Research paper

Suicidal risk and protective factors in major affective disorders: A prospective cohort study of 4307 participants[☆]

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ABSTRACT

Background: Suicidal behavior is strongly associated with major affective disorders, but there is a need to quantify and compare specific risk and protective factors in bipolar disorder (BD) and major depressive disorder (MDD).
Methods: In 4307 extensively evaluated major affective-disorder participants with BD (n = 1425) or MDD (n = 2882) diagnosed by current international criteria, we compared characteristics among those with versus without suicidal acts from illness-onset through 8.24 years of follow-up.
Results: Suicidal acts were identified in 11.4 % of participants; 25.9 % were violent and 6.92 % (0.79 % of all participants) were fatal. Associated *risk factors* included: diagnosis (BD > MDD), manic/psychotic features in first-episodes, family history of suicide or BD, separation/divorce, early abuse, young at illness-onset, female sex with BD, substance abuse, higher irritable, cyclothymic or dysthymic temperament ratings, greater long-term morbidity, and lower intake functional ratings. *Protective factors* included marriage, co-occurring anxiety disorder, higher ratings of hyperthymic temperament and depressive first episodes. Based on multivariable logistic regression, five factors remained significantly and independently associated with suicidal acts: BD diagnosis, more time depressed during prospective follow-up, younger at onset, lower functional status at intake, and women > men with BD.
Limitations: Reported findings may or may not apply consistently in other cultures and locations.
Conclusions: Suicidal acts including violent acts and suicides were more prevalent with BD than MDD. Of identified risk (n = 31) and protective factors (n = 4), several differed with diagnosis. Their clinical recognition should contribute to improved prediction and prevention of suicide in major affective disorders.

1. Introduction

Suicide is a major international public health concern, leading to >700,000 deaths/year (WHO, 2021). Nearly half of those dying by suicide have had at least one diagnosed psychiatric disorder in the year before death (Yeh et al., 2019). We have found suicidal risks to be particularly high in those diagnosed with bipolar disorder (BD), those who have experienced psychotic or mixed manic-depressive features, or have co-occurring substance abuse, and with sufficiently severe major

depressive disorders (MDD) which required hospitalization (Baldessarini et al., 2019; Baldessarini and Tondo, 2020). Recently estimated lifetime prevalence of suicide attempt was as high as 33.9 % [95 % CI: 31.3–36.6 %] among 33,719 participants diagnosed with BD (Dong et al., 2019a) and 31.0 % [27.0–34.0] in 27,340 diagnosed with MDD (Dong et al., 2019b). We also found the rate of suicide attempts with BD to be approximately twice that associated with MDD (Baldessarini and Tondo, 2020).

The suicide-associated standardized mortality ratio (SMR) in high-

risk clinical conditions including major affective disorders can reach 20 times greater than in the age- and sex-matched general population (Harris and Barraclough, 1997; Tondo and Baldessarini, 2015). Not only is the prevalence of suicidal behavior associated with affective disorders far higher than in the general population, but the proportion of fatalities among attempts also is much greater (Baldessarini, 2019). The ratio of attempts/suicides (A/S) was much lower (greater lethality) among those with BD versus MDD, indicating that BD not only presents a higher risk of suicidal acts but evidently also that attempts are associated with greater intent to die or more lethal methods (Tondo et al., 2021).

Suicidal risk factors associated with major affective disorders include a history of even mild hypomanic (mixed) features, which doubled the lifetime risk of suicide attempt with MDD (Choi et al., 2019). We found that risk of suicide attempts differed little between BD type I (BD1) and type II (BD2) (Tondo et al., 2016), but that violent suicidal acts were nearly twice more likely with BD1, whereas BD2 participants were more likely to report suicidal ideation without acts (Tondo et al., 2022). For those with affective disorders, previous suicide attempt is a particularly powerful predictor of future suicidal behavior: approximately 40 % of those diagnosed with BD or MDD with a history of attempt later died of suicide (Malhi et al., 2018; Tondo et al., 2020).

We found previously that several risk factors for suicidal behavior were more associated with BD than MDD (Baldessarini et al., 2019). These included substance abuse, more than four previous depressive episodes, higher ratings of dysthymic or cyclothymic affective temperament, and prior physical or sexual abuse or trauma (Baldessarini et al., 2019). Other clinical suicidal risk factors which we found to be associated with BD more than MDD have included mixed-agitated-dysphoric moods, rapid mood-shifts, and impulsive behavior (Tondo et al., 2021).

Some observations suggest that suicide attempts in BD participants are associated with higher levels of aggression and impulsivity but less hopelessness than with MDD (Zalsman et al., 2006), and with binge eating behavior, lifetime history of a rapid-cycling illness course, and younger age at illness-onset (Bobo et al., 2018), and attempts were especially likely within the initial years of illness (Tondo et al., 2007; Dome et al., 2019). Based on multivariable regression modeling, other clinical features significantly associated with life-threatening suicide attempts in BD included a history of sexual abuse, more hospitalizations for depression, suicidal thoughts when depressed, and cluster-B personality disorder features (Leverich et al., 2003). However, in another study only a history of suicide attempt and the proportion of time depressed in the past year were significantly associated with suicidal behaviors during two years of follow-up of 1556 BD participants (Marangell et al., 2006). Finally, in a recent nationwide study of 1673 BD participants, among other risk factors, psychiatric hospitalization within the past year and presence of psychotic symptoms were associated with lifetime risk of suicide attempt (Buoli et al., 2022).

For MDD a recent meta-analysis identified as suicidal risk factors: alcohol or drug abuse, previous suicidal behaviors, co-occurring anxiety disorders, history of school truancy or suspension, severe depression, sexual abuse, parental separation during childhood, and recent losses or other stressful life events (Li et al., 2022). Additional features associated with suicide attempts with MDD included: presence of melancholic (Xin et al., 2018) or psychotic symptoms (Zhou et al., 2020) and binge-eating (Baek et al., 2018). Moreover, in a six-year longitudinal study of 1713 MDD participants, younger age, less education, unemployment, insomnia, antidepressant use, previous suicide attempt, and current suicidal thoughts independently predicted a future suicide attempt (Eikelenboom et al., 2019). MDD participants with versus without a suicidal first-degree relative did not differ regarding history of aggressive or impulsive behavior, nor by age at illness-onset or at first suicide attempt (Fornaro et al., 2018). Other MDD participants with suicide attempts experienced more and more severe depressive episodes, more suicidal ideation, younger age at illness-onset, had higher harm-avoidance scores, and a less supportive social environment than those without attempts (Perroud et al., 2010). Other investigations with MDD

participants have noted associations of suicide attempt with the frequency and severity of depressions, occurrence of psychotic symptoms, alcohol abuse, borderline disorder personality traits, and childhood physical abuse (Chen et al., 2014; Aaltonen et al., 2016). Additional risk factors included previous hospitalizations, early illness-onset, more depression at intake and presence of mixed features or agitation, as well as unemployment or poor social support (Tondo et al., 2007; Chen et al., 2014; Holma et al., 2014; Baldessarini et al., 2019).

Despite the substantial literature on risk factors for suicidal behavior, most previous studies have considered risks in MDD or BD participants separately and used cross-sectional rather than prospective analyses. Moreover, even among the few head-to-head comparisons of factors across participants with major affective disorders evaluated under the same conditions, some findings have been inconsistent (Zalsman et al., 2006; Tondo et al., 2007; Pawlak et al., 2013; Chen et al., 2014; Holma et al., 2014; Aaltonen et al., 2016; Baldessarini et al., 2019). Most reports have agreed that BD carried higher suicidal risk than MDD (Zalsman et al., 2006; Tondo et al., 2007; Chen et al., 2014; Baldessarini et al., 2019). However, this diagnostic association remains inadequately explained (Holma et al., 2014).

The relationship between comorbid anxiety disorders and suicidal behavior with major affective disorders remains controversial. Some reports suggest that co-occurring anxiety disorders were not associated with an increased risk for suicide attempts in those with major affective disorders (Nakagawa et al., 2008; Guillaume et al., 2010; Pawlak et al., 2013; Chen et al., 2014; Abreu et al., 2018). In particular, with MDD and a history of suicide attempt, co-occurring panic disorder appeared to *reduce* risk of future attempts, especially if they involved careful planning and relatively lethal methods; also, severity of depression and aggressive-impulsive traits did not predict planning or lethality of attempts (Nakagawa et al., 2009). Inconsistently, however, other investigations found that such conditions increased risk of suicidal behavior (Simon et al., 2004, 2007; Bolton et al., 2010; Li et al., 2022). Also, among hospitalized MDD participants, co-occurring panic-agoraphobia *increased* risk of suicidal behavior (Brown et al., 2010) as did co-occurring post-traumatic stress disorder (PTSD) in 1433 participants with recurrent, early-onset MDD (Stevens et al., 2013).

Finally, lack of association of suicidal behavior was found with family history of suicides or attempts, presence of psychotic symptoms or irritability, co-occurring personality disorder, or substance abuse with either BD or MDD (Pawlak et al., 2013). Further research is needed to replicate and determine the magnitude of effect of most of these factors and their differential distribution with BD versus MDD, as suggested by the report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder (Schaffer et al., 2015).

Based on this background, the present study aimed to compare rates of a broad range of descriptive and clinical characteristics, including prospectively evaluated morbidity, among MDD and BD participants with versus without suicidal acts who were followed systematically for at least one year under the same conditions of observation and assessment. We hypothesized that rates of suicidal behavior and of some associated risk and protective factors would differ by diagnosis. We propose that clarification and quantification of such differences between BD and MDD study participants should help to improve clinical assessment and efforts to prevent suicide and risk-stratification in these high-risk populations.

2. Methods

2.1. Participants

The study sample includes consecutive adult participants evaluated and followed at specialized outpatient clinics for affective disorders: the Lucio Bini Mood Disorders Centers in Cagliari, Sardinia and Rome, Italy. Participants were clinically diagnosed with a major affective disorder (BD1, BD2, MDD), updated to Diagnostic and Statistical Manual of

Mental Disorders-edition 5-Text Revision (DSM-5-TR) criteria (APA, 2022). They underwent systematic initial and repeated diagnostic evaluations during follow-up, using semi-structured interviews in use since 1977, all by the same affective disorder expert (LT) with verification by clinical colleagues, leading to construction of individual life-charts. Morbidity was assessed and quantified (on a per year basis) during prospective follow-up assessments for participants followed for at least one year after intake to avoid distortions of annualized rates by short exposures. Clinical data acquired were recorded systematically and converted to digitized form, updated at least annually, with diagnoses updated to meet DSM-5-TR criteria. Written, informed consent was provided by all participants for collection and analysis of clinical data to be presented anonymously in aggregate and coded form, following procedures in accordance with requirements of Italian law (IMEF, 2014) and with the Helsinki Declaration.

2.2. Clinical measures

We assessed information about morbidity both pre-intake and during follow-up and considered *demographic*, *general descriptive*, and *clinical factors*. In order to enrich documentation based on clinical observations by LT, standardized self-report and clinical rating scales with reported evidence good-excellent validity and reliability were utilized. These include affective temperament scores with the 39-item version of the self-assessment TEMPS-A scale (Akiskal et al., 2005), depression severity using the 21-item Hamilton Depression Rating Scale (HDRS$_{21}$) (Hamilton, 1960), likelihood of lifetime presence of BD with the Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000); current [hypo]manic status with the Young Mania Rating Scale (YMRS) (Young et al., 1978), anxiety with the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), and functional status assessed with the Global Assessment of Functioning (GAF) [DSM-IV]. Values >1 for item 9 of the HDRS and ≥2 for item 5 of the YMRS supported the specification of mixed features, defined accordingly to DSM-5-TR criteria.

Illness course-related variables included: ages at first symptoms, first syndromal episode, first diagnosis and first treatment, and type and duration of first lifetime episode (depressive, psychotic, manic or hypomanic ["(hypo)manic"], or mixed). Moreover, we assessed the predominant (>50 % of recurrences) course-sequence (Depression-[Hypo] mania-euthymic Interval [DMI] or [Hypo]mania-Depression-Interval [MDI]) and presence of rapid-cycling (≥4 episodes in the previous 12 months, as defined by the DSM-5-TR criteria); predominant polarity (>50 % of time ill in depression vs. [hypo]mania); and factors associated with *morbidity* based on life-charting. These measures included the prospectively observed annual frequency of illness-episodes (all episodes, depressions, [hypo]manias) and the average percentage of time in [hypo]mania or depression or total proportion of time ill during follow-up, as well as presence of episodes with mixed manic-depressive or psychotic features, predominant mood, and rapid (within one week) switching from depression to [hypo]mania during treatment with an antidepressant.

For the period of follow-up, we also compared prevalence of particular types of treatment, including with lithium salts, anticonvulsants, antidepressants, antipsychotics, or benzodiazepines, as well as psychotherapy (including mainly cognitive behavioral therapy, but also psychoeducation and supportive efforts). Psychotherapeutic treatments were decided clinically by LT based on diagnosis and repeated assessments of symptomatic presentations and were provided by specialized psychotherapists at the study centers.

Violent suicidal acts were classified according to the methods used. Following Asberg's criteria (Åsberg et al., 1976) and as supported in other studies (Giner et al., 2014; Peñas-Lledó et al., 2015), we defined as violent acts: hanging attempts, use of firearms, jumping from heights, self-stabbing, car crash, self-immolation, gas poisoning, drowning, electrocution, and jumping into a moving vehicle.

2.3. Data analysis

Data are presented as means with 95 % confidence intervals [CI]. Sociodemographic and selected clinical data were analyzed for differences between participants with versus without at least one suicide attempt, using contingency tables (χ^2) for categorical measures and analysis of variance (*t*-test) for continuous measures. Given the high number of study participants, specific tests for normality of data distribution were not required. Subgroup comparisons were ranked as rate ratios (RR) of magnitudes of measures between those with versus without suicidal acts. We also used multivariable logistic regression modeling to identify factors that were significantly and independently associated with suicidal acts as a categorical outcome. Statistical significance was limited to guiding selection of initial measures for further analyses, but we also generally considered two-tailed $p \leq 0.01$ to indicate particularly interesting findings as well as to compensate for multiple comparisons. Analyses employed commercial software: *Statview.5* (SAS Institute, Cary, NC) for spreadsheets, and *Stata.17* (StataCorp, College Station, TX) for analyses.

3. Results

3.1. Participant characteristics

Study participants were 4307 consecutive, consenting adults who met DSM-5-TR diagnostic criteria for a major affective disorder (1425 BD [718 BD1 and 707 BD2] and 2882 MDD). They were evaluated and followed systematically by a single mood-disorder expert (LT) for an average of 8.24 years [CI: 7.81–8.67]. Participants had been ill for a total of 13.6 [12.2–14.0] years since illness-onset. A majority were women (63.1 % [61.6–64.5]), and current age averaged 46.3 [45.8–46.8] years. Of the 4307 study participants, 491 (11.4 % [10.5–12.4]) made at least one suicide attempt since the onset of affective illness. In 127 of 4307 participants (2.95 % [2.46–5.00] or 25.9 % [22.0–30.0] of the 491 with suicidal acts), the suicidal acts were violent. Acts were fatal in 34 of 491 participants with suicidal acts (6.92 % [4.84–9.84], or 0.79 % [0.55–1.10] of all 4307 participants). Age at first lifetime suicide attempt averaged 34.6 years [33.2–36.0], or at 12.0 years [11.9–12.1] from illness onset.

3.2. Suicidal risks in BD versus MDD study participants

Overall, 51.8 % [49.2–54.4] of BD participants and 25.8 % [24.2–27.4] with MDD reported some form of suicidality including suicidal ideation, attempts or fatalities (Table 1). That is, BD participants were twice as likely to have been suicidal in ideation or behavior, and the risk of nonfatal suicide attempt was 3.87-times higher with BD than with MDD (20.3 % vs. 5.24 %). The rate of suicide attempt (per 100,000 [100k] person-exposure-years [PEY]) was 2.44-times higher with BD than with MDD (1122 [997–1258] versus 460 [388–538]). In addition, the rate of suicide was 2.66-times higher with BD than with MDD (89.2 [74.5–99.8] vs. 33.5 [16.7–59.9] per100k PEY). BD participants also had more violent suicidal acts than those diagnosed with MDD (6.60 % vs. 1.15 % of participants, and 12.7 % vs. 4.50 % of attempts and suicides). We found no significant difference between the diagnostic groups in the ratio of rates of attempts/suicides (A/S = 12.6 BD and 13.7 MDD) which were much lower than ratios of ≥30 reported for the general population (Baldessarini, 2019), indicating high lethality of suicide attempts with both diagnoses (Table 1). The mean latency (years) from illness-onset to a first suicide attempt was somewhat longer with BD (12.7) than MDD (11.0).

3.3. Factors associated with suicidal acts

We identified 21 categories of risk factors (31 factors) and 4 potentially protective factors associated with suicide attempts and suicide

Table 1
Comparison of suicidal risks in 4307 BD vs. MDD participants.

Measure	Magnitude [95%CI]		Rate ratio	χ² or t-score	p-Value
	BD	MDD			
Participants	1425	2882	1/2.02	–	–
Women (%)	57.4 [54.8–59.9]	65.4 [63.6–67.1]	1/1.14	26.3	<0.0001
Age (years)	45.9 [45.1–46.7]	46.5 [45.9–47.2]	1/1.01	1.16	0.25
Exposure (years)	18.1 [17.3–18.8]	11.4 [11.0–11.9]	1.59	15.9	<0.0001
PEY (person-exposure-years)	25,793	32,855	1/1.27	–	–
Suicidal ideation or acts (%)	51.8 [49.2–54.4]	25.8 [24.2–27.4]	2.01	286	<0.0001
Suicidal acts (%)	21.9 [19.8–24.1]	5.62 [4.80–6.53]	3.90	258	<0.0001
Suicide attempts (%)	20.3 [18.2–22.5]	5.24 [4.45–6.12]	3.87	432	<0.0001
Suicides (%)	1.61 [1.03–2.41]	0.38 [0.19–0.68]	4.24	18.5	<0.0001
Violent acts (%)	6.60 [5.36–8.01]	1.15 [0.79–1.60]	5.74	89.9	<0.0001
Violent acts (% of acts)	12.7 [10.4–15.4]	4.50 [3.11–6.26]	2.82	31.7	<0.0001
Attempt rate (A: per 100 k PEY)	1122 [997–1258]	460 [388–538]	2.44	221	<0.0001
Suicide rate (S: per 100 k PEY)	89.2 [74.5–99.8]	33.5 [16.7–59.9]	2.66	49.9	<0.0001
Attempt/Suicide rate ratio (A/S)	13.9 [13.1–14.8]	15.6 [14.0–17.3]	1/1.12	1.21	0.27
Years to first suicidal act	12.7 [11.8–13.0]	11.0 [10.3–11.7]	1.15	2.67	0.003

Abbreviations: *A/S*: attempt/suicide ratio; *BD*: bipolar disorder; *CI*: 95 % confidence interval; *MDD*: major depressive disorder; *PEY*; participant-exposure years (N x time). Rates and the A/S ratio are based on per 100,000 persons/year (100k PEY).

among study participants based on bivariate analyses (Table 2). By the RR of measures in those with versus without suicidal acts, associations ranked: diagnosis of BD vs. MDD, prospective hospitalizations/year, substance abuse (drugs, alcohol, cigarettes), marriage failure, family history in first-degree relatives (ranking as: suicide, BD, % of relatives affected, mood disorder, and any psychiatric disorder), early sexual or physical abuse, prospective proportion of time in [hypo]mania, non-depressive first lifetime major episode of illness, prospective [hypo]manias/year, prospective depressions/year, unemployment, prospective % of time ill, women > men with BD but not MDD, temperament ratings (TEMPS: irritable, cyclothymic, and dysthymic), prospective %-time depressed, prospective episodes/year, younger at illness-onset and currently, low population density (living in non-urban areas, as we reported previously (Tondo et al., 2006; Azcueta et al., 2021)), higher intake rating of depression (HDRS), lower intake rating of functional status (GAF), and evidence of a secular trend toward more suicidal behavior with more recent years of intake. Four apparently *protective* factors included: having married, co-occurrence of an anxiety disorder, greater score for hyperthymic temperament, and depression as a first episode (Table 2).

3.4. Comparisons by diagnosis

We compared the magnitude of differences of associated factors between study participants with versus without suicidal acts for those diagnosed with BD or MDD (Fig. 1). Most differences between diagnoses were small; notable exceptions were substance abuse, more recent birth

Table 2
Factors associated with suicidal acts in 4307 major affective disorder participants.

Factor	Rate or mean [95%CI]		Ratio	p-Value (t-score or χ²)
	Suicidal	Nonsuicidal		
Greater with suicidal acts				
1. Diagnosis			3.79	<0.0001 (258)
All BD	22.5 [20.3–24.7]			
MDD	5.93 [5.10–6.86]			
2. Hospitalized/year (%)	8.46 [4.97–11.9]	2.61 [1.65–3.57]	3.24	<0.0001 (4.40)
3. Substance abuse				
Any substance (%)	22.3 [18.7–26.4]	9.65 [8.72–10.6]	2.31	<0.0001 (68.1)
Alcohol (%)	32.2 [24.6–40.5]	16.2 [14.1–18.5]	1.99	<0.0001 (21.9)
Drugs	12.8 [9.87–16.2]	7.23 [6.42–8.11]	1.77	<0.0001 (17.5)
Cigarettes/day	9.71 [8.37–11.1]	8.13 [7.55–8.71]	1.12	0.03 (2.15)
4. Separated/divorced (%)	20.2 [15.5–25.6]	9.66 [8.51–10.9]	2.09	<0.0001 (27.6)
5. Family history (%)				
Suicide	11.6 [8.65–15.1]	5.83 [4.99–6.78]	1.99	<0.0001 (19.1)
BD	31.3 [26.7–36.1]	19.3 [17.7–20.8]	1.62	<0.0001 (29.6)
Rate (% of relatives)	28.9 [26.1–31.7]	25.4 [24.3–26.5]	1.14	0.02 (2.35)
Mood disorder	63.7 [58.7–68.5]	56.2 [54.2–58.1]	1.13	0.005 (7.76)
Any psychiatric	71.0 [66.4–75.4]	63.2 [61.4–65.0]	1.12	0.002 (8.38)
6. Early abuse (%)				
Sexual	24.1 [18.0–31.2]	13.3 [10.9–16.0]	1.81	0.0004 (12.6)
Physical	18.5 [13.0–25.1]	10.3 [8.16–12.7]	1.80	0.003 (9.10)
7. Time [hypo]manic (%)	8.87 [7.23–10.5]	4.95 [4.37–5.53]	1.79	<0.0001 (5.44)
8. First episode [hypo]manic, mixed or psychotic	17.0 [13.8–20.6]	10.0 [9.06–11.0]	1.70	<0.0001 (21.2)
9. [Hypo]manias/year	0.46 [0.37–0.54]	0.27 [0.24–0.31]	1.69	<0.0001 (4.39)
10. Depressions/year	0.68 [0.57–0.79]	0.50 [0.44–0.55]	1.69	0.003 (3.00)
11. Unemployment (%)	12.0 [9.17–15.3]	7.66 [6.81–8.58]	1.57	0.001 (10.2)
12. Time ill (%)	29.0 [26.3–31.7]	19.3 [17.9–20.7]	1.50	<0.0001 (5.74)
13. Sex in BD (%)			(1.45)	0.0004 (12.6)
Women	25.8 [21.8–28.9]	–		
Men	17.8 [14.8–21.1]			
14. Temperament ratings (TEMPS)				
Irritable	2.16 [1.81–2.51]	1.51 [1.38–1.64]	1.43	<0.0001 (3.97)
Cyclothymic	6.11 [5.58–6.65]	4.96 [4.73–5.19]	1.23	<0.0001 (4.13)
Dysthymic	4.23 [3,88–4.58]	3.49 [3.33–3.65]	1.21	<0.0001 (3.94)
15. Time depressed (%)	20.2 [17.5–22.9]	14.3 [13,1–15.5]	1.41	<0.0001 (4.28)
16. Episodes/year	1.13 [0.93–1.31]	0.77 [0.69–0.85]	1.34	<0.0001 (3.97)
17. Age (years)				
Onset	25.2 [25.6–28.7]	33.5 [30.4–32.0]	1/1.33	<0.0001 (9.78)

Table 2 (*continued*)

Factor	Rate or mean [95%CI]		Ratio	*p*-Value
	Suicidal	Nonsuicidal		(*t*-score or χ^2)
Current	44.6 [43.1–46.1]	46.5 [45.9–47.0]	1/ 1.04	0.02 (2.27)
18. Population density/km^2	886 [801–971]	993 [963–1023]	1/ 1.12	0.02 (2.33)
19. Intake depression (HDRS)	16.5 [14.9–18.1]	14.7 [14.0–15.4]	1/ 1.12	0.04 (2.11)
20. Lower functioning (GAF)	59.2 [56.4–62.0]	65.4 [63.2–65.6]	1/ 1.10	<0.0001 (4.17)
21. Secular trend (entry year)	2002 [2001–2003]	1997 [1996–1998]	1/ 1.01	<0.0001 (8.38)
Greater without suicidal acts				
1. Ever married (%)	42.8 [38.3–47.4]	66.2 [52.5–55.7]	1/ 1.26	<0.0001 (21.9)
2. Anxiety disorder (%)	55.6 [48.5–62.5]	66.2 [63.1–69.1]	1/ 1.19	0.004 (8.56)
3. Hyperthymic temperament	3.10 [2.76–3.44]	3.58 [3.42–3.75]	1/ 1.15	0.01 (2.53)
4. Depressive first episode	69.9 [65/7–74.0]	79.1 [77.8–80.4]	1/ 1.13	<0.0001 (21.2)

Ratios in parentheses are for comparisons of suicidal subgroups.

Abbreviations: *BD*: bipolar disorder; *BMI*: body-mass index; *CI*: 95 % confidence interval; *DMI*: depression–[hypo]mania–euthymic-interval course pattern; *GAF*: Global Assessment of Functioning scale; *HARS*: Hamilton Anxiety Rating Scale; *HDRS*: Hamilton Depression Rating Scale; *MDD*: major depressive disorder; *MDI*: [hypo]mania–depression–euthymic-interval course pattern; *TEMPS-A*: Temperament Evaluation of the Memphis, Pisa, Paris and San Diego Autoquestionaire; *YMRS*: Young Mania Rating Scale. Factors are ranked by the ratio of values with/ without or without/with suicidal acts within and between each group of factors. There was little difference in risk of suicidal acts between BD1 (24.7 % [20.7–29.1]) and BD2 (24.0 % [19.9–28.6]) participants ($\chi^2 = 0.05$, $p = 0.82$). Other factors not significantly associated with suicidal acts included: parental age at participant's birth, educational level, socioeconomic status, rating of anxious temperament, sex in MDD, any co-occurring psychiatric or neuropsychiatric diagnosis except anxiety disorder, seasonality of illness, duration of first lifetime episode, course sequence (DMI vs. MDI), presence of rapid-cycling, predominant polarity with BD, and occurrence of rapid switching from depression to [hypo]mania with BD, general medical comorbidities, religious practice, intake ratings of [hypo]mania (YMRS) or anxiety (HARS), intake body-mass index (BMI), thyroid status (TSH or T4) or serum lipid concentrations (cholesterol, triglycerides), and coffee consumption (cups/day). Also, none of the types of treatment provided (including antidepressants vs. mood-stabilizers or antipsychotics) was significantly associated with occurrence of suicidal behaviors.

year and early sexual abuse selectively associated with BD. Relatively strongly associated with MDD were: hospitalization rate, family history of suicide, separation or divorce, and protective effects of older age at intake, co-occurring anxiety disorders, older onset age, being married and having children.

3.5. Factors not significantly associated with suicidal acts

Based on bivariate analyses (Table 2 footnotes), factors found not to be significantly associated with suicidal behavior included diagnosis of BD1 versus BD2 (risk of suicidal acts with BD1 was 24.7 % [20.7–29.1] and with BD2 24.0 % [19.9–28.6]; $\chi^2 = 0.79$, $p = 0.37$). Other factors not significantly associated with suicidal acts included: parental age at participant's birth, educational level, socioeconomic status, rating of anxious temperament (TEMPS-A), sex in MDD, any co-occurring psychiatric diagnosis except anxiety disorders, seasonality of illness, duration of first lifetime episode, course sequence (DMI vs. MDI), presence of rapid-cycling, predominant polarity, and occurrence of rapid switching from depression to [hypo]mania—all with BD, as well as general medical comorbidities, religious practice, intake ratings of [hypo]mania (YMRS) or anxiety (HARS), intake body-mass index (BMI), thyroid status (serum concentrations of thyroid stimulating hormone [TSH] and

thyroxin [T4]) or serum lipid concentrations (cholesterol, triglycerides), and coffee consumption (cups/day). Also, none of the types of treatment provided (including antidepressants vs. mood-stabilizers or antipsychotics, with or without psychotherapeutic intervention) was significantly associated with occurrence of suicidal behaviors.

Finally, we found a significantly but selectively greater risk of suicidal acts among women than men with BD (25.8 % [22.8–28.9] vs. 17.8 [14.8–21.1]; $\chi^2 = 12.6$, $p = 0.0004$) but not with MDD (5.83 [4.82–6.99] vs. 6.13 [4.72–7.81]; $\chi^2 = 0.10$, $p = 0.75$). In contrast, there was a higher risk of violent suicidal acts among men than women (3.71 % [2.84–4.76] vs. 2.50 % [1.95–3.16]; $\chi^2 = 5.10$, $p = 0.02$). Overall, risk of suicidal behavior by diagnosis and sex ranked: women with BD > men with BD > men with MDD > women with MDD.

3.6. Multivariable modeling

Factors reported for bivariate analyses in Table 2 and other selected factors were entered stepwise, from greatest to least different with versus without suicidal acts. Five factors remained significantly and independently associated with suicidal acts: [a] BD > MDD diagnosis, [b] younger at illness-onset, [c] greater %-time depressed in follow-up, [d] lower functional status at intake (GAF), and [e] women > men overall (Table 3).

4. Discussion

This study involved a large cohort of 4307 major affective disorder participants with DSM-5-TR BD (n = 1425) or MDD (n = 2882) who were ill for a total of 13.6 years and systematically followed prospectively for an average of 8.24 years under stable conditions of repeated observation and assessment. We compared a broad range of descriptive and clinical features among those with versus without suicidal acts since illness-onset. Several noteworthy findings emerged. First, 11.4 % of the participants experienced at least one suicide attempt since the onset of their affective illness; 8.58 % of these acts were violent, and 6.92 % were fatal. BD participants were nearly four-times more likely to have suicidal acts than those with MDD (21.9 % vs. 5.62 %), with a 2.66-times higher suicide rate (89.2 vs. 33.3 per 100 k PEY) and 5.74-times more violent acts (6.60 % vs. 1.15 % of participants; Table 1). These suicide rates were 3.6–9.5-times higher than the average international suicide rate of 9.4/100 k PEY (WHO, 2019). Violent acts were much more prevalent among men (11.0 % [8.47–13.9]) than in women (7.20 % [5.64–9.04]; $\chi^2 = 6.25$, $p = 0.01$). The attempt/suicide (A/S) ratio, at 13.9 and 15.6 for BD and MDD, respectively, was much lower (higher risk of suicide) than estimates of 30–40 in the general population (Baldessarini, 2019), indicating relatively high levels of *lethality* of attempts in the present cohort.

The lifetime prevalence of participants with suicidal acts overall (11.4 %) was lower than has been reported in some previous reviews regarding BD (34 %) and MDD (31 %) (Dong et al., 2019a, 2019b), but more consistent with other reports in which 19.9 % of BD participants and 9.5 % with MDD attempted suicide during a limited exposure time of 18-months of follow-up (Holma et al., 2014). Other data pooled from six studies yielded an average rate of suicide attempts of 12 % (range: 9.0 %–19 %) with MDD, 17 % with BD1 (10 %–38 %), and 24 % with BD2 (18 %–56 %) (Goodwin and Jamison, 2007). A large, long-term study involving follow-up from illness-onset found similar lifetime rates of suicide attempts of 7.77 % with BD and 6.67 % with MDD (Nordentoft et al., 2011). Contrarily, another long-term follow-up investigation found *higher* rates of suicide with MDD than with BD (Angst et al., 2002). Such rates may well be sensitive to effects of treatment and the specialized nature of the clinic setting involved in the present study.

The present findings confirm and extend reports that BD participants had higher risks of suicide and attempts than those diagnosed with MDD (Zalsman et al., 2006; Goodwin and Jamison, 2007; Tondo et al., 2007;
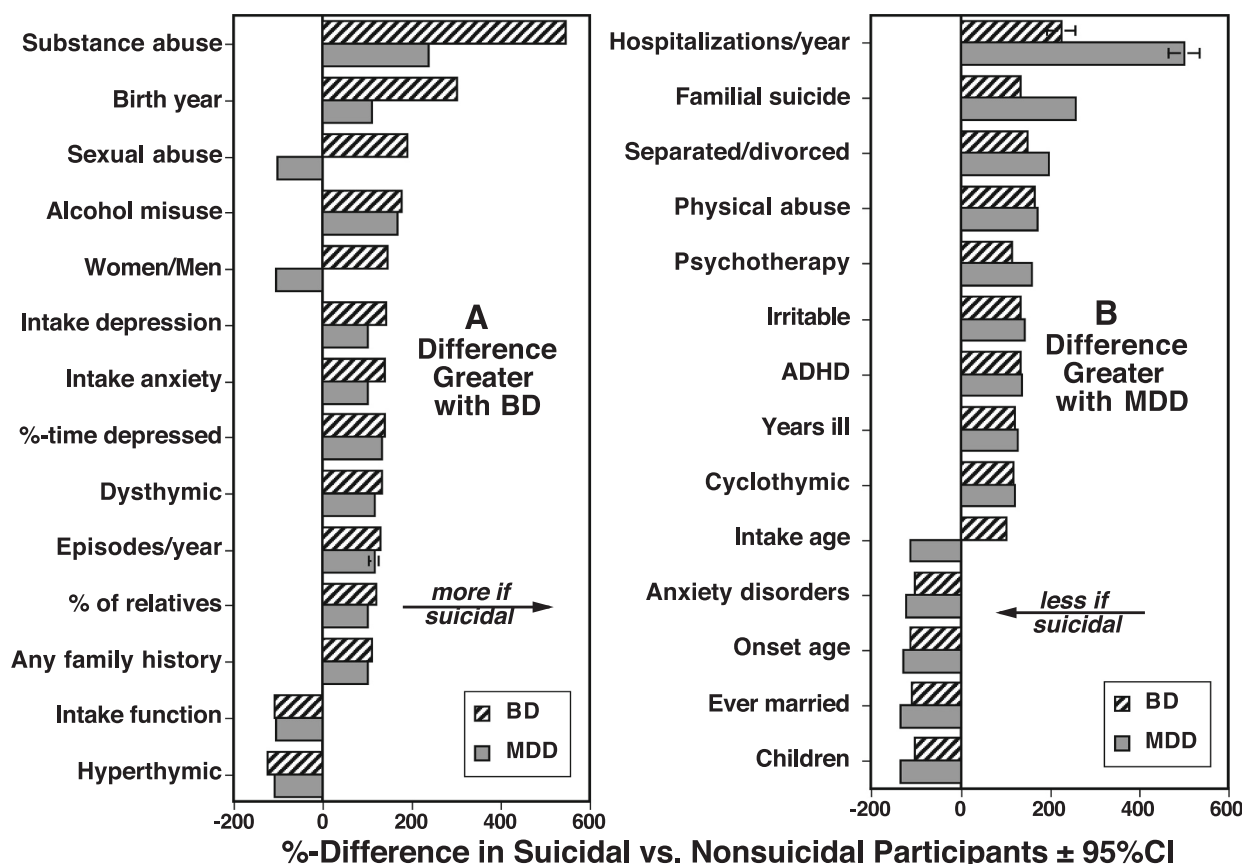
Fig. 1. Difference (%, with 95 % confidence interval [CI]) in prevalence or magnitude of factors associated with suicidal acts among 4307 study participants diagnosed with bipolar disorder (bipolar disorder [BD], n = 1425; striped bars) or major depressive disorder ([MDD], n = 2882; shaded bars). Factors in panel A differ more with vs. without suicidal acts with bipolar disorder (BD); in panel B differences are larger with vs. without suicidal acts with MDD; both are ranked by differences. Bars to the right of the null (>0) indicate differences greater with than without suicidal behavior (risk factors); those to the left (<0, negative values) are greater among nonsuicidal participants (possibly protective factors). Some measures are larger with suicidal BD but smaller with suicidal MDD (sexual abuse, sex-difference, and intake age); others are consistently smaller among suicidal participants (e.g., higher intake Global Assessment of Functioning [GAF], hyperthymic temperament rating, co-occurring anxiety disorders, onset-age, having been married, and greater number of children). ADHD = attention deficit-hyperactivity disorder.

Table 3
Multivariable logistic model of factors significantly and independently associated with suicidal acts in 4307 affective disorder participants.

Factor	OR [95 % CI]	χ^2	*p*-Value
BD vs. MDD diagnosis	2.44 [1.52–3.91]	13.8	0.0002
Younger at onset	1.02 [1.01–1.03]	12.9	0.0003
%-Time depressed in follow-up	1.01 [1.00–1.02]	7.43	0.006
Functioning at intake (GAF)	1.01 [1.00–1.02]	9.93	0.01
Women > men	1.53 [1.00–2.33]	3.86	0.05

Abbreviations: *BD*: bipolar disorder; *GAF*: Global Assessment of Functioning Scale; *MDD*: major depressive disorder. Other factors from Table 2, as well as intake age and years of exposure in follow-up were not associated with suicidal acts in this multivariable modeling.

Chen et al., 2014; Michaels et al., 2018; Baldessarini et al., 2019). The findings also support investigations reporting that BD participants and men displayed more violent acts than with MDD or among women (Zalsman et al., 2006; Tondo et al., 2007; Baldessarini et al., 2019, 2020).

Factors found in the present study to be associated with suicidal behavior accord with some other studies. Plausible demographic factors include marital separation or divorce, and perhaps early sexual abuse more than physical abuse, both of which may be associated with psychiatric illness or substance abuse among family members (Etain et al., 2013; Pawlak et al., 2013; Shabani et al., 2013; Goldberg et al., 2019). In

a postmortem study of over 19 million deaths among those diagnosed with MDD or BD, co-occurring substance abuse was associated with elevated risks for suicide in both men and women (Yoon et al., 2011). Among identified risk factors, several may be related to familial risk of suicide or to the presence of undiagnosed BD, including possible BD among depressed participants who make serious suicide attempts and have a family history of suicide attempts (Guillaume et al., 2010). As expected, we also found that some indices of greater illness severity were associated with suicidal acts. These included more hospitalizations/year, presence of psychotic features, as well as less successful functioning, as have been reported previously (Pawlak et al., 2013; Chen et al., 2014; Coentre et al., 2017; Aaltonen et al., 2019; Yates et al., 2019; Zhou et al., 2020; Buoli et al., 2022).

The current observation of more suicide attempts among women than men with BD selectively, and significantly more violent acts and fatalities among men confirms recognized gender-related risks found in most cultures (Holma et al., 2014; Baldessarini, 2019; Baldessarini et al., 2019). High rates of suicide among women in China are an exception (Phillips et al., 2002). The association of greater risk of suicide attempt among women versus men in BD selectively is not due to the predominance of women in the present study, and its basis remains unknown. Plausible areas to consider may include potential sex differences in details of psychopathology with BD versus MDD, including general emotional instability. In the present study there were no sex differences in morbidity (%-time in prospective follow-up depressed, [hypo]manic,

or ill) but women scored higher for cyclothymia. We also found that ratings of irritable, cyclothymic and dysthymic temperament were associated with greater risk of suicidal behavior, whereas hyperthymic temperament may be protective (Table 2), as we have noted previously (Vázquez et al., 2018; Baldessarini et al., 2017, 2019; Tondo et al., 2018). Cyclothymia in particular may reflect emotional instability as a potential contributing factor for risk of suicidal behavior, perhaps particularly among women (Miola et al., 2021).

Greater affective morbidity appeared to be a consistent risk factor for suicidal behavior (Tables 2 and 3), whether measured as a higher proportion of time ill, either in depression or [hypo]mania, or a higher annual episode frequency, both of which arose notwithstanding the potential "diluting" effect of greater exposure time (more years of illness, and younger onset age). Time spent in high-risk illness phases represents a crucial determinant of overall risk for suicidal acts among those with major affective disorders (Isometsä, 2014). Previous studies have emphasized the importance to suicidal risk with BD of time spent in depressive versus manic morbidity (Kupka et al., 2007; Valtonen et al., 2007, 2008; Holma et al., 2014; Miller et al., 2014; Tondo et al., 2017; Michaels et al., 2018). Other reports have noted that BD2 and BD1 participants who follow the DMI course-sequence, tend to be "depression-prone" (Koukopoulos et al., 2013; Tondo et al., 2017), although the DMI course in BD did not emerge as a risk factor in the present study. The relative prominence and clinical importance of depressive phases in BD as well as representing the essence of MDD have been recognized for more than a century (Kraepelin, 1921; Trede et al., 2005). Moreover, as we have reported previously, the depressive phases of BD continue to be particularly difficult to treat and to prevent with currently available treatments (Baldessarini, 2013; Baldessarini et al., 2020), which are only partially effective long-term for both BD and MDD (Forte et al., 2015).

Of note, a first-lifetime suicide attempt occurred at an average of 11–13 years from illness-onset in the present sample, with much shorter latency in some cases, potentially even before diagnosis and a secure treatment program is initiated, especially for BD (Scott et al., 2022). With BD, the delay from illness-onset to secure diagnosis and stable treatment averages 6–8 years and can be more than a decade following onset in adolescence (Dagani et al., 2017). This often prolonged latency leaves open the possibility that risk of suicide may sometimes arise before a secure treatment regimen is established. Moreover, latency to first suicidal behavior may be relatively short if initial clinical assessment is occasioned by a suicide attempt.

The present findings also are consistent with previous reports of higher rates of suicidal behavior with early-onset BD and MDD (Perlis et al., 2004; Tozzi et al., 2011; Korten et al., 2012; Coryell et al., 2013; Sung et al., 2013; Herzog et al., 2021; Miola et al., 2022). This association is likely to reflect the nature or duration of psychopathological features associated with early-onset of affective disorders as well as the simple statistical effect of longer exposure times.

A possible protective role of co-occurring anxiety against suicidal behavior emerged as a substantial effect (Table 2) and is consistent with some previous reports (Placidi et al., 2000; Grunebaum et al., 2005). Nevertheless, this association should be viewed cautiously as several studies have yielded contradictory findings of higher suicidal risk with anxiety (Sareen et al., 2005; Bolton et al., 2010; Sala et al., 2012) and others did not find any association of anxiety symptoms or syndromes with suicidal risk (Oquendo et al., 2004; Valtonen et al., 2006; Nakagawa et al., 2008; Holma et al., 2014; Abreu et al., 2018).

Findings that years of birth and of clinic-entry were later among study participants with suicidal behavior may suggest a secular trend toward rising suicidal risk over time. Such a trend is at variance with recent decreases in international suicide rates in many countries, including in Europe, and is not readily explained (Dattani et al., 2023). However, it is possible that over the years specialized clinics have increasingly attracted more severely ill participants.

Finally, the results of multivariable modeling (Table 3) support the basic conclusion that having BD (BD1 or BD2) presents greater risk for suicidal behavior than does MDD. In addition, longer time ill and earlier onset were associated with suicidal risk and may in part reflect the greater chance of becoming suicidal with longer exposure time and more prolonged illness. On the other hand, the observed greater suicidal risk with a higher proportion of time ill indicates that greater morbidity or more intensive affective illness is a relevant risk factor. The observed risk factor of suicide in first-degree relatives is consistent with a possible genetic contribution to suicidal risk (Baldessarini and Hennen, 2004). Finally, the effect of sex and its interaction with diagnosis was complex and its basis uncertain.

Clinical implications of the present findings support the hypothesis that cyclothymia, as an expression of emotional instability, should be carefully considered among possible risk factors for suicidal behavior, especially in women. Our findings also emphasize the need for thorough risk assessment for potential lethality associated with planned methods of suicide in the presence of suicidal ideation, especially in men with BD. In general, clinical recognition of risk and protective factors identified in the current study should inform efforts to stratify suicide risk in an effort to improve preventive strategies in such high-risk populations.

4.1. Limitations

There is a risk of incomplete or inaccurate detection of suicidal events and associated factors, some of which depend on clinical histories. Such ascertainment errors probably are similarly likely between the groups compared. Second, data from nonpsychiatric controls were not available for comparison, but suicidal risk would be low among healthy controls, who moreover were not required for comparing suicidal versus nonsuicidal participants with major affective disorders. Third, bivariate testing of large numbers of risk and protective factors can yield chance associations with suicidal behavior. Factors with strong preliminary associations with suicidal behavior were further tested with multivariable regression modeling, as well as by comparing the magnitude of observed bivariate associations overall and between diagnostic and suicidal groups. Finally, the present findings may not apply consistently in other cultures, locations, or times and the strong reliance on clinical assessments by a single expert may introduce bias, though is unlikely to affect comparisons by sex, diagnosis, or suicidal status.

4.2. Conclusions

The present findings in a large, extensively evaluated adult major affective disorder cohort with systematic, prospective follow-up for several years provide a solid basis for comparison of suicidal risks between BD and MDD participants, as well as in identifying risk and protective factors for suicidal behavior. As expected, suicidal risks among study participants diagnosed with BD were much greater than with MDD but similar with BD1 and BD2 diagnoses. Participants with suicidal acts differed in many ways from those without, yielding 31 types of apparent risk factors and four protective factors, five of all of which were sustained by multivariable regression modeling. Most factors were similar among BD and MDD participants, though substance abuse, year of birth, and sexual abuse were more prominent or later with BD, and hospitalization rate, familial suicide, and divorce were greater with MDD. In general, the present findings confirm and clarify some previously reported, but sometimes inconsistent, findings, as well as extending the range of factors considered for both BD and MDD participants evaluated both retrospectively and prospectively under consistent circumstances.

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had no input into data analysis, MS preparation, or reporting.

CRediT authorship contribution statement

Alessandro Miola: data organization, literature review, MS preparation; *Leonardo Tondo*: data collection and analysis, MS preparation; *Marco Pinna:* data collection, MS preparation; *Martina Contu*: data collection, MS preparation; *Ross J. Baldessarini*: data analysis, literature review and MS preparation.

Declaration of competing interest

AM, LT, MP, MC, RJB have no conflict of interest to declare.

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