDRS17 item 3[f]	Levels (n)	67/2/3/0/0	44/1/0/0/0	1.97		2	0.37
IDS-SR30 item 18[g]	Levels (n)	49/13/6/0	42/0/1/0	12.09		2	0.00
$HDRS_{17}$ sum-score (item 3 excl.)	Mean (SD)	2.65 (2.38)	0.96 (1.33)		−4.94	113.83	<0.00
IDS-SR30 sum-score (item 18 excl.)	Mean (SD)	15.72 (9.55)	4.86 (3.33)		−8.58	89.88	<0.00

χ^2: chi-square test statistic (ordinal variables: linear by linear); df: degrees of freedom; P: P-value; T: independent samples T test statistics.
Age, gender, children, living situation, education level, working class, west European (73/45); Netherlands (69/45); smoking (72/45).
alcohol items (62/43); life time, last 10 years (72); $HDRS_{17}$ intake sum-score (72/45); $IDS\text{-}SR_{30}$ intake sum-score (68/43).
HC, never-depressed controls; HDRS, Hamilton Depression Rating Scale; IDS-SR30, Inventory of Depressive Symptomatology (self-report); rrMDD, remitted recurrent major depressive disorder.

[a] Employment status: low/middle/high/never worked.

[b] Smoking: never/past/current.

[c] Level of alcohol use (week); I never drink alcoholic beverages during the week/<1 day in 4 weeks/1–3 days in 4 weeks/1 day during the week/2 days during the week/3 days during the week/4 days during the week.

[d] Number of alcohol drinks; 0.5/1/1.5/2/2.5/3/4/5/6/7/8/9/>10.

[e] Level of alcohol use (weekend); I never drink alcoholic beverages during the weekend/<1 weekend-day in 4 weekends/1–3 weekend-days in 4 weekends/1 day during the weekend/2 days during the weekend/3 days during the weekend.

[f] $HDRS_{17}$ item 3 range: 0. absent; 1. feels life is not worth living; 2. wishes he/she were dead or any thoughts of possible death to self; 3. ideas or gestures of suicide; 4. attempts of suicide.

[g] $IDS\text{-}SR_{30}$ item 18 range: 0. I do not think of suicide or death; 1. I feel that life is empty or wonder if it is worth living; 2. I think of suicide or death several.times a week for several minutes; 3. I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

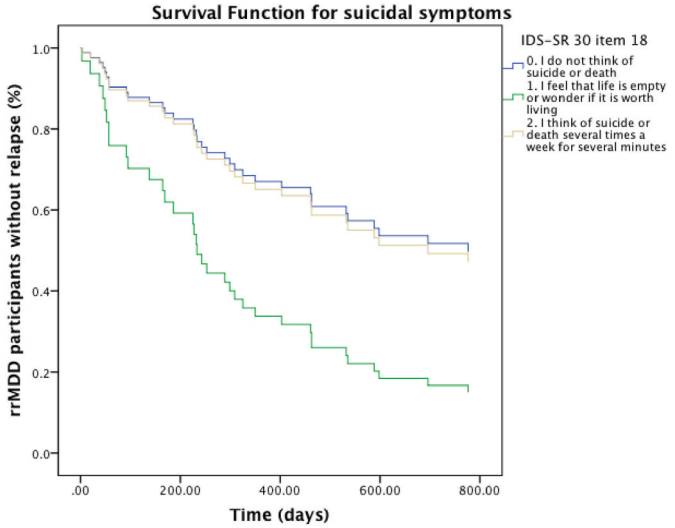

Fig. 2. Cox regression analysis $IDS\text{-}SR_{30}$. Baseline $IDS\text{-}SR_{30}$: rrMDD: score 0 (n = 49) score 1 (n = 13) score 2 (n = 6). Kaplan Meier analyses showed time to recurrence: median estimate IDS_{30} item 18 score 0 = 776, IDS_{30} item 18 score 1 = 169, IDS_{30} item 18 score 2 = 463. Mean estimate IDS_{30} item 18 score 0 = 610, IDS_{30} item 18 score 1 = 328, IDS_{30} item 18 score 2 = 557.

might contribute to a better characterization of MDD patients at risk for recurrence.

Our primary analysis showed that a score of one on the $IDS\text{-}SR_{30}$; feeling that life is empty or wondering if it's worth living, was predictive for future recurrence in rrMDD independently of other residual depressive symptoms, with a hazard ratio of almost three (HR 2.71). Surprisingly, a score of two or three on suicidal ideation on the $IDS\text{-}SR_{30}$ was not significantly associated with MDD recurrence. This might be explained by the fact that we were not able to derive sufficient power, because these scores were rare in our remitted population.

Our secondary analysis showed that a higher degree of suicidal ideation was associated with increased depressive symptom severity over time. This finding is in line with current literature (Dold et al., 2018b), moreover, we extended these findings by providing longitudinal data in a recurrent sample. As participants in previous studies (Dunlop et al., 2019; Musliner et al., 2016; Sokero et al., 2006; Uher et al., 2011) were only followed for a short period of time (≤3 consecutive months after achieving remission), this study adds relevant long-term information about suicidal ideation in recurrent MDD over time. In general, previous studies in recurrent MDD focused on overall depressive symptomatology and did not specifically explore baseline suicidal ideation in relation to recurrent depression, or only in relation to treatment effect (Dunlop et al., 2019; Musliner et al., 2016; Uher et al., 2011).

4.1. Suicidal ideation and depression

While research shows strong relationships between suicide and depression, it also suggests important distinctness. While depression predicts suicidal ideation, it does not predict suicidal behavior, and the majority of depressed people do not engage in suicidal behaviors (Fehling and Selby, 2021). Moreover, treatments targeting depression specifically do not necessarily decrease suicidal ideation and behaviors (Fehling and Selby, 2021). Currently the fifth edition of the DSM suggests Suicidal Behavior Disorder as a condition for further study, indicating that risk factors for the Suicidal Behavior Disorder are among

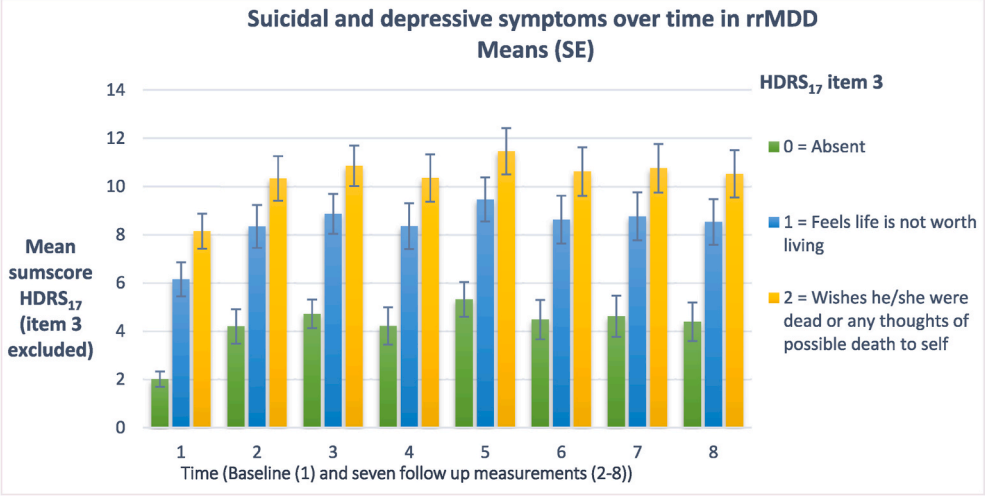

Fig. 3. Mixed model analysis $HDRS_{17}$ scores. $HDRS_{17}$ scores, item 3 suicidal symptoms: score of one, $\beta = 4.15$; score of two, $\beta = 6.14$. Estimated marginal means of residual depressive symptoms for different measurement moments for each level of self-reported suicidal ideation on that measurement moment.

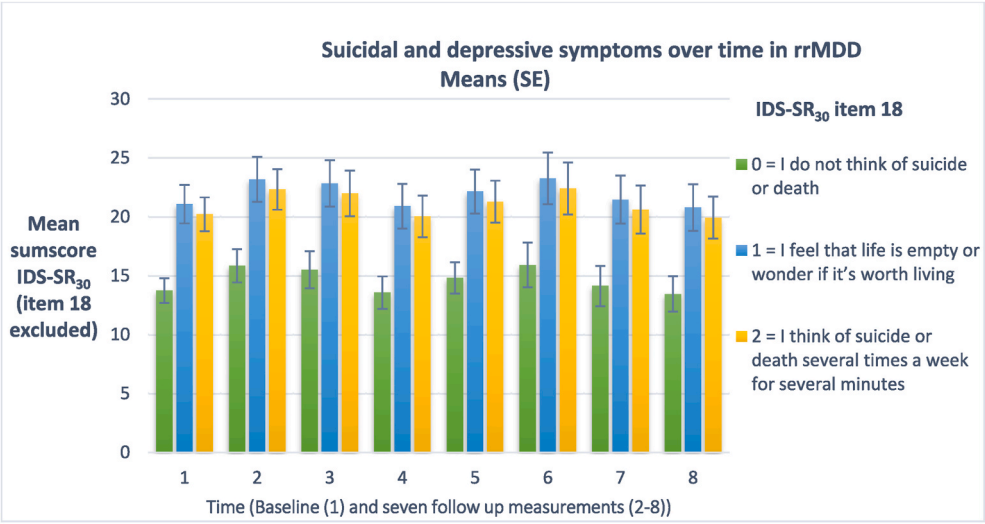

Fig. 4. Mixed model analysis $IDS\text{-}SR_{30}$ scores. $IDS\text{-}SR_{30}$ scores, item 18 suicidal symptoms: score of one, $\beta = 7.05$; score of two, $\beta = 6.93$. Estimated marginal means of residual depressive symptoms for different measurement moments for each level of self-reported suicidal ideation on that measurement moment.

others, mental illnesses (Fehling and Selby, 2021). Although the DSM-5 does not specify treatment options for Suicidal Behavior Disorder, it describes that treatment of an underlying mental or physical illness may alleviate suicidal impulses or improve coping with the source of distress. According to the current criteria the diagnosis is not applied to suicidal ideation. Interestingly, the clinical significance of passive suicidal ideation remains understudied and poorly understood, although a recent meta-analysis found that passive suicidal ideation is highly correlated to the presence of mental disorders, such as depression and anxiety, psychological factors related to suicide, suicide attempts, and even suicide deaths (Liu et al., 2020).

Earlier research suggests that suicidal ideation in depression arise as part of recurrent thinking patterns, that are established during early depressive episodes (Lau et al., 2004). Consequently, an association is formed between depressed mood and suicidal ideation. Future low mood could then activate suicidal thinking and with every reactivation such thinking patterns are more easily re-synthesized, e.g. cognitive reactivity (Figueroa et al., 2015; Lau et al., 2004). However, it remains unclear whether the effectiveness of treatments for MDD to alleviate suicidal ideation is related to depressive symptoms, cognitive reactivity or a combination of both (Sokero et al., 2006). Therefore, future research should examine whether current evidence based relapse prevention interventions, for example Preventive Cognitive Therapy (PCT), except its effect by reducing persistent suicidal thoughts and residual depressive symptoms in the remitted phase of recurrent MDD (Bockting et al., 2005, 2015; Breedvelt et al., 2020).

4.2. *Clinician-rated versus self-reported suicidal symptoms in MDD*

Interestingly, we found discrepancies between clinician-rated and self-reported suicidal symptoms in the rrMDD group. Self-reported suicidal symptoms were almost four times higher (27.9% versus 6.9%) compared to clinician-rated suicidal symptoms in rrMDD at baseline. A possible explanation for the differences in the prevalence of suicidal symptoms as measured by the $HDRS_{17}$ versus the $IDS\text{-}S_{R30}$ may be that a $HDRS_{17}$ score ≤ 7 was an inclusion criterium at baseline, whereas the $IDS\text{-}SR_{30}$ score was not used as an inclusion criterion. This may have lead to the selection of patients with a low $HDRS_{17}$ score, without selection of (low) $IDS\text{-}SR_{30}$ scores.

Moreover, there is heterogeneity in item scores. Besides differences

in psychometric properties, differences in item content or labelling and differences in the time of questionnaire administration might explain the heterogeneity. Furthermore, the discrepancy between clinician-rated and self-reported suicidal symptoms could be due to a different interpretation of suicidal thoughts by clinicians, lower willingness to report suicidal thoughts to clinicians or that clinicians are more reluctant to ask carefully about suicidal thoughts. This finding signifies differences in detecting suicidal ideation between clinician-rated versus self-reported instruments. Therefore, it seems relevant to combine self-reported questions regarding suicidality with clinican-rated questions, also during remission.

5. Strengths

We extended previous findings by providing longitudinal data in a highly recurrent, remitted sample. This study design enabled to investigate how baseline suicidal symptoms longitudinally relate to MDD recurrence and (residual) depressive symptoms. Further, we evaluated both clinician-rated and self-reported suicidal symptoms and depressive symptomatology using two different instruments, namely the $HDRS_{17}$ and IDS-SR_{30} (Helmreich et al., 2011; Rush et al., 2000).

6. Limitations

First, we used the suicidal item of scales primarily designed to measure depression severity to capture suicidal ideation (Desseilles et al., 2012). Nevertheless, our approach is in line with most research, since the use of a single item proved to be a valid approach to assess suicidality when compared with e.g. Beck scale for suicide ideation (BSS) (Desseilles et al., 2012). However, we do recommend for future research to use questionnaires primarily designed for measuring suicidal ideation. Second, a score of 1 ("I feel that life is empty or wonder if it is worth living") was the only level of the self-reported suicidality predictive for MDD recurrence. The feeling of life being empty could relate more to depression than to suicidal ideation. However, hopelessness and pessimism for the future have been extensively associated with suicidal thoughts and behavior even when controlling for depression (Fehling and Selby, 2021). Third, as in most longitudinal research, we also encountered loss of follow up of study participants in our follow up period of 2.5 years. However, despite the characteristics of our patient population and the length of the follow up period, the loss of follow up of study participants stayed relatively small. Still, we conducted analyses that incorporate loss of follow up (e.g. cox regression analysis, mixed model analysis). Nevertheless, loss of follow up of study participants could have led to decreased power in the statistical analyses. Fourth, we used a sample of individuals aged 35–65 years old. Additional research using a broader sample will be necessary to determine whether or not these findings are generalizable. Fifth, including participants who at baseline did not use psychotropic drugs is a strength, precluding influence of medication use on our results, however it could lead to inclusion of participants who previously experienced little benefit, or on the other hand, participants who had a good response on medication and therefore stopped in remission status (Mocking et al., 2016). This may limit the generalizability of our findings.

7. Conclusions

Our findings indicate that rrMDD participants who self-report suicidal symptoms after clinical remission might be at risk for recurrence, independent of other residual depressive symptoms. Moreover, we found differences between clinician-rated and self-reported suicidal symptoms in the rrMDD group. Consequently, we recommend to closely monitor suicidal symptoms during MDD remission, preferably including self-reported questionnaires apart from clinician based assessments. Increases of self-reported suicidal ideation and/or behavior might be indicative for impeding relapse. Besides suicidal symptoms, we recommend to monitor residual depressive symptoms, to further investigate the course of residual depressive and suicidal symptoms over time in rrMDD, preferably using the experience sampling method (ESM) with more frequent measurements over time to enable time lagged analyses.

Author statement

Individual author contributions

CH: Conceptualization; Data curation; Formal analysis; Investigation;Methodology; Software; Writing - original draft; Review & editing.

RM: Conceptualization; Data curation; Formal analysis; Methodology; Software; Writing - original draft; Supervision; Review & editing.

JZ: Supervision; Writing - review & editing.

CF: Writing - review & editing.

AS: Writing - review & editing.

DD: Writing - review & editing.

HR: Conceptualization; Data curation; Methodology; Supervision; Writing - review & editing.

CB: Supervision; Writing - review & editing.

AL: Supervision; Writing - review & editing.

Contributors

N/A.

Role of the funding source

None.

Role of the sponsor

N/A.

Ethics committee approval

N/A.

Declaration of competing interest

Declaration of interest: A. Lok is a member of the suicide advisory board of Janssen.

Acknowledgement

N/A.

References

Aleman, A., Denys, D., 2014. A road map for suicide research and prevention. Nature 509, 421–423.

Baldessarini, R.J., Tondo, L., 2020. Suicidal risks in 12 DSM-5 psychiatric disorders. J. Affect. Disord. 271 https://doi.org/10.1016/j.jad.2020.03.083.

Bhagwagar, Z., Cowen, P.J., 2008. It's not over when it's over": persistent neurobiological abnormalities in recovered depressed patients. Psychol. Med. https://doi.org/10.1017/S0033291707001250.

Bockting, C.L., Hollon, S.D., Jarrett, R.B., Kuyken, W., Dobson, K., 2015. A lifetime approach to major depressive disorder: the contributions of psychological interventions in preventing relapse and recurrence. Clin. Psychol. Rev. https://doi.org/10.1016/j.cpr.2015.02.003.

Bockting, C.L.H., Schene, A.H., Koeter, H.W.J., Wouters, L.F., Huyser, J., Kamphuis, J.H., Spinhoven, P., Assies, H., Lok, A., Nabarro, G., Visser, I., Wekking, E., 2005. Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. J. Consult. Clin. Psychol. 73, 647–657. https://doi.org/10.1037/0022-006X.73.4.647.

Bockting, C.L.H., Spinhoven, P., Koeter, M.W.J., Wouters, L.F., Schene, A.H., 2006. Prediction of recurrence in recurrent depression and the influence of consecutive episodes on vulnerability for depression: a 2-year prospective study. J. Clin. Psychiatr. 67, 747–755. https://doi.org/10.4088/JCP.v67n0508.

Breedvelt, J.J.F., Brouwer, M.E., Harrer, M., Semkovska, M., Ebert, D.D., Cuijpers, P., Bockting, C.L.H., 2020. Psychological interventions as an alternative and add-on to

antidepressant medication to prevent depressive relapse: systematic review and meta-analysis. Br. J. Psychiatry 1–8. https://doi.org/10.1192/bjp.2020.198.
Cavanagh, J.T.O., Carson, A.J., Sharpe, M., Laure, S.M., 2003. Psychological autopsy studies of suicide: a systemic review. Psychol. Med. 33, 395–405.
Conradi, H.J., de Jonge, P., Ormel, J., 2008. Prediction of the three-year course of recurrent depression in primary care patients: different risk factors for different outcomes. J. Affect. Disord. 105, 267–271. https://doi.org/10.1016/j.jad.2007.04.017.
Conwell, Y., Duberstein, P.R., Cox, C., Herrmann, J.H., Forbes, N.T., Caine, E.D., 1996. Relationships of age and axis I diagnoses in victims of completed suicide: a psychological autopsy study. Am. J. Psychiatr. 153, 1001–1008. https://doi.org/10.1176/ajp.153.8.1001.
Courtet, P., 2010. Le risque suicidaire dans la dépression récurrente. Encephale. https://doi.org/10.1016/S0013-7006(10)70044-0.
Desseilles, M., Perroud, N., Guillaume, S., Jaussent, I., Genty, C., Malafosse, A., Courtet, P., 2012. Is it valid to measure suicidal ideation by depression rating scales? J. Affect. Disord. 136, 398–404. https://doi.org/10.1016/j.jad.2011.11.013.
Dold, M., Bartova, L., Fugger, G., Kautzky, A., Souery, D., Mendlewicz, J., Papadimitriou, G.N., Dikeos, D., Ferentinos, P., Porcelli, S., Serretti, A., Zohar, J., Montgomery, S., Kasper, S., 2018a. Major depression and the degree of suicidality: results of the European group for the study of resistant depression (GSRD). Int. J. Neuropsychopharmacol. 21, 539–549. https://doi.org/10.1093/ijnp/pyy009.
Dold, M., Bartova, L., Fugger, G., Kautzky, A., Souery, D., Mendlewicz, J., Papadimitriou, G.N., Dikeos, D., Ferentinos, P., Porcelli, S., Serretti, A., Zohar, J., Montgomery, S., Kasper, S., 2018b. Major depression and the degree of suicidality: results of the European group for the study of resistant depression (GSRD). Int. J. Neuropsychopharmacol. 21, 539–549. https://doi.org/10.1093/ijnp/pyy009.
Dong, M., Zeng, L.N., Lu, L., Li, X.H., Ungvari, G.S., Ng, C.H., Chow, I.H.I., Zhang, L., Zhou, Y., Xiang, Y.T., 2019. Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. Psychol. Med. 49 https://doi.org/10.1017/S0033291718002301.
Dunlop, B.W., Polychroniou, P.E., Rakofsky, J.J., Nemeroff, C.B., Craighead, W.E., Mayberg, H.S., 2019. Suicidal ideation and other persisting symptoms after CBT or antidepressant medication treatment for major depressive disorder. Psychol. Med. 49, 1869–1878. https://doi.org/10.1017/S0033291718002568.
Fehling, K.B., Selby, E.A., 2021. Suicide in DSM-5: current evidence for the proposed suicide behavior disorder and other possible improvements. Front. Psychiatr. https://doi.org/10.3389/fpsyt.2020.499980.
Figueroa, C.A., Ruhé, H.G., Koeter, M.W., Spinhoven, P., Van Der Does, W., Bockting, C. L., Schene, A.H., 2015. Cognitive reactivity versus dysfunctional cognitions and the prediction of relapse in recurrent major depressive disorder. J. Clin. Psychiatr. 76, 1306–1312. https://doi.org/10.4088/JCP.14m09268.
Hamilton, 1967. Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296. https://doi.org/10.1111/j.2044-8260.1967.tb00530.x.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.
Harrington, D., Oldfield, R.C., King, N.S., Crawford, S., Wenden, F.J., Moss, N.E., Wade, D.T., McCrimmon, A.W., Smith, A.D., McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., Argeriou, M., Ryan, J.J., Lopez, S.J., Wechsler, D., Drozdick, L.W., Wahlstrom, D., Zhu, J., Weiss, L.G., McCrimmon, A.W., Smith, A.D., Hare, R.D., First, M., Spitzer, R.L., Gibbon, M.L., Williams, J., 2012. Structured clinical interview for DSM-IV-TR Axis I disorders, research version, non-patient edition. J. Psychoeduc. Assess. 31, 337–341.
Helmreich, I., Wagner, S., Mergl, R., Allgaier, A.K., Hautzinger, M., Henkel, V., Hegerl, U., Tadić, A., 2011. The Inventory of Depressive Symptomatology (IDS-C28) is more sensitive to changes in depressive symptomatology than the Hamilton Depression Rating Scale (HAMD17) in patients with mild major, minor or subsyndromal depression. Eur. Arch. Psychiatr. Clin. Neurosci. 261, 357–367. https://doi.org/10.1007/s00406-010-0175-1.
Hjelmeland, H., Dieserud, G., Dyregrov, K., Knizek, B.L., Leenaars, A.A., 2012. Psychological autopsy studies as diagnostic tools: are they methodologically flawed? Death Stud. 36 https://doi.org/10.1080/07481187.2011.584015.
Israel, J.A., 2010. The impact of residual symptoms in major depression. Pharmaceuticals. https://doi.org/10.3390/ph3082426.
Judd, L.L., Akiskal, H.S., Maser, J.D., Zeller, P.J., Endicott, J., Coryell, W., Paulus, M.P., Kunovac, J.L., Leon, A.C., Mueller, T.I., Rice, J.A., Keller, M.B., 1998. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J. Affect. Disord. 50, 97–108. https://doi.org/10.1016/S0165-0327(98)00138-4.
Judd, L.L., Akiskal, H.S., Paulus, M.P., 1997. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. J. Affect. Disord. 45, 5–17. https://doi.org/10.1016/S0165-0327(97)00055-4.
Keller, M.B., 2003. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. J. Am. Med. Assoc. https://doi.org/10.1001/jama.289.23.3152.
Kessing, L.V., Andersen, P.K., Mortensen, P.B., 1998. Recurrence in affective disorder: I. Case register study. Br. J. Psychiatry 172, 23–28. https://doi.org/10.1192/bjp.172.1.23.
Kessing, L.V., Hansen, M.G., Andersen, P.K., Angst, J., 2004. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. Acta Psychiatr. Scand. 109, 339–344. https://doi.org/10.1046/j.1600-0447.2003.00266.x.
Lau, M.A., Segal, Z.V., Williams, J.M.G., 2004. Teasdale's differential activation hypothesis: implications for mechanisms of depressive relapse and suicidal behaviour. Behav. Res. Ther. 42, 1001–1017. https://doi.org/10.1016/j.brat.2004.03.003.
Liu, R.T., Bettis, A.H., Burke, T.A., 2020. Characterizing the phenomenology of passive suicidal ideation: a systematic review and meta-analysis of its prevalence, psychiatric comorbidity, correlates, and comparisons with active suicidal ideation. Psychol. Med. https://doi.org/10.1017/S003329171900391X.
Madsen, T., Buttenschøn, H.N., Uher, R., Behrendt-Møller, I., Perroud, N., Maier, W., Hauser, J., Dernovsek, M.Z., Henigsberg, N., Souery, D., Rietschel, M., McGuffin, P., Aitchison, K.J., Mors, O., Köhler-Forsberg, O., 2019. Trajectories of suicidal ideation during 12 weeks of escitalopram or nortriptyline antidepressant treatment among 811 patients with major depressive disorder. J. Clin. Psychiatr. https://doi.org/10.4088/JCP.18m12575.
Mocking, R.J.T., Figueroa, C.A., Rive, M.M., Geugies, H., Servaas, M.N., Assies, J., Koeter, M.W.J., Vaz, F.M., Wichers, M., Straalen, J.P. Van, Raedt, R. De, Bockting, C. L.H., Harmer, C.J., Schene, A.H., Ruhé, H.G., 2016. Vulnerability for New Episodes in Recurrent Major Depressive Disorder : Protocol for the Longitudinal DELTA-Neuroimaging Cohort Study 6, pp. 1–18. https://doi.org/10.1136/bmjopen-2015-009510.
Mojtabai, R., 2001. Residual symptoms and impairment in major depression in the community. Am. J. Psychiatr. 158, 1645–1651. https://doi.org/10.1176/appi.ajp.158.10.1645.
Mueller, T.I., Leon, A.C., Keller, M.B., Solomon, D.A., Endicott, J., Coryell, W., Warshaw, M., Maser, J.D., 1999. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am. J. Psychiatr. 156, 1000–1006. https://doi.org/10.1176/ajp.156.7.1000.
Musliner, K.L., Munk-Olsen, T., Eaton, W.W., Zandi, P.P., 2016. Heterogeneity in long-term trajectories of depressive symptoms: patterns, predictors and outcomes. J. Affect. Disord. https://doi.org/10.1016/j.jad.2015.12.030.
Oquendo, M.A., Baca-Garcia, E., 2014. Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations. World Psychiatr. 13, 128–130. https://doi.org/10.1002/wps.20116.
Park, Y.-M., Lee, B.-H., Lee, S.-H., 2014. The association between serum lipid levels, suicide ideation, and central serotonergic activity in patients with major depressive disorder. J. Affect. Disord. https://doi.org/10.1016/j.jad.2014.01.016.
Pompili, M., 2019. Critical appraisal of major depression with suicidal ideation. Ann. Gen. Psychiatr. 18, 1–5. https://doi.org/10.1186/s12991-019-0232-8.
Pu, S., Setoyama, S., Noda, T., 2017. Association between cognitive deficits and suicidal ideation in patients with major depressive disorder. Sci. Rep. https://doi.org/10.1038/s41598-017-12142-8.
Ribeiro, J.D., Huang, X., Fox, K.R., Franklin, J.C., 2018. Depression and hopelessness as risk factors for suicide ideation, attempts and death: meta-analysis of longitudinal studies. Br. J. Psychiatry. https://doi.org/10.1192/bjp.2018.27.
Rush, A.J., Carmody, T., Reimitz, P.E., 2000. The inventory of depressive symptomatology (IDS): clinician (IDS-C) and Self-Report (IDS-SR) ratings of depressive symptoms. Int. J. Methods Psychiatr. Res. 9 https://doi.org/10.1002/mpr.79.
Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The inventory of depressive symptomatology (IDS): psychometric properties. Psychol. Med. 26, 477–486. https://doi.org/10.1017/S0033291700035558.
Sokero, P., Eerola, M., Rytsälä, H., Melartin, T., Leskelä, U., Lestelä-Mielonen, P., Isometsä, E., 2006. Decline in suicidal ideation among patients with MDD is preceded by decline in depression and hopelessness. J. Affect. Disord. 95, 95–102. https://doi.org/10.1016/j.jad.2006.04.028.
Tada, M., Uchida, H., Suzuki, T., Abe, T., Pollock, B.G., Mimura, M., 2014. Baseline difference between patients' and clinicians' rated illness severity scores and subsequent outcomes in major depressive disorder: analysis of the STAR*D data. J. Clin. Psychopharmacol. 34, 297–302. https://doi.org/10.1097/JCP.0000000000000112.
Ten Doesschate, M.C., Bockting, C.L.H., Koeter, M.W.J., Schene, A.H., 2010. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. J. Clin. Psychiatr. 71, 984–991. https://doi.org/10.4088/JCP.08m04858blu.
Uher, R., Mors, O., Rietschel, M., Rajewska-Rager, A., Petrovic, A., Zobel, A., Henigsberg, N., Mendlewicz, J., Aitchison, K.J., Farmer, A., McGuffin, P., 2011. Early and delayed onset of response to antidepressants in individual trajectories of change during treatment of major depression: a secondary analysis of data from the genome-based therapeutic drugs for depression (GENDEP) study. J. Clin. Psychiatr. 72, 1478–1484. https://doi.org/10.4088/JCP.10m06419.
Uher, R., Perlis, R.H., Placentino, A., Dernovšek, M.Z., Henigsberg, N., Mors, O., Maier, W., McGuffin, P., Farmer, A., 2012. Self-report and clinician-rated measures of depression severity: can one replace the other? Depress. Anxiety 29, 1043–1049. https://doi.org/10.1002/da.21993.
Williams, J.M.G., Crane, C., Barnhofer, T., Van Der Does, A.J.W., Segal, Z.V., 2006. Recurrence of suicidal ideation across depressive episodes. J. Affect. Disord. 91, 189–194. https://doi.org/10.1385/BTER:109:2:189.
World Health Organisation, 2016. WHO | Suicide Data. WHO Website.
Zimmerman, M., Posternak, M.A., Chelminski, I., 2007. Heterogeneity among depressed outpatients considered to be in remission. Compr. Psychiatr. 48, 113–117. https://doi.org/10.1016/j.comppsych.2006.10.005.