Mixed Features and Nonfatal Suicide Attempt Among Individuals With Major Depressive Episode:

Insights From the French MHGP Survey

Hugo Peyre, MD, PhD; Nicolas Hoertel, MD, PhD; Baptiste Pignon, MD, PhD; Ali Amad, MD, PhD; Jean-Luc Roelandt, MD, PhD; Imane Benradia, PhD; Pierre Thomas, MD, PhD; Guillaume Vaiva, MD, PhD; Pierre-Alexis Geoffroy, MD, PhD; Emilie Olié, MD, PhD; and Philippe Courtet, MD, PhD

Abstract

Background: This study explores among individuals with a major depressive episode (MDE) the potential impact of mixed features on the risk of suicide attempt, suicidal thoughts, self-harm intentions, and thoughts of death.

Methods: Data from the French Mental Health in General Population (MHGP) survey (1999–2003) were analyzed, including 128 participants meeting *DSM-5* criteria for MDE with mixed features (MDE with at least 3 manic symptoms) and 3,312 participants experiencing MDE without mixed features. Our primary analysis focused on suicide attempt, with additional examination of recent suicidal thoughts, self-harm intentions, and thoughts of death. Multivariable regression models were performed to adjust for potential confounding variables, including sociodemographics, previous suicide attempt, number of depressive symptoms, and psychiatric comorbidity.

Results: MDE with mixed features was significantly associated with an increased risk of suicide attempt (adjusted odds ratio [AOR] = 1.69; 95% CI, 1.26–2.25). This association did not significantly differ between men and women. Furthermore, the number of manic symptoms demonstrated a dose-dependent relationship with an increased risk of suicide attempt (AOR = 1.18; 95% CI, 1.07–1.30; $P < .001$). Mixed features were also associated with suicide attempt among individuals with MDE and without recent suicidal thoughts (AOR = 2.74; 95% CI, 1.36–5.54).

Conclusion: This study underscores the importance of assessing mixed features when evaluating the risk of suicide attempt in individuals with MDE. Mechanisms underlying this association might be independent of progression from thoughts of death to suicidal thoughts, suicidal intention, and ultimately, suicide attempt.

J Clin Psychiatry 2024;85(4):24m15445

Author affiliations are listed at the end of this article.

Major depression is a leading source of disease burden, characterized by complex patterns of recurrence and persistence and increased risk of suicide.[1] The prevalence of a lifetime history of suicide attempt among patients with major depressive disorders is estimated at 30%–40%[2,3] and about 50% among patients with bipolar disorder.[4–6] Major depressive episodes (MDEs) and their severity are associated with an increased risk of suicide attempt.[7] Although clinical evaluations aim to capture a broad range of symptoms and comorbidities, their ability to predict suicide attempt can be limited by the complex interplay of diverse medical, psychological, and social contributive factors.[8] Furthermore, the impact of specific features of MDEs that contribute to suicide attempt is not fully elucidated.[9]

The polythetic nature of MDE criteria in classifications inevitably results in diagnostic heterogeneity within the category.[10,11] Additional heterogeneity arises from the frequent co-occurrence of MDE with symptoms of other psychiatric disorders, particularly when symptoms from the opposite polarity (ie, manic symptoms) are present. Recognizing this, the *DSM-IV* identified mixed episodes where individuals met all criteria for both an MDE and a manic episode simultaneously. However, this potentially too restrictive approach was criticized.[12] To address this issue, the *DSM-5* introduced the mixed features specifier of

Scan Now

See supplementary material for this article at Psychiatrist.com

Editor's Note
We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

Clinical Points

- Mixed features in a major depressive episode (MDE) are linked to a higher risk of suicide attempts, emphasizing the need to assess manic symptoms as part of risk evaluation.
- Patients with MDE should be screened for manic symptoms, even if they lack suicidal thoughts, to better identify those at risk for suicide attempts.

MDE, which identifies MDE with at least 3 nonoverlapping manic symptoms present during the majority of days in the current or most recent episode.[13] However, this specifier has also been criticized for excluding overlapping symptoms such as irritability, psychomotor agitation, and distractibility and for not fully capturing the dimensional interplay between symptoms of opposite poles.[12,14–16]

Studies have shown that MDE with mixed features is associated with bipolar disorder, different responses to pharmacologic treatments,[17–19] and poorer outcomes.[20–23] Prior studies suggest a link between mixed features and an increased risk of suicide attempt,[24–28] although not all.[29,30] Most of these studies have focused on samples of participants with bipolar disorder.[25,28,30] Therefore, it would be valuable to examine this association in a sample that includes both participants with and without bipolar disorder. Additionally, previous studies were hampered by a limited number of potential confounders, such as comorbid psychiatric disorders and the severity of MDE.[24,27] Furthermore, the mechanisms underlying this association remain poorly known. Specifically, it is unclear whether the increased risk of suicide attempt follows a sequence involving thoughts of death, suicidal thoughts, and ultimately suicidal behavior.[31,32] Understanding the relationship between MDE with mixed features and suicide attempt is crucial for informing suicide prevention strategies and enhancing patient outcomes.

In this study, we used data from the French Mental Health in General Population (MHGP) survey to examine the association between MDE with mixed features and the risk of suicide attempt, while adjusting for a wide range of sociodemographic and clinical factors. Based on prior studies, we hypothesize that MDE with mixed features is associated with an increased risk of suicide attempt. We also investigated whether the severity of manic symptoms is associated with a dose-dependent increase in the risk of suicide attempt and examined potential differences between sexes. Additionally, we assessed whether excluding prior suicide attempt and analyzing individual manic symptoms altered the associations observed. Finally, we conducted separate analyses to explore the associations between mixed features and suicide attempt in participants with and without bipolar disorder.

METHODS

MHGP Survey

The cross-sectional MHGP survey, conducted by the World Health Organization Collaborating Centre (WHO-CC), interviewed 38,694 subjects in France between 1999 and 2003. These subjects were selected in 47 different sites (900 subjects per site) by a quota sampling method.[33] This method develops a sample of subjects with the same characteristics as the general population in terms of age, sex, educational level, and occupational category, according to census figures from 1999 provided by the French National Institute for Statistics and Economic Studies. Subjects were included in the study if they met the following criteria: (1) provided informed consent to participate in the survey, (2) spoke French, (3) were aged 18 and above, and (4) were neither institutionalized (such as hospitals, long-term care facilities, or other residential institutions) nor homeless. Additional methodological details can be found elsewhere.[34–36] The study was approved by the "Commission Nationale Informatique et Liberté" and the "Comité consultatif sur le traitement de l'information en matière de recherche."[37(p1548)]

Study Sample

The study focuses on participants diagnosed with MDE from the MHGP survey. The analysis sample included individuals with various diagnoses, including major depressive disorder and bipolar disorder, to capture the full spectrum of mania and depression in a transdiagnostic manner. Participants were classified into 2 subgroups: (1) those with MDE and mixed features and (2) those with MDE without mixed features.

Main Measures

For each subject, the Mini-International Neuropsychiatric Interview (MINI, French version 5.0.0), a structured diagnostic interview, was used to screen for lifetime psychiatric symptoms and disorders (according to the *International Classification of Diseases, Tenth Revision* [*ICD-10*]), as well as nonfatal suicidal behaviors and thoughts (suicide attempt, suicidal thoughts, self-harm intentions, and thoughts of death). The MINI has been validated in the general population and has good to very good validity, reliability (inter-rater and test-retest), sensitivity, and specificity for psychiatric disorders.[38,39] A 3-day training course about MINI administration, organized by the WHO-CC, was given to the MHGP survey evaluators (ie, nursing students and psychologists).[40]

Nonfatal suicidal behaviors and thoughts. Nonfatal suicidal behaviors and thoughts were assessed over the past month using the following questions: "In the past month, have you (1) thought that you would be better off dead, or wished you were dead? (thoughts of death), (2) wanted to

harm yourself? (self-harm intentions), (3) thought about suicide? (suicidal thoughts), and (4) made a suicide attempt? (suicide attempt)." The occurrence of a lifetime history of suicidal attempt was also assessed.

Symptoms of manic episode. The symptoms of manic episode were assessed over the past month. Participants answered 9 additional questions from the MINI if they had experienced during at least 1 week any of these symptoms: "(1) Have you ever had a period where you felt so excited or full of energy that it got you into trouble, or people around you thought you weren't in your usual state? (2) Have you ever had a period where you were so irritable that you ended up insulting people, shouting, or even fighting?" Among the 9 additional questions, 7 were nonoverlapping contrapolar symptoms according to *DSM-5*[1] (see Supplementary Table 1 for details).

Covariates

Psychiatric disorders. Psychiatric disorders were also assessed using the MINI, including MDE, bipolar disorder, generalized anxiety disorder (GAD), agoraphobia, panic disorder, social anxiety disorder (SAD), posttraumatic stress disorder (PTSD), alcohol use disorder (AUD), substance use disorder (SUD), and psychotic disorder.

Symptoms of MDE. The symptoms of MDE were assessed over the past 2 weeks. Participants answered 7 additional questions from the MINI if they had experienced any of these 3 symptoms: "(1) Have you felt sad, down, or depressed most of the time during the day, nearly every day? (2) Have you almost always felt like you have lost interest or pleasure in things you usually enjoy? (3) Have you felt tired, lacking in energy almost all the time?"

Sleep problems. Sleep problems were assessed over the past 2 weeks using the question: "Did you have sleep problems (difficulty falling asleep, nocturnal awakenings, or early awakenings, hypersomnia) almost every night?"

Sociodemographic characteristics. The following sociodemographic characteristics were collected: age, sex, education level, marital status, and household income, which was categorized as low (<1,650€/household monthly), medium (1,650–3,200€), or high (>3,200€).

Statistical Analysis

Our analyses were conducted among participants who experienced an MDE assessed according to *ICD-10* criteria in the past 15 days. Among these respondents, we identified those with and without mixed features based on the simultaneous presence of at least 3 manic symptoms.

The primary model focused on recent suicide attempt. A multivariable regression model was performed to determine whether MDE with mixed features was associated with recent suicide attempt, while adjusting for sociodemographic characteristics (age, sex, education level, marital status, and income level), history of suicide attempt, severity of depressive symptoms (using the sum of depression symptoms excluding suicidal ideation), comorbid psychiatric disorders (GAD, agoraphobia, panic disorder, SAD, PTSD, AUD, SUD, and psychotic disorder), and the presence of sleep difficulties (degrees of freedom = 20).

We conducted additional analyses as follows.

Additional analysis 1. We ran the same model, but this time including the severity of nonoverlapping contrapolar symptoms (using the sum of manic symptoms, ie, ranging from 0 to 9) instead of the mixed features binary variable. The aim of this additional analysis was to examine whether the severity of manic symptoms was linked to a dose-effect increase in suicide attempt risk (degrees of freedom = 20).

Additional analysis 2. We reproduced the same analyses while focusing on 3 other measures of nonfatal suicidal behaviors and thoughts, namely suicidal thoughts, self-harm intentions, and thoughts of death (degrees of freedom = 20). The aim of these supplemental analyses was to examine whether the risk of nonfatal suicidal behaviors and thoughts was associated with mixed features and followed a progression from thoughts of death to suicidal thoughts, suicidal intention, and ultimately suicide attempt.

Additional analysis 3. Then, we reran our multivariable regression models excluding the variable "previous history of suicidal attempt" to examine potential overadjustment (degrees of freedom = 19).

Additional analysis 4. Given the limited sample size of participants with mixed features, both with and without bipolar disorder, we faced power constraints for subgroup analyses. To address this, we employed Bayesian logistic regression using Markov chain Monte Carlo (MCMC) methods (using SAS PROC MCMC[41]). The logistic regression models were executed with 10,000 iterations to estimate the association of mixed features with recent suicide attempt, while accounting for covariates.

Additional analysis 5. We conducted the main model separately in participants with or without thoughts of death, with or without suicidal thoughts, and with or without suicidal intention, in order to explore more in-depth the potential influence of mixed features on the risk of suicide.

Additional analysis 6. To determine whether this association varies by sex, we reproduced the main model previously described while including in addition an interaction term sex × mixed features (degrees of freedom = 21).

Additional analysis 7. We modified our main model by replacing the "mixed features" variable with each individual manic symptom in separate models. This analysis enabled us to identify which specific manic symptoms (including overlapping symptoms) were most strongly associated with the risk of suicide attempt (degrees of freedom = 20).

All analyses were performed using SAS software, version 9.4.[42] Multiple imputation (N = 50) was performed for handling missing data. The percentage of missing data was up to 3.3% (household income) for sociodemographic variables and up to 22.3% (previous suicide attempt) for clinical variables. Because

Table 1.

Sociodemographic and Clinical Characteristics of Participants With MDE With and Without Mixed Features[a]

Characteristic	MDE with mixed features, N = 128 % or mean (SD)	MDE without mixed features, N = 3,312 % or mean (SD)	*P* value
Sociodemographics			
Age, y	35.2 (13.3)	43.9 (18.9)	**<.001**
Male	48.4	37.2	**<.001**
Income level			
Low	37.4	26.6	**.030**
Medium	50.4	59.2	
High	12.2	14.2	
Education			
No education or elementary level	6.3	6.5	.395
College level	53.1	58.7	
University level	40.6	34.8	
Marital status			
Never married	46.0	32.3	**.005**
Married	32.5	42.3	
Separated or widowed	21.4	21.4	
Psychiatric symptoms and disorders			
Previous suicidal attempt	50.0	21.1	**<.001**
Depressive symptoms severity	7.2 (1.4)	6.2 (1.5)	**<.001**
Manic symptoms severity	5.51 (1.62)	0.02 (0.17)	**<.001**
Psychotic disorder	78.2	42.6	**<.001**
Agoraphobia	18.8	6.9	**<.001**
Panic disorder	42.2	15.6	**<.001**
SAD	25.6	11.8	**<.001**
GAD	27.3	30.7	.426
PTSD	9.4	2.0	**<.001**
Drug SUD	19.5	6.0	**<.001**
Alcohol SUD	24.2	9.6	**<.001**
Sleep problems	75.8	67.7	.055
Suicide risk			
Suicide attempt	21.9	3.4	**<.001**
Suicidal thoughts	40.6	18.8	**<.001**
Self-harm intention	35.2	10.5	**<.001**
Thoughts of death	50.0	29.4	**<.001**

[a]Boldface indicates $P < .05$.
Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, PTSD = posttraumatic stress disorder, SAD = social anxiety disorder, SUD = substance use disorder.

our approach was both semiconfirmatory and semiexploratory, and in order to limit type I error inflation, statistical significance was evaluated using a 2-sided design with α set a priori at 0.01.

RESULTS

Of 4,425 participants meeting *ICD-10* criteria for MDE, 985 (22.3%) were excluded because of missing data. Of the 3,440 remaining participants, 3.7% (N = 128) had mixed features (MDE with at least 3 manic symptoms, see Supplementary Table 1), and 96.3% (N = 3,312) without mixed features.

Among the 128 respondents with MDE and mixed features, 82 (64.1%) had bipolar disorder and also met the criteria for a full mixed episode (ie, the simultaneous presence of MDE and hypomania/mania). In contrast, 46 (35.9%) participants with MDE and mixed features had a diagnosis of unipolar major depressive disorder. Additionally, among the participants with MDE but without mixed features, 42 (1.3%) met the criteria for lifetime bipolar disorder.

Individuals with MDE with mixed features were significantly younger (35.2 years, SD = 13.3) compared to those without mixed features (43.9 years, SD = 18.9). Among participants with MDE, mixed features were significantly associated with previous suicide attempt, a lifetime history of all psychiatric disorders assessed except GAD, and increased risk of recent nonfatal suicidal behaviors and thoughts, including increased prevalence of suicide attempt, suicidal thoughts, self-harm intentions, and thoughts of death (Table 1).

Table 2.

Multivariate Regression Model Examining the Association Between Mixed Features and Suicide Attempt Among Participants With MDE (N = 3,440)[a]

	Suicide attempt			
	OR mean	95% CI		*P* value
Age, y	0.98	0.97	1.00	.037
Sex (ref. female)	1.07	0.87	1.31	.543
Income level (ref. high)				
Low	1.28	0.87	1.88	.203
Medium	1.40	0.98	1.99	.061
Education (ref. university level)				
No education or elementary level	1.02	0.59	1.75	.945
College level	1.07	0.77	1.48	.692
Marital status (ref. never married)				
Married	0.70	0.52	0.96	.025
Separated or widowed	**1.72**	**1.25**	**2.35**	**.001**
Previous history of suicidal attempt	**5.15**	**3.86**	**6.86**	**<.001**
Depressive symptoms severity	**1.36**	**1.18**	**1.58**	**<.001**
Psychotic disorder	1.18	0.96	1.46	.117
Agoraphobia	0.91	0.67	1.24	.558
Panic disorder	1.09	0.85	1.39	.495
SAD	1.09	0.83	1.43	.543
GAD	1.01	0.79	1.29	.938
PTSD	1.35	0.91	2.00	.134
Drug SUD	0.96	0.71	1.31	.813
Alcohol SUD	1.06	0.83	1.36	.627
Sleep problems	1.12	0.86	1.46	.406
Mixed features	**1.69**	**1.26**	**2.25**	**<.001**

[a]Boldface indicates $P < .01$.
Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, OR = odds ratio, PTSD = posttraumatic stress disorder, SAD = social anxiety disorder, SUD = substance use disorder.

In our main analysis, MDE with mixed features was significantly associated with increased risk of recent suicide attempt (adjusted OR [AOR] = 1.69; 95% CI, 1.26–2.25) (Table 2). Additionally, previous suicidal attempt, severity of depressive symptoms, and marital status (separated or widowed vs never married) were also significantly associated with recent suicide attempt.

Additional Analyses

Additional analysis 1. Among the 128 participants experiencing MDE with mixed features, the mean number of nonoverlapping manic symptoms was 5.51 (SD = 1.62) with 82 of them (64.1%) meeting the criteria for a full mixed episode (ie, the simultaneous presence of *ICD-10* criteria for MDE and hypomania/mania). The severity of manic symptoms was associated with an increased risk of recent suicide attempt (AOR = 1.18; 95% CI, 1.07–1.30; $P < .001$), meaning that an increase of 1 manic symptom was associated with an 18% increase in the risk of suicide attempt (Figure 1).

Additional analysis 2. In comparison to MDE without mixed features, MDE with mixed features was not significantly associated with recent suicidal thoughts (AOR 95% CI, 0.93–1.42), thoughts of death (AOR 95% CI, 0.97–1.44), and self-harm intentions (AOR 95% CI, 1.07–1.67; $P = .011$) (Table 3).

Additional analysis 3. Similar results were obtained when excluding the variable "previous history of suicidal attempt" from the multivariable analysis models (see Supplementary Table 2 for details). Mixed features were found to be significantly associated only with recent self-harm intentions (AOR = 1.45; 95% CI, 1.17–1.79; $P = .001$).

Additional analysis 4. We conducted separate primary analyses for participants with and without bipolar disorder using Bayesian logistic regression with MCMC methods. This approach revealed that mixed features were more strongly associated with recent suicide attempt in participants with bipolar disorder (AOR = 5.47; 95% CI, 3.60–8.30, see Supplementary Table 3 and Supplementary Figure 1) compared to the nonbipolar group (AOR = 1.36; 95% CI, 0.87–2.12).

Additional analysis 5. When we ran the primary model separately in participants with or without thoughts of death, with or without suicidal thoughts, and with or without suicidal intentions, the association of mixed features with recent suicide attempt remained significant in participants without suicidal thoughts (AOR = 2.74; 95% CI, 1.36–5.54) but not in the 5 other subgroups (Table 4).

Additional analysis 6. Finally, the effect of mixed features on risk of suicide attempt did not significantly differ between men and women (AOR of the interaction term sex × mixed features = 1.02; 95% CI, 0.77–1.35; $P = .885$).

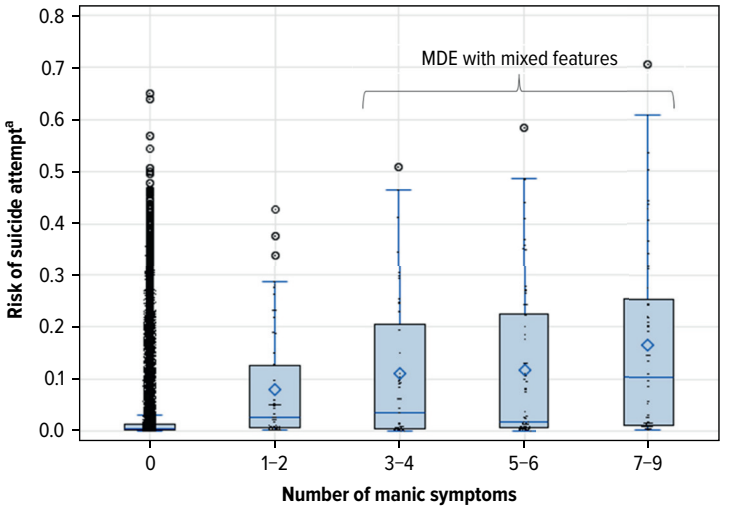
Additional analysis 7. Several manic symptoms were significantly associated with an increased risk of suicide attempt (see Supplementary Table 3 for details). Specifically, the need for excessive physical activity, reduced need for sleep, and racing thoughts were the 3 symptoms most strongly associated to a higher risk of suicide attempt. Interestingly, overlapping symptoms such as irritability and distractibility were also significantly associated with an increased risk of suicide attempt.

DISCUSSION

Our study aimed to investigate the association between MDE with mixed features and the risk of suicide attempt. We found that among individuals with MDE, the presence of mixed features was independently associated with suicide attempt, in line with most prior research.[24–28] Additionally, our findings confirm that a history of suicide attempt and the severity of depressive symptoms are significant predictors of nonfatal suicidal behaviors and thoughts. Importantly, we observed that the number of manic symptoms was linked in a dose-dependent manner to the risk of suicide attempt, underscoring the critical need to actively assess manic symptoms in individuals with MDE to more accurately evaluate suicide risk.

Figure 1.

Relationship Between the Number of Manic Symptoms and the Risk of Suicide Attempt[a]



[a]Based on a residuals of model adjusted for sociodemographic characteristics (age, sex, education level, marital status, and income level), history of suicide attempt, severity of depressive symptoms (using the sum of depression symptoms excluding suicidal ideation), comorbid psychiatric disorders (generalized anxiety disorder, agoraphobia, panic disorder, social anxiety disorder, posttraumatic stress disorder, alcohol use disorder, substance use disorder, and psychotic disorder), and the presence of sleep difficulties (degrees of freedom = 19). The central box displays the interquartile range, which encompasses the 25th to 75th percentiles of the data. The line within the box denotes the median value. The diamonds indicate the mean values of the dataset. Error bars extend from the edges of the box to the minimum and maximum values, excluding outliers (individual points beyond the error bars).
Abbreviation: MDE = major depressive episode.

Our results suggest that MDE with mixed features may primarily elevate the behavioral components of suicide risk, rather than the cognitive components of suicide risk. Indeed, MDE with mixed features was not significantly associated with suicidal thoughts, thoughts of death, or self-harm intentions. However, in supplementary analyses when excluding the variable previous history of suicidal attempt (Supplementary Table 2), mixed features were found to be significantly associated with self-harm intentions. Moreover, mixed features were particularly significantly associated with suicide attempt among individuals without recent suicidal thoughts. These findings suggest that the presence of mixed features may influence the pathway to suicide attempt through mechanisms distinct from the progression of suicidal ideation. However, future prospective studies are needed to confirm these findings and determine whether mixed features are associated with the full spectrum of nonfatal suicidal behaviors and thoughts. An alternative hypothesis that cannot be ruled out by our study is that mixed features may heighten impulsivity and thereby lower the threshold from suicidal ideation to act.[31,32]

The increased risk of suicide attempt associated with the presence of mixed features was consistent in both men and women. Although we cannot rule out that this result could be due to insufficient statistical power due to the relatively limited number of men with MDE with mixed features in our study, this result suggests that mixed features are unlikely to explain the higher rates of suicide attempt observed in women than in men.[43] This suggests that the impact of mixed features on suicide risk might be consistent in both men and women, which is valuable for developing sex-equivalent assessment and intervention strategies.

We found that mixed features are more strongly associated with recent suicide attempt in participants with bipolar disorder (with full mixed episode, mean number of nonoverlapping manic symptoms was 5.89 [SD = 1.51]) than in those without bipolar disorder (mean number of nonoverlapping manic symptoms was 4.80 [SD = 1.57]). Additionally, our study found that the strength of the association between mixed features and suicide attempt increased with the number of manic symptoms, highlighting a dose-dependent relationship: individuals with more severe manic symptoms had a higher likelihood of recent suicide attempt. Future research with a larger sample of patients experiencing MDE with mixed features but without meeting the criteria

Table 3.

Multivariate Regression Model Examining the Association of Mixed Features With Suicidal Thoughts, Self-Harm Intention, and Thoughts of Death, Among Participants With MDE (N = 3,440)[a]

	Suicidal thoughts				Self-harm intention				Thoughts of death			
	OR mean	95% CI		*P* value	OR mean	95% CI		*P* value	OR mean	95% CI		*P* value
Age, y	1.00	0.99	1.00	.539	**0.98**	**0.97**	**0.99**	**<.0001**	**1.02**	**1.01**	**1.03**	**<.0001**
Sex (ref. female)	1.04	0.94	1.15	.430	0.96	0.84	1.09	.485	0.94	0.86	1.02	.142
Income level (ref. high)												
Low	1.06	0.90	1.26	.481	0.97	0.79	1.18	.751	1.14	0.99	1.30	.059
Medium	0.91	0.79	1.03	.138	0.93	0.79	1.11	.425	0.87	0.78	0.98	.018
Education (ref. University level)												
No education or elementary level	1.15	0.90	1.49	.268	1.20	0.84	1.70	.319	1.07	0.86	1.32	.540
College level	0.97	0.83	1.12	.654	1.07	0.87	1.31	.527	0.96	0.84	1.08	.478
Marital status (ref. never married)												
Married	**0.77**	**0.67**	**0.90**	**.001**	**0.72**	**0.59**	**0.86**	**.001**	**0.76**	**0.67**	**0.85**	**<.0001**
Separated or widowed	**1.25**	**1.06**	**1.47**	**.008**	**1.33**	**1.07**	**1.64**	**.009**	1.15	1.00	1.32	.048
Previous history of suicidal attempt	**1.83**	**1.66**	**2.02**	**<.0001**	**1.92**	**1.70**	**2.17**	**<.0001**	**1.54**	**1.41**	**1.69**	**<.0001**
Depressive symptoms severity	**1.37**	**1.28**	**1.47**	**<.0001**	**1.45**	**1.33**	**1.59**	**<.0001**	**1.31**	**1.23**	**1.38**	**<.0001**
Psychotic disorder	1.01	0.92	1.11	.817	1.01	0.89	1.14	.869	1.10	1.01	1.20	.023
Agoraphobia	**1.28**	**1.09**	**1.51**	**.002**	1.24	1.02	1.50	.028	**1.28**	**1.10**	**1.49**	**.001**
Panic disorder	1.11	0.98	1.26	.107	**1.23**	**1.06**	**1.44**	**.006**	1.10	0.99	1.23	.088
SAD	1.02	0.88	1.17	.810	1.09	0.92	1.29	.341	1.04	0.92	1.18	.539
GAD	1.05	0.94	1.17	.380	1.12	0.97	1.30	.111	1.06	0.97	1.17	.204
PTSD	1.34	1.03	1.73	.027	**1.48**	**1.12**	**1.96**	**.006**	1.23	0.96	1.57	.106
Drug SUD	1.10	0.92	1.31	.309	0.97	0.79	1.19	.752	1.04	0.88	1.23	.648
Alcohol SUD	1.13	0.98	1.31	.097	**1.26**	**1.07**	**1.49**	**.006**	1.17	1.02	1.33	.022
Sleep problems	0.98	0.88	1.10	.780	0.95	0.82	1.10	.484	0.99	0.90	1.08	.803
Mixed features	1.15	0.93	1.42	.187	1.34	1.07	1.67	.011	1.18	0.97	1.44	.096

[a]Boldface indicates $P < .01$.
Abbreviations: GAD = generalized anxiety disorder, MDE = major depressive episode, OR = odds ratio, PTSD = posttraumatic stress disorder, SAD = social anxiety disorder, SUD = substance use disorder.

for a manic episode is essential. This will help clarify whether the heightened suicide risk is specific to those with concurrent bipolar disorder, or if it also applies to individuals without bipolar disorder. Furthermore, overlapping symptoms such as irritability and distractibility were significantly associated with an increased risk of suicide attempt. Together, these findings contribute to the debate on including overlapping symptoms in the assessment of mixed features and may support a dimensional approach to understanding the coexistence of manic symptoms within MDE.[12,14–16]

Our study has several limitations. First, the assessment of MDE symptoms and manic symptoms was based on different time frames, with MDE symptoms evaluated over a period of 15 days and manic symptoms over 1 month. Therefore, our identification of mixed features did not allow us to perfectly operationalize the *DSM-5* criteria, as we were unable to determine whether manic symptoms were present during the majority of days of the episode of depression.[44] Second, due to the cross-sectional nature of the study and the different time frames used for assessing suicide attempt, manic symptoms, and depressive symptoms, their temporal order cannot be precisely determined. Thus, measures of association reported in the study do not imply any causal association. Third, our study did not assess personality disorders, such as borderline personality disorder, which

Table 4.

Multivariate Regression Model Examining the Association Between Mixed Features and Suicide Attempt Among Participants Experiencing an MDE With or Without Thoughts of Death, With or Without Suicidal Thoughts, and With or Without Suicidal Intentions[a]

	Suicide attempt			
	OR mean	95% CI		*P* value
Suicidal thoughts				
Without	**2.74**	**1.36**	**5.54**	**.005**
With	1.45	1.00	2.08	.047
Self-Harm intention				
Without	1.50	0.89	2.53	.129
With	1.57	1.06	2.34	.025
Thoughts of death				
Without	2.14	1.08	4.22	.029
With	1.57	1.11	2.24	.011

[a]Boldface indicates $P < .01$.
Abbreviation: OR = odds ratio.

are known to be associated with increased risk of nonfatal suicidal behaviors and thoughts and to frequently co-occur with major depressive disorder and bipolar disorder. Another limitation was that the exploration of suicide risk was implemented through open-ended questions in our study and not through dedicated structured scales. Future studies using such scales are needed to confirm our results. Finally, the quota method was used to select the subjects, and not a probabilistic one, which could affect the representativeness of the sample population.

CONCLUSION

In a large sample of the French population, we found that, among individuals with MDE, and particularly among those without suicidal thoughts, mixed features were significantly associated with suicide attempt, independent of a wide range of sociodemographic and clinical characteristics. This study may contribute to advance in our understanding of the complex relationship between MDE with mixed features and suicide attempt. Systematically assessing manic symptoms among patients with MDE, in addition to other known risk factors for suicide, may help clinicians identify those at increased risk of suicide attempt and support strategies to mitigate this risk.

Article Information

Published Online: November 6, 2024. https://doi.org/10.4088/JCP.24m15445

Submitted: May 26, 2024; accepted September 13, 2024.

To Cite: Peyre H, Hoertel N, Pignon B, et al. Mixed features and nonfatal suicide attempt among individuals with major depressive episode: insights from the French MHGP survey. *J Clin Psychiatry.* 2024;85(4):24m15445.

Author Affiliations: Centre de Ressource Autisme Languedoc-Roussillon et Centre d'Excellence Sur l'Autisme et les Troubles du Neurodéveloppement (CeAND), CHU Montpellier, Montpellier, France (Peyre); Université Paris-Saclay, UVSQ, Inserm, CESP, Team DevPsy, Villejuif, France (Peyre); Department of Psychiatry, AP-HP Centre, DMU Psychiatrie et Addictologie, Corentin-Celton Hospital, Issy-les-Moulineaux, France (Hoertel); INSERM 1266, Psychiatry and Neurosciences Center, Paris, France (Hoertel); Université Paris Cité, Paris, France (Hoertel); Université Paris Est Créteil, INSERM, IMRB, AP-HP, Hôpitaux Universitaires H. Mondor, DMU IMPACT, Fondation FondaMental, Créteil, France (Pignon); Lille Neurosciences and Cognition, Lille University Hospital, University of Lille, and National Institute of Health and Medical Research, U1172, Lille, France (Amad, Thomas, Vaiva); Fédération Régionale de Recherche en Santé Mentale (F2RSM) Hauts-de-France, Lille, France (Amad, Thomas, Vaiva); EPSM Lille Métropole; Centre Collaborateur de l'Organisation Mondiale de la Santé pour la Recherche et la Formation en Santé Mentale; Équipe Eceve Inserm UMR 1123, Hellemmes, France (Roelandt, Benradia); Centre National de Ressources & Résilience (Cn2r Lille—Paris), Lille, France (Vaiva); Département de Psychiatrie et d'Addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hopital Bichat—Claude Bernard, Paris, France (Geoffroy); Centre ChronoS, GHU Paris—Psychiatry and Neurosciences, Paris, France (Geoffroy); NeuroDiderot, Inserm, Université Paris Cité, Paris, France (Geoffroy); Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, Montpellier, France (Olié, Courtet); Department of Emergency Psychiatry and Post-Acute Care, CHU Montpellier, Montpellier, France (Olié, Courtet); Fondation FondaMental, Créteil, France (Olié, Courtet).

Corresponding Author: Hugo Peyre, MD, PhD, CHU Montpellier, 291 Ave du Doyen Giraud, 34295 Montpellier Cedex 5, France (hugo.peyre@chu-montpellier.fr).

Relevant Financial Relationships: None.

Funding/Support: None.

Supplementary Material: Available at Psychiatrist.com.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed., Text Revision (DSM-5-TR). American Psychiatric Publishing; 2022.
2. Riera-Serra P, Navarra-Ventura G, Castro A, et al. Clinical predictors of suicidal ideation, suicide attempts and suicide death in depressive disorder: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2024;274:1543–1563.
3. Isometsä E. Suicidal behaviour in mood disorders—who, when, and why? *Can J Psychiatry*. 2014;59(3):120–130.
4. Sokero TP, Melartin TK, Rytsälä HJ, et al. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J Clin Psychiatry*. 2003;64(9):1094–1100.
5. Valtonen H, Suominen K, Mantere O, et al. Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry*. 2005;66(11):1456–1462.
6. Malone KM, Haas GL, Sweeney JA, et al. Major depression and the risk of attempted suicide. *J Affect Disord*. 1995;34(3):173–185.
7. Hawton K, Casañas I Comabella C, Haw C, et al. Risk factors for suicide in individuals with depression: a systematic review. *J Affect Disord*. 2013;147(1–3):17–28.
8. Hoertel N, Sabatier J, Blanco C, et al. Contributing factors to heterogeneity in the timing of the onset of nonfatal suicidal behavior: results from a nationally representative study. *J Clin Psychiatry*. 2020;81(3):19m13017.
9. Orsolini L, Latini R, Pompili M, et al. Understanding the complex of suicide in depression: from research to clinics. *Psychiatry Investig*. 2020;17(3):207–221.
10. Lynall ME, McIntosh AM. The heterogeneity of depression. *Am J Psychiatry*. 2023;180(10):703–704.
11. Corponi F, Anmella G, Pacchiarotti I, et al. Deconstructing major depressive episodes across unipolar and bipolar depression by severity and duration: a cross-diagnostic cluster analysis on a large, international, observational study. *Transl Psychiatry*. 2020;10(1):241.
12. Koukopoulos A, Sani G. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. *Acta Psychiatr Scand*. 2014;129(1):4–16.
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. American Psychiatric Publishing; 2013.
14. Ostacher MJ, Suppes T. Depression with mixed features in major depressive disorder: a new diagnosis or there all along? *J Clin Psychiatry*. 2018;79(2):17ac11974.
15. Malhi GS, Irwin L, Hamilton A, et al. Modelling mood disorders: an ACE solution? *Bipolar Disord*. 2018;20(suppl 2):4–16.
16. Mineo L, Rodolico A, Spedicato GA, et al. Exploration of mood spectrum symptoms during a major depressive episode: the impact of contrapolarity-results from a transdiagnostic cluster analysis on an Italian sample of unipolar and bipolar patients. *Eur Psychiatry*. 2022;65(1):e30.
17. Stahl SM, Morrissette DA, Faedda G, et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr*. 2017;22(2):203–219.
18. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry*. 2013;170(11):1249–1262.
19. Yan R, Marshall T, Khullar A, et al. Patient-reported outcomes on sleep quality and circadian rhythm during treatment with intravenous ketamine for treatment-resistant depression. *Ther Adv Psychopharmacol*. 2024;14:20451253241231264.
20. Natale A, Mineo L, Fusar-Poli L, et al. Mixed depression: a mini-review to guide clinical practice and future research developments. *Brain Sci*. 2022;12(1):92.
21. Mineo L, Rodolico A, Spedicato GA, et al. Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria. *Bipolar Disord*. 2022;24(5):530–538.
22. Fornaro M, Fusco A, Novello S, et al. Predictors of treatment resistance across different clinical subtypes of depression: comparison of unipolar vs. bipolar cases. *Front Psychiatry*. 2020;11:438.
23. Hoertel N, Le Strat Y, Limosin F, et al. Prevalence of subthreshold hypomania and impact on internal validity of RCTs for major depressive disorder: results from a national epidemiological sample. *PLoS One*. 2013;8(2):e55448.
24. Balázs J, Benazzi F, Rihmer Z, et al. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. *J Affect Disord*. 2006;91(2–3):133–138.
25. Judd LL, Schettler PJ, Akiskal H, et al. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. *J Affect Disord*. 2012;138(3):440–448.

26. Perugi G, Angst J, Azorin JM, et al. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry*. 2015;76(3): e351–e358.
27. Sverdlichenko I, Jansen K, Souza LDM, et al. Mixed episodes and suicide risk: a community sample of young adults. *J Affect Disord*. 2020;266: 252–257.
28. Goldberg JF, Garno JL, Leon AC, et al. Association of recurrent suicidal ideation with nonremission from acute mixed mania. *Am J Psychiatry*. 1998;155(12): 1753–1755.
29. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry*. 2009;166(2):173–181.
30. Persons JE, Coryell WH, Solomon DA, et al. Mixed state and suicide: is the effect of mixed state on suicidal behavior more than the sum of its parts? *Bipolar Disord*. 2018;20(1):35–41.
31. Popovic D, Vieta E, Azorin JM, et al. Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disord*. 2015;17(7): 795–803.
32. Wang L, He CZ, Yu YM, et al. Associations between impulsivity, aggression, and suicide in Chinese college students. *BMC Public Health*. 2014;14(1):551.
33. Lunsford TR, Lunsford BR. The research sample, part I: sampling. *JPO J Prosthet Orthot*. 1995;7(3). https://journals.lww.com/jpojournal/Fulltext/1995/00730/The_Research_Sample,_Part_I__Sampling.8.aspx.
34. Pignon B, Geoffroy PA, Thomas P, et al. Prevalence and clinical severity of mood disorders among first-second- and third-generation migrants. *J Affect Disord*. 2017;210:174–180.
35. Pignon B, Peyre H, Szöke A, et al. A latent class analysis of psychotic symptoms in the general population. *Aust N Z J Psychiatry*. 2018;52(6):573–584.
36. Pignon B, Amad A, Pelissolo A, et al. Increased prevalence of anxiety disorders in third-generation migrants in comparison to natives and to first-generation migrants. *J Psychiatr Res*. 2018;102:38–43.
37. Brito MA, Amad A, Rolland B, et al. Religiosity and prevalence of suicide, psychiatric disorders and psychotic symptoms in the French general population. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(8):1547–1557.
38. Lecrubier Y, Sheehan D, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Eur Psychiatry*. 1997;12(5):224–231.
39. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33;quiz 34–57.
40. Caria A, Roelandt JL, Bellamy V, et al. Santé Mentale en Population Générale: Images et Réalités (SMPG): Présentation de La méthodologie d'enquête. *Encephale*. 2010;36(3):1–6.
41. Ames AJ, Samonte K. Using SAS PROC MCMC for item response theory models. *Educ Psychol Meas*. 2015;75(4):585–609.
42. SAS. *Users' Guide Statistics Version 9.4*. SAS; 2013.
43. Bommersbach TJ, Rosenheck RA, Petrakis IL, et al. Why are women more likely to attempt suicide than men? Analysis of lifetime suicide attempts among US adults in a nationally representative sample. *J Affect Disord*. 2022;311:157–164.
44. Zimmerman M, Mackin D. Validity of the DSM-5 Mixed Features Specifier Interview. *Bipolar Disord*. 2024;26(5):479–487.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Mixed Features and Nonfatal Suicide Attempt Among Individuals With Major Depressive Episode: Insights From the French MHGP Survey

Authors: Hugo Peyre, MD, PhD; Nicolas Hoertel, MD, PhD; Baptiste Pignon, MD, PhD; Ali Amad, MD, PhD; Jean-Luc Roelandt, MD, PhD; Imane Benradia, PhD; Pierre Thomas, MD, PhD; Guillaume Vaiva, MD, PhD; Pierre-Alexis Geoffroy, MD, PhD; Emilie Olié, MD, PhD; Philippe Courtet, MD, PhD

DOI Number: 10.4088/JCP.24m15445

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Percentage of endorsement of manic symptoms in participants with major depressive Episode (MDE) with mixed features.

		MDE with mixed features N=128
	Non-overlapping contrapolar symptoms	Percentage of symptom endorsement
A1. Have you ever had a period where you felt so elated or full of energy that it caused problems, or that people around you thought you were not in your usual state?	Yes	83.3
A2. Have you ever had a period where you were so irritable that you ended up insulting people, shouting, or even fighting?	No	76.3
B1. Did you need so much physical activity that you couldn't stay still?	Yes	78.2
B2. Did you speak non-stop or so fast that people couldn't understand you?	Yes	58.3
B3. Did your thoughts race so quickly in your head that you couldn't keep up with them?	Yes	76.3
B4. Were you so active that your loved ones worried about you?	Yes	57.1
B5. Did you need less sleep than usual?	Yes	58.9
B6. Did you feel like you could do things that others couldn't, or that you were someone particularly important?	Yes	47.4
B7. Were you so easily distracted that even the slightest interruption made you lose track of what you were doing or thinking?	No	69.9
B8. Did some activities seem so enjoyable or tempting to you that you tended to overlook the risks or difficulties they might entail (such as making impulsive purchases, driving recklessly, etc.)?	Yes	68.6
B9. Were your sexual desires so strong that you engaged in unusual sexual activity for you?	Yes	25.2

Supplementary Table 2. Multivariate regression model examining the association of mixed features with suicidal thoughts, self-harm intention, and thoughts of death, among participants with MDE (N=3440). Models without previous history of suicidal attempt.

		Suicidal thoughts				Self-harm intention				Thoughts of death			
		OR mean	IC95%		p-value	OR mean	IC95%		p-value	OR mean	IC95%		p-value
Age (years)		1,00	0,99	1,00	0,199	0,97	0,97	0,98	0,000	1,02	1,01	1,02	0,000
Sex (ref. Female)		1,01	0,92	1,11	0,842	0,92	0,82	1,05	0,208	0,92	0,85	1,01	0,066
Income level (ref. High)	Low	1,12	0,96	1,30	0,139	1,07	0,89	1,30	0,460	1,17	1,02	1,34	0,021
	Medium	0,91	0,80	1,03	0,132	0,93	0,78	1,10	0,394	0,88	0,79	0,99	0,033
Education (ref. University level)	No education or elementary level	1,16	0,91	1,49	0,226	1,22	0,87	1,72	0,248	1,08	0,87	1,33	0,490
	College level	0,99	0,85	1,14	0,840	1,08	0,88	1,31	0,454	0,97	0,85	1,10	0,600
Marital status (ref. Never married)	Married	0,79	0,69	0,90	0,001	0,75	0,63	0,89	0,001	0,76	0,68	0,86	0,000
	Separeted or Widowed	1,28	1,09	1,50	0,002	1,35	1,10	1,67	0,004	1,18	1,03	1,35	0,021
Depressive symptoms severity		1,38	1,29	1,48	0,000	1,48	1,35	1,61	0,000	1,31	1,24	1,39	0,000
Psychotic disorder		1,06	0,97	1,17	0,214	1,06	0,94	1,20	0,335	1,14	1,05	1,23	0,002
Agoraphobia		1,34	1,14	1,56	0,000	1,31	1,09	1,57	0,004	1,32	1,14	1,53	0,000
Panic disorder		1,19	1,05	1,34	0,005	1,33	1,15	1,54	0,000	1,16	1,04	1,29	0,010
SAD		1,02	0,89	1,17	0,821	1,07	0,91	1,27	0,406	1,04	0,92	1,18	0,530
GAD		1,11	0,99	1,23	0,064	1,19	1,03	1,37	0,016	1,10	1,00	1,21	0,039
PTSD		1,39	1,08	1,78	0,010	1,53	1,17	2,01	0,002	1,27	0,99	1,62	0,056
Drug SUD		1,16	0,98	1,37	0,092	1,04	0,86	1,27	0,681	1,08	0,92	1,27	0,348
Alcohol SUD		1,23	1,07	1,42	0,003	1,39	1,18	1,63	0,000	1,24	1,09	1,41	0,001
Sleep problems		1,01	0,91	1,12	0,871	0,98	0,85	1,13	0,766	1,00	0,92	1,10	0,933
Mixed features		1,25	1,02	1,53	0,028	1,45	1,17	1,79	0,001	1,26	1,03	1,52	0,021

In bold p-value < 0.01. SAD: Social Anxiety Disorder; GAD: Generalized Anxiety Disorder; PTSD: Post Traumatic Stress Disorder. SUD: Substance Use Disorder.

Supplementary Table 3. Multivariate regression model examining the association of individual manic symptoms and the risk of suicide attempt (N=3440).

	Suicide attempt			
	OR mean	**IC95%**		**p-value**
A1. Have you ever had a period where you felt so elated or full of energy that it caused problems, or that people around you thought you were not in your usual state?	**1.52**	**1.12**	**2.06**	**0.007**
A2. Have you ever had a period where you were so irritable that you ended up insulting people, shouting, or even fighting?	**1.55**	**1.17**	**2.06**	**0.002**
B1. Did you need so much physical activity that you couldn't stay still?	**1.72**	**1.26**	**2.35**	**0.001**
B2. Did you speak non-stop or so fast that people couldn't understand you?	1.43	1.01	2.03	0.042
B3. Did your thoughts race so quickly in your head that you couldn't keep up with them?	**1.64**	**1.22**	**2.22**	**0.001**
B4. Were you so active that your loved ones worried about you?	**1.59**	**1.14**	**2.21**	**0.006**
B5. Did you need less sleep than usual?	**1.81**	**1.29**	**2.55**	**0.001**
B6. Did you feel like you could do things that others couldn't, or that you were someone particularly important?	1.58	1.06	2.37	0.026
B7. Were you so easily distracted that even the slightest interruption made you lose track of what you were doing or thinking?	**1.55**	**1.13**	**2.11**	**0.006**
B8. Did some activities seem so enjoyable or tempting to you that you tended to overlook the risks or difficulties they might entail (such as making impulsive purchases, driving recklessly, etc.)?	**1.61**	**1.17**	**2.23**	**0.004**
B9. Were your sexual desires so strong that you engaged in unusual sexual activity for you?	1.36	0.79	2.33	0.264

In bold p-value < 0.01.

Supplementary Figure 1. Adjusted odds ratios from Bayesian logistic regression models using MCMC methods for the impact of mixed features on recent suicide attempt.